Reducing the burden of mental illness and behavioral disorders through research on mind,

Science Update

August 28, 2007

Suspect Schizophrenia Genes Act Together to Thwart Working Memory

Two gene variants implicated in schizophrenia interact to degrade the brain's ability to process information, NIMH researchers have discovered. The interaction impaired working memory — retaining information from moment to moment. Such thinking problems are a hallmark of this severe mental illness that affects about one percent of the population.

Functional magnetic resonance imaging (fMRI) scans revealed an interaction between suspect versions of the genes that produced inefficient activity and poor connectivity in a key thinking circuit during a working memory task. Previous studies have shown that this circuit functions abnormally in schizophrenia.

The researchers scanned 29 healthy subjects while they performed working memory tasks — first easy and then hard — to gauge how the genes affected information processing in the circuit. The fMRI scanner produces pictures of how active parts of the brain are at any given moment by tracking the destination of oxygenated blood.

Joseph Callicott, M.D., Hao Yang Tan, M.D., and colleagues in the NIMH Genes, Cognition and Psychosis Program, reported on their findings in the July 24, 2007 Proceedings of the National Academy of Sciences.

"Much like a weak radio station drowned out by static, communications between brain cells were hampered by weakened signals relative to the background noise level in the circuit," explained Callicott.
The circuit handles communications between the executive hub at the front of the brain called the prefrontal cortex, and the middle areas important for processing information known as the parietal lobes.

While previous imaging studies had focused on individual genes, the new study shows that combinations of genes can thwart information processing, as likely occurs in schizophrenia. Schizophrenia is thought to stem from complex interactions among multiple genes and environmental factors. The \texttt{COMT} gene and \texttt{GRM3} gene have been implicated in schizophrenia.

People typically inherit two copies of genes, one from each parent, so some people have two different versions while other have two of the same version. The two versions of the \texttt{COMT} gene, called "Val" and "Met," result from variation in just one letter of the genetic code. To maximize gene-influenced differences in brain activity, the researchers selected people who each had two copies of the "Val" gene version. These participants showed the working memory deficit if they also had two copies the \texttt{GRM3} gene "A" version. Subjects with two copies of the \texttt{COMT} "Met" gene version were protected against the adverse interactive effects on working memory.

When the working memory task got harder, \texttt{COMT} "Val" carriers' brain activity soared in an area at the top of the prefrontal cortex; an area on the side of the cortex was also activated. But \texttt{COMT} "Met" carriers, who performed better on the task, activated only the top area, and to a lesser degree (see brain graphic below).

The over-activation in the top prefrontal area in the \texttt{COMT} "Val" carriers showed that it was processing information inefficiently — "much like a car with engine trouble that's working too hard and overheating," said Callicott. Activation of the side prefrontal area in the "Val" carriers appears to be the brain attempting to compensate for this, he added.

There was also evidence of poorer connections in the functioning of brain circuitry during working memory in those with the schizophrenia-related gene versions.

The "A" version of \texttt{GRM3} is associated with weaker signals transmitted via the messenger chemical glutamate, while the \texttt{COMT} "Val" version is associated with weaker dopamine activity. The \texttt{COMT} "Met" version is marked by increased dopamine activity.

"Schizophrenia involves abnormalities in dopamine and glutamate," noted Callicott. "Interacting genes can affect the workings of key chemical messenger systems to impair the efficiency of communications signals in a circuit implicated in schizophrenia. Imaging these interactions deepens our understanding of disease mechanisms and may help point the way to improved treatment."
Functional MRI data superimposed on a 3-D anatomic MRI reconstruction of the brain shows areas (red) where activity differed during the easy and hard working memory tasks. Subjects with two copies of schizophrenia-related versions of two genes overactivated an area at the top (red circle) of the prefrontal cortex. They also activated an area at the side of the cortex (blue circle). By contrast, subjects with two copies of other common versions activated only the top (red circle) area - and to a lesser degree. The overactivation of the top area and likely compensatory activation of the side area indicates inefficient information processing, which was reflected in poorer performance on the task by those with the suspect gene versions.

Source: Joseph Callicott, M.D., NIMH Genes, Cognition and Psychosis Program
Subjects with two copies of the schizophrenia-implicated COMT gene "Val" version and the GRM3 gene "A" version (VV+AA) showed the highest activation in the top prefrontal cortex area (red circle in above graphic) during working memory tasks. This indicated the least efficient information processing, compared to other gene combinations. The darker red bars reflect heightened activation levels during the hard working memory task (2-back).

Source: Joseph Callicott, M.D., NIMH Genes, Cognition and Psychosis Program


Jules Asher

Posted: 08/28/2007
Reducing the burden of mental illness and behavioral disorders through research on mind, brain, and behavior

Science Update

June 4, 2007

Antipsychotic Medications for Schizophrenia on Equal Footing in Improving Patients' Thinking Skills

Patients with schizophrenia taking antipsychotic medications experience a small improvement in thinking and reasoning skills (neurocognition), but no one medication appears to be better than the others in improving these skills during the first two crucial months of treatment, according to the latest results from the NIMH-funded Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE). The study was published in the June 2007 issue of the Archives of General Psychiatry.

Neurocognitive impairment is often a central feature of schizophrenia, and one of the disease’s most troublesome and difficult-to-treat symptoms. However, medications for schizophrenia currently do not target neurocognitive symptoms specifically.
In the CATIE trial, patients were randomly assigned to take either perphenazine—an older, first-generation antipsychotic medication—or one of several newer, second-generation medications (olanzapine, quetiapine, risperidone, or ziprazidone). Richard Keefe, PhD of Duke University, and colleagues evaluated the neurocognitive skills of 817 CATIE participants who completed an initial evaluation before the study began and, after being on the same medication for two months, underwent a second evaluation. Keefe and colleagues measured any neurocognitive change by comparing pre- and post-test results from 11 examinations designed to test an individual’s thinking, memory, reasoning and problem-solving abilities. They found a small rate of improvement among all the treatment groups, but no treatment group appeared to benefit more than the others.

The results run contrary to previous studies, and the widely held belief, that the newer, second-generation antipsychotics are better than the older medications in improving schizophrenia patients’ cognitive skills.

The researchers also retested participants remaining in the trial after six months and after 18 months. After six months, no differences among the medication groups emerged in the 523 remaining participants. After 18 months, 303 participants remained; those who had taken the older antipsychotic perphenazine for the duration of the study showed slightly more neurocognitive improvement than those taking the newer, second-generation medications. However, because so few participants remained at this point, the researchers could not conclude that perphenazine had any advantage over the other medications.

The overall neurocognitive improvement remained small among all treatment groups, and most of the improvement occurred in the early stages of treatment. “What happens during the first few months of treatment is the most important indicator of success,” said Dr. Keefe. “But the neurocognitive benefits over the long term were limited. We clearly need new treatments that will improve schizophrenia patients’ cognitive skills.”

Posted: 06/04/2007
Violence in Schizophrenia Patients More Likely Among Those with Childhood Conduct Problems

Some people with schizophrenia who become violent may do so for reasons unrelated to their current illness, according to a new study analyzing data from the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE). CATIE was funded by the National Institutes of Health's National Institute of Mental Health (NIMH). The study was published online on June 30, 2007, in the journal Law and Human Behavior.

"Most people with schizophrenia are not violent," said NIMH Director Thomas R. Insel, M.D. "But this study indicates that the likelihood of violence is higher among people with schizophrenia who also have a history of other disorders, namely childhood conduct problems."

Using data from 1,445 CATIE participants, Jeffrey Swanson, Ph.D., of Duke University, and colleagues examined the relationship between childhood antisocial behavior, including conduct disorder symptoms, and adult violence among people with schizophrenia. The overall percentage of participants who committed acts of violence was 19 percent. Those with a history of childhood conduct problems reported violence twice as frequently (28 percent) as those without conduct problems (14 percent). In both groups, violence was more likely among those who were unemployed or underemployed,
living with family or in restrictive settings (such as a halfway house or hospital), been recently arrested, or involved with the police.

Violence was associated with alcohol and substance abuse in both groups. But unlike the group without childhood conduct problems, violence in the group with childhood conduct problems was associated even with levels of alcohol and substance use considered below the threshold for abuse.

The researchers also found that psychotic symptoms were not significantly associated with violence among those participants with a history of childhood conduct problems. In contrast, the presence of psychotic symptoms was associated with an increase in violence among participants without a history of childhood conduct problems.

Swanson and colleagues theorize that there may be two pathways in which adults with schizophrenia may become violent—one in which pre-existing conditions like that of antisocial conduct in childhood, regardless of the presence of psychotic symptoms, may link to violence, and one in which psychotic symptoms of schizophrenia themselves may link to violence.

Based on their theory, the researchers suggest that the antipsychotic medications used to treat psychosis may not be sufficient to treat violent symptoms in people who are at a higher risk due to pre-existing antisocial conduct conditions.

The researchers note that other studies have already found a strong link between childhood conduct problems and adult violence, with or without the presence of schizophrenia. This study adds evidence to the notion that a more targeted treatment should be employed for schizophrenia patients with conduct disorder histories.

"Doctors should take into account their patients' histories before deciding on a treatment approach," said Dr. Swanson. "They should consider specific interventions aimed at preventing further violence, especially among their schizophrenia patients who have a history of childhood conduct problems.

The National Institute of Mental Health (NIMH) mission is to reduce the burden of mental and behavioral disorders through research on mind, brain, and behavior. More information is available at the NIMH website.

The National Institutes of Health (NIH) - The Nation's Medical Research Agency - includes 27 Institutes and Centers and is a component of the U. S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical, and translational medical research, and it investigates the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit http://www.nih.gov.

Posted: 07/2/2007
New Details in Schizophrenia Treatment Trial Emerge

Two new studies from the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) provide more insights into comparing treatment options, and to what extent antipsychotic medications help people with schizophrenia learn social, interpersonal and community living skills. The new studies are published in the March 2007 issue of the American Journal of Psychiatry. CATIE, a $42.6 million, multi-site study, was funded by the National Institutes of Health's National Institute of Mental Health (NIMH).

Comparing Newer Antipsychotic Medications After Older One Fails

Quetiapine, and to some extent olanzapine, may be more effective than risperidone among patients who were originally taking, but had to discontinue, perphenazine—an older, first generation antipsychotic medication. However, patient responses varied considerably.

"CATIE continues to fine-tune our understanding of how our arsenal of antipsychotic medications work in real-world settings, but it also is revealing to us what questions we still must address," said NIMH Director Thomas R. Insel, M.D.

Of the 257 patients who were initially randomized to perphenazine in the CATIE study, 192 discontinued the medication for various reasons, including ineffectiveness and
intolerable side effects. Among those who discontinued, 114 agreed to be re-randomized to one of three newer antipsychotic medications—olanzapine, quetiapine or risperidone.

T. Scott Stroup, M.D., MPH, of the University of North Carolina at Chapel Hill, and colleagues compared the effectiveness of the medications by determining how long patients stayed on their assigned medication. Those taking quetiapine stayed on the longest—averaging about ten months before discontinuing. Those taking olanzapine discontinued after an average of about seven months, and those taking risperidone discontinued after an average of four months.

Although the discontinuation results suggest that olanzapine was generally on par with quetiapine, patients taking olanzapine experienced more side effects. While none of those taking quetiapine discontinued use due to weight gain or metabolic side effects, 13 percent of those assigned to olanzapine discontinued it due to weight gain or metabolic problems, and 5 percent of those on risperidone did so.

"These results reinforce the fact that finding the most effective medication for each patient sometimes means trying multiple medications," said Dr. Stroup. "They remind us of the considerable variability in clinical circumstances and of our need to be responsive to an individual's needs and preferences."

**Schizophrenia Patients' Social and Community Living Skills Improve Modestly While on Antipsychotic Medications**

Patients with schizophrenia taking antipsychotic medications experience modest improvements in social, interpersonal and community living (psychosocial) skills, regardless of what antipsychotic medication they are taking.

Improvements in psychosocial skills among patients with schizophrenia have been notoriously difficult to achieve, even when the more disruptive symptoms of the disease can be controlled. "Helping patients with schizophrenia restore their psychosocial functioning remains a challenge," said NIMH Director Thomas R. Insel, M.D. "These CATIE results reinforce the growing understanding that we must do a better job of helping patients get their life skills back on track."

Marvin Swartz, M.D., of Duke University and colleagues evaluated the social and vocational functioning, interpersonal relationships, and psychological well-being of 455 participants—about one-third of all patients in the CATIE study—who completed an initial evaluation before the study began and were available to provide data after 12 months of treatment. In the first phase of the CATIE study, patients were randomly assigned to take either perphenazine—an older, first-generation antipsychotic medication—or one of several newer, second-generation medications (olanzapine, quetiapine, risperidone, or ziprasidone).

The researchers found that those patients who stuck with their initial treatment showed some improvement in their psychosocial functioning, and there were no differences
among the medications in making these gains. The results are consistent with previously reported CATIE results in which few differences were seen among perphenazine and the newer, second-generation antipsychotic medications in effectively reducing symptoms.

The patients who made the greatest gains were the ones with the poorest community living skills at the beginning of the study, but they were also more likely to discontinue treatment early in the process. As noted in previous CATIE reports, many patients discontinued their initial treatments because of intolerable side effects or ineffectiveness.

"Over the long run patients are more likely to function better in the community if they are able to stay on their initial treatment, especially those who are the most impaired," said Dr. Swartz. "More intensive rehabilitative interventions and outreach may help patients stick with their treatment and make greater gains."

Patients who made few gains in community living skills were those with higher-level psychosocial skills at the beginning of the study. Swartz and colleagues posit that patients encountered a "ceiling effect" at which point additional psychosocial skill improvement was unlikely without additional rehabilitative treatment.

"Overall, the findings reiterate the widely held belief that antipsychotic medications alone are not sufficient in helping patients make meaningful gains in real-world functioning," said Dr. Swartz. "Dedicated rehabilitative services that help patients learn to function at work and in social settings are sorely needed."

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The National Institutes of Health (NIH) — The Nation's Medical Research Agency - includes 27 Institutes and Centers and is a component of the U. S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical, and translational medical research, and it investigates the causes, treatments, and cures for both common and rare diseases. Visit the NIH website for more information about its programs.


Posted: 03/01/2007
Reducing the burden of mental illness and behavioral disorders through research on mind, brain, and behavior

NIMH Perspective on Antipsychotic Reimbursement: Using Results from the CATIE Cost Effectiveness Study

The recent publication (December 1, 2006, American Journal of Psychiatry) of the cost-effectiveness results from the National Institute of Mental Health (NIMH)-funded Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) has raised questions among advocates, families, and clinicians about reimbursement policies for antipsychotic medications.

Antipsychotics have now become the fourth largest group of medications prescribed in the United States, with a collective cost expected to surge past $10 billion this year. About 80 percent of the prescriptions for antipsychotics are paid via the public sector. The new atypical medications, representing 90 percent of the current market, are approximately 10 times the cost of the older conventional antipsychotics.

In a report in the September 22, 2005, New England Journal of Medicine, the CATIE research team compared discontinuation rates with four atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) and one older conventional
antipsychotic (perphenazine). The results demonstrated few differences overall among the various medications. The older medication, perphenazine, was as well tolerated as the newer compounds and as effective as three of the four newer drugs. The fourth compound, olanzapine, was slightly better than all the others in terms of discontinuation and hospitalization rates but was also associated with higher rates of weight gain and metabolic side effects.

The December 1, 2006 study analyzed the economic implications of the CATIE results and found that, because perphenazine was as effective overall and less expensive, the older antipsychotic medications such as perphenazine still have a valuable role in treating schizophrenia. The results should encourage doctors to reconsider the use of these older medications as another choice for patients with schizophrenia. This study should help expand the current list of medications most commonly used for schizophrenia, rather than restrict or reduce access to any of the antipsychotic medications. NIMH believes that this is important for the following reasons:

- Although the CATIE results suggest little difference in the overall effectiveness for the entire cohort, individual patients respond differently to different medications. To say the medications are equivalent is not to say they are identical. There is substantial variability in the response of individuals to these treatments. Future studies will focus on predicting individual patterns of response.
- There are additional outcomes to consider. Upcoming reports will describe the effectiveness of these various medications on quality of life and cognitive deficits. Cognitive impairment is a central clinical feature of schizophrenia and is strongly associated with functional outcomes.
- CATIE was limited to people with chronic schizophrenia who were moderately treatment-resistant. People with acute, first onset schizophrenia and those with other psychotic disorders were not included in this study. These patients may respond differently to antipsychotic medications.
- CATIE was an 18-month study. While this is longer than most clinical trials it is not long enough to fully consider whether patients would develop serious long-term side effects such as tardive dyskinesia, diabetes, or other medical conditions that can develop even years after starting medication.

Taking all these points into consideration, NIMH holds that families and physicians need more, not fewer, choices for addressing schizophrenia. A one-size-fits-all approach for treating schizophrenia could be harmful, essentially turning the clock back 40 years to an era when conventional antipsychotics were the only medications available for patients with this chronic, disabling disorder affecting 3.2 million Americans.

Updated: 12/01/2006
Older Medication May Be More Cost-Effective for Some Patients with Schizophrenia

A new study analyzing the economic implications of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) concludes that the older (first generation) antipsychotic medication perphenazine was less expensive and no less effective than the newer (second generation) medications used in the trial during initial treatment, suggesting that older antipsychotics still have a role in treating schizophrenia. The study,
published in the *American Journal of Psychiatry* on December 1, 2006, was funded by the National Institutes of Health's National Institute of Mental Health (NIMH).

The $42.6 million CATIE trial aimed to help doctors and the 2.4 million Americans who suffer from chronic schizophrenia tailor treatments to individual needs. It is the first study to directly compare several second generation antipsychotic medications and a representative first generation antipsychotic medication.

"The results from CATIE should encourage doctors to reconsider the use of perphenazine as another choice for patients with schizophrenia," said NIMH Director Thomas Insel, M.D.

More than 90 percent of antipsychotic prescriptions are written for second generation medications, despite the fact they are more expensive than the first generation agents used to treat schizophrenia. The majority of clinicians have traditionally believed that the newer antipsychotics are more effective and better tolerated than older agents, and many experts argued that these advantages justified the difference in cost.

Robert Rosenheck, M.D., of Yale University, and colleagues analyzed costs and quality-of-life factors associated with each of the five medications used in Phase 1 of the CATIE trial—olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. They found that total monthly health costs, a figure that includes both average medication costs and inpatient and outpatient costs, were up to 30 percent lower for those taking the perphenazine than for those taking the second generation medications. In addition, the researchers found no statistically significant difference in overall effectiveness between perphenazine and the second generation antipsychotics, with regard to symptom relief and side effect burden.

The findings echo what was implied in the results of the first phase of CATIE, expanding the treatment options for patients with schizophrenia. It casts doubt on the notion that the second generation antipsychotics are better than the first generation antipsychotics, and suggests that perphenazine and other first generation antipsychotics may be just as beneficial for some patients.

Still, several conditions of CATIE limit any firm conclusions about perphenazine's perceived advantages. Not all patients respond the same to different medications. In addition, the study lasted 18 months—long enough to determine how patients respond to and initially tolerate the drugs, but not long enough to consider some serious long-term side effects, such as development of the movement disorder tardive dyskinesia (TD), diabetes, cardiovascular problems, or other medical conditions that can develop even years after a patient with chronic schizophrenia starts taking an antipsychotic medication. Despite these caveats, the study results suggest new ways of thinking about medication treatments for schizophrenia.

"These results encourage doctors to revisit the older medication as an alternative, especially if a treatment change is warranted," said Dr. Rosenheck. "By showing that
perphenazine and possibly other older antipsychotics may be on equal footing with the second generation antipsychotics, CATIE has opened the door to more choice in treatment options."

The National Institute of Mental Health (NIMH) mission is to reduce the burden of mental and behavioral disorders through research on mind, brain, and behavior. More information is available at the NIMH website. The National Institutes of Health (NIH) — The Nation’s Medical Research Agency — includes 27 Institutes and Centers and is a component of the U. S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical, and translational medical research, and it investigates the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit http://www.nih.gov.


Posted: 12/01/2006
Studies Offer New Information About Treatment Choices for Schizophrenia (Phase 2 Results)

A national clinical trial comparing clozapine with other new-generation antipsychotic medications for the treatment of chronic schizophrenia has shown that people who switched to clozapine from their first medication because it failed to manage symptoms adequately were twice as likely to continue treatment as patients who switched to other antipsychotic medications. A companion study found that for people who switched to new-generation antipsychotic medications other than clozapine, those who took olanzapine and risperidone continued taking their medication longer than people taking quetiapine and ziprasadone. The results of the trial, which was funded by the National Institute of Mental Health (NIMH), part of the National Institutes of Health, were published in two papers in the April 2006 issue of the *American Journal of Psychiatry*.

The results of CATIE — Clinical Antipsychotic Trials of Intervention Effectiveness — offer the 2.4 million adults in the United States with chronic schizophrenia and their doctors information that can help tailor treatments to the individual needs of patients. In phase 2 of this study, 543 people were studied in 57 different treatment sites to provide guidance to help doctors determine what to do next when patients need to change medications, a common occurrence in treating schizophrenia. Research has shown that patients who consistently receive treatment do much better than those who stop taking their medications, so finding the right treatment is crucial.

The lead investigators for the two studies in phase 2 of CATIE were Jeffrey A. Lieberman, M.D., of Columbia University and the New York State Psychiatric Institute; Scott Stroup, M.D., of the University of North Carolina at Chapel Hill; and Joseph McEvoy, M.D., of Duke University. These studies were the next step for patients who did not do well on their first medication in phase 1 of the trial, results of which were published in the *New England Journal of Medicine* in September 2005.

Phase 2 of CATIE compared the medications, called "atypical antipsychotics," with each other in two different groups of participants. In one group, patients who had stopped taking a phase 1 medication because symptoms were not adequately relieved were randomly assigned to get one of four medications: clozapine, olanzapine, quetiapine, or risperidone. In that group, clozapine was the most effective. Forty-four percent of the patients who changed to clozapine stayed on it for the rest of the 18-month study, compared with 18 percent of patients who had changed to the other medications. On
average, patients stayed on clozapine for 10 months, while patients on any of the other medications stayed on them for only 3 months.

However, not all patients can or want to take clozapine, because it may cause serious side effects in some people, including inflammation of the heart muscle, and agranulocytosis, which is a dangerous drop in levels of white blood cells that are part of the immune system. As a result, patients taking clozapine require close monitoring. Although the patients who took clozapine in this study tolerated it fairly well overall, one person developed agranulocytosis.

There were other phase 1 patients who had stopped taking their medication because of side effects or because they told their doctors they wanted to change medications. These patients, as well as patients who wanted more symptom relief but didn't want to take clozapine, took part in a different phase 2 medication trial. In this part of the trial, clozapine was not included, and ziprasidone, the newest of the atypical medications available in the early stages of CATIE, was compared with the other three (olanzapine, quetiapine, or risperidone). Ziprasidone is known to have very different side effects, and it does not usually cause weight gain, as the other medications do.

Overall, patients in this phase 2 group stayed on risperidone seven months and on olanzapine just over six months, compared to four months on quetiapine and less than three months on ziprasidone. Until phase 2 was completed, neither patients nor researchers knew which medications were given, unless it was clozapine, because of the need for close monitoring. None of the patients were given a placebo — "blank" pill — for comparison.

Future CATIE reports will address a number of topics, such as cost-effectiveness, quality of life, and predictors of response, and will provide a more detailed picture of the interaction between patient characteristics, medications, and outcomes. CATIE is part of an overall NIMH effort to conduct "practical" clinical trials that address public health issues important to people affected by major mental illnesses in real-world settings.

Other study authors from phase 2 include:

- Sonia M. Davis, M.D., Dr.PH, University of North Carolina
- Herbert Y. Meltzer, M.D., Vanderbilt University Medical Center
- Robert A. Rosenheck, M.D., Yale University
- Marvin S. Swartz, M.D., Duke University
- Diana O. Perkins, M.D., M.P.H., University of North Carolina
- Richard S. E. Keefe, Ph.D., Duke University
- Clarence E. Davis, Ph.D., University of North Carolina
- Joanne Severe, M.S., National Institute of Mental Health
- John K. Hsiao, M.D., National Institute or Mental Health
Related Information

For more information on CATIE phase 2, visit:

- Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): NIMH Study To Guide Treatment Choices for Schizophrenia
- Questions and Answers About the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) — Phase 2 Results

For more information on CATIE phase 1, visit:

- NIMH Study To Guide Treatment Choices for Schizophrenia
- Questions and Answers About the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) — Phase 1 Results

For general information on CATIE, visit:

- Clinical Antipsychotic Trials of Intervention Effectiveness at ClinicalTrials.gov

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Posted: 04/01/2006
Questions and Answers About the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) — Phase 1 Results

September 2005

1. What is the CATIE study?

A. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study, funded by the NIH's National Institute of Mental Health, is a nationwide public health focused clinical trial comparing the effectiveness of older (first available in the 1950s) and newer (available since the 1990s) antipsychotic medications used to treat schizophrenia. These newer medications, known as atypical antipsychotics, cost roughly 10 times as much as the older medications. CATIE is the largest, longest, and most comprehensive independent trial ever done to examine existing therapies for this disease. Schizophrenia is a brain disorder characterized by hallucinations, delusions, and disordered thinking. The course of schizophrenia is variable, but usually is recurrent and chronic, often causing severe disability. Previous studies have shown that taking antipsychotic medications consistently is far more effective than taking no medicine and that the drugs are necessary to manage the disease. The aim of the CATIE study was to determine which medications provide the best treatment for schizophrenia.

To read the full press release, visit this link
2. Why is CATIE important?

A. Many studies have tested new antipsychotic medications in schizophrenia. Most of these were conducted by pharmaceutical companies,\(^1\) to obtain Food and Drug Administration (FDA) approval to market a new drug. These studies were usually short-term (4 to 8 weeks), focused on limited outcomes, enrolled a narrow range of patients, and studied only one or two medications at a time. By contrast, CATIE compared four of the newer medications to one another, and to an older medication. Participants in CATIE were followed for 18 months so that investigators could evaluate longer-term patient outcomes. The more than 1400 participants in the study included those with physical or other mental health problems in addition to schizophrenia. CATIE was conducted at many different treatment sites, broadly representative of the real life settings where patients receive their care. The results from CATIE will be applicable to the wide range of people with schizophrenia in the United States.

3. How will the results of CATIE affect the care doctors provide patients?

A. For the first time, doctors and people with schizophrenia will have extensive information on antipsychotic medications from a single, large, long-term study directly comparing the drugs to each other. CATIE greatly enhances the knowledge available to guide treatment choices for people with schizophrenia. CATIE provides new information on the efficacy and side effects of antipsychotic drugs, compared head to head, helping doctors determine the appropriateness of specific medications in individual patients. The combination of maximizing the benefits while minimizing the side effects increases the likelihood that a person with schizophrenia will stay on their antipsychotic medication, a necessary ingredient for managing symptoms and reducing the risk of relapse.

4. Which medications were studied in CATIE and how was medication chosen for each patient?

A. All medications included in the study were FDA-approved antipsychotic medications used in the treatment of schizophrenia. No placebo treatments were used. Patients were randomly assigned to a medication; study participants and their doctors could not choose which medication to take, and neither the investigators nor the patients knew which antipsychotic a patient was on. This type of study, a "double-blind randomized clinical trial," produces objective results, since researchers' and participants' will have no expectations about how well a medication might work to influence the outcome. In the first phase of CATIE, patients were randomly assigned to one of four newer, "atypical" antipsychotics: olanzapine (Zyprexa®), quetiapine (Seroquel®), risperidone (Risperdal®), and ziprasidone (Geodon®); or to the older, "typical" medication, perphenazine (Trilafon®). Dose range for each medication was chosen based on advice from experienced clinicians, clinical practice patterns from national pharmacy databases, and discussions with the drug manufacturers. Patients continued to take this medication for the next 18 months, or until the medication could not control their symptoms adequately,
or they developed an intolerable side effect, or they decided to stop the medication, or withdraw from the study for some other reason.

**CATIE Study Medications**

**Older Medication:**
Perphenazine (Trilafon®)

**Newer Medication:**
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Ziprasidone (Geodon®)

(Aripiprazole [Abilify®] was not approved by the FDA in time to be included in this phase of the study.)

5. **Why was perphenazine chosen as the older medication rather than haloperidol?**

A. Haloperidol was one of the most widely prescribed of the older antipsychotics before the "atypical" newer antipsychotics became available in the 1990s. It remains the most frequently used comparison drug in industry-sponsored clinical trials. However, patients who take haloperidol experience high rates of movement side effects, called extrapyramidal side effects (EPS), such as rigidity and stiff movements, persistent muscle spasms, tremors, and uncontrollable restlessness. Because many individuals find EPS particularly difficult to tolerate, haloperidol is an unpopular treatment choice for many people with schizophrenia. Although EPS is associated to some degree with all the older "typical" antipsychotic medications, perphenazine is an effective older antipsychotic that is less likely to produce EPS. This made it a good choice to use as the representative of the older medications in this study.

6. **How did researchers measure how well the medications worked?**

A. For patients with schizophrenia, staying on medication is critical to controlling symptoms and preventing relapse. Previous studies have shown that antipsychotic treatment is far better than no treatment. Although the medications alone are not sufficient to cure the disorder, they are necessary to manage it. Thus, it is essential for doctors to find a medication that is both effective and tolerable for a patient. This is why the primary measure of treatment success in the CATIE study was how long a patient benefited from and thus stayed on a medication before they or their doctor decided that it had to be changed. Investigators also recorded why a patient stopped a medication: if the medication did not control symptoms, or if the side effects were not tolerable, or if the patient chose to stop treatment for some other reason. In addition to this primary outcome, the study also examined medication effects on the symptoms of schizophrenia, as well as other important outcomes such as overall level of function.
7. What are the most important results of the CATIE study?

A. Overall, the medications were comparably effective but were associated with high rates of discontinuation due to intolerable side effects or failure to adequately control symptoms. One new medication, olanzapine, was slightly better than the other drugs but also was associated with significant weight-gain as a side-effect. Surprisingly, the older, less expensive medication (perphenazine) used in the study generally performed as well as the four newer medications. The study supplies important new information that will help doctors and patients choose the most appropriate medication according to the patients' individual needs.

At the beginning of the study, patients were randomly assigned to receive one of the five medications. Almost three quarters of patients switched from their first medication to a different medication. The patients started on olanzapine were less likely to be hospitalized for a psychotic relapse and tended to stay on the medication longer than patients taking other medications. However, patients on olanzapine also experienced substantially more weight gain and metabolic changes associated with an increased risk of diabetes than those participants taking the other drugs.

Perphenazine (the older medication) equally as effective as the other three newer medications (risperidone, quetiapine, and ziprasidone) and was as well tolerated as the newer drugs. The three newer medications performed similarly to one another.

Contrary to expectations, movement side effects (rigidity, stiff movements, tremor, and muscle restlessness) primarily associated with the older medications were not seen more frequently with perphenazine than with the newer drugs. The advantages of olanzapine — in symptom reduction and duration of treatment — over perphenazine were modest and must be weighed against the increased side effects of olanzapine.

Thus, taken as a whole, the newer medications have no substantial advantage over the older medication used in this study. An important issue still to be considered is individual differences in patient response to these drugs.

Several factors, such as adequacy of symptom relief, tolerability of side effects, and treatment cost, influence a person's willingness and ability to stay on medication. Patients and doctors must carefully evaluate the trade off between effectiveness, side effects, and cost in choosing an appropriate medication. Doctors must carefully monitor the physical health of their patients as well as the symptoms of psychosis.

8. Do these results indicate that physicians should alter their treatment plans for patients with schizophrenia?

A. This study provides the largest, longest, and most comprehensive independent trial ever conducted to study existing therapies for this disease. It will provide valuable information to help physicians and patients choose the most appropriate medication for them. There is considerable variation among individuals; what works for one does not
necessarily work for another. It is important to have a variety of treatment options. The CATIE study provides specific information, on therapeutic effects as well as side effects, about those options.

9. Who participated in CATIE?

A. CATIE participants included people with schizophrenia from across the country — 57 different clinical sites in 24 states — being treated in a variety of settings (e.g. private clinics, academic centers, Veterans Administration hospitals, and public mental health centers). The patients enrolled in CATIE broadly reflect the three million people with schizophrenia in the U.S. today. CATIE participants had chronic schizophrenia and were in need of antipsychotic treatment. The only patients excluded were those who were in a first episode of psychosis, those with treatment-resistant schizophrenia, and those with serious and unstable medical conditions.

**CATIE Participants**

- Patients Enrolled: 1,460
- Mean Age: 40.6
- Gender: 74% male
- Race: 40% non-white; 12% Hispanic
- Average Length of Illness: 14.4 years

10. Who conducted CATIE?

A. After a competitive, peer-reviewed process, NIMH selected the University of North Carolina (UNC) to implement CATIE. The trial is led by Dr. Jeffrey Lieberman, Principal Investigator (now at Columbia University), and co-investigators including Scott Stroup, M.D., M.P.H., Diana Perkins M.D., M.P.H., Ed Davis, Ph.D. (UNC), Joseph McEvoy, M.D., Marvin Swartz, M.D., Richard Keefe, Ph.D. (Duke University), Robert Rosenheck, M.D. (Yale University), and NIMH staff. Quintiles, a private contract research organization (CRO), assisted with study implementation and data analysis of the trial. The $42.6 million study was conducted over a five-year period at 57 clinical sites across the country.

11. What role did the pharmaceutical companies have in CATIE?

A. The pharmaceutical companies donated the study medications and provided advice about the optimal dose for that company's medication. The pharmaceutical companies had no other input into the design or implementation of the study, no involvement in planning or conducting the data analysis, and did not participate in preparing manuscripts for publication. The medications used in the study and their manufacturers included:

- olanzapine (Zyprexa®), manufactured by Eli Lilly and Company
- perphenazine (Trilafon®), Schering-Plough and Novartis
- quetiapine (Seroquel®), manufactured by Astra Zeneca Corporation
- risperidone (Risperdal®), manufactured by Janssen Pharmaceuticals
• ziprasidone (Geodon®), manufactured by Pfizer, Inc.

12. What other information will doctors and patients be able to learn from CATIE in the future?

A. The investigators will continue to study other important outcomes, including cost-effectiveness, quality of life, and predictors of response. As additional results from CATIE are analyzed, disseminated, and put into context, the hope is that the cumulative findings will yield a more complete picture of the interaction between patient characteristics, medication, environment, and outcomes.

References


Updated: 10/11/2006
Questions and Answers About the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) — Phase 2 Results

April 1, 2006

1. Q. What is the goal of phase 2 of the CATIE study?

A. The primary purpose of the CATIE study was to provide information to guide the everyday treatment of people with schizophrenia. The goal of phase 2 of CATIE was to provide guidance for doctors and patients facing the dilemma of choosing which antipsychotic medication to try next if the first antipsychotic medication was not satisfactory.

Two articles in the April 1, 2006 issue of the American Journal of Psychiatry (1, 2) describe results from phase 2 of CATIE, the National Institute of Mental Health's (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

In phase 1 of CATIE, people with schizophrenia were randomly assigned to receive treatment with one of the newer (introduced in the last decade), "atypical" antipsychotic medications: olanzapine (Zyprexa®), quetiapine (Seroquel®), risperidone (Risperdal®), or ziprasidone (Geodon®), or an older "conventional" medication, perphenazine (Trilafon®). Approximately one-quarter of all the participants were satisfied with the level of symptom relief they experienced from this first antipsychotic medication, were able to tolerate its side effects, and stayed on it for the entire 18 months of the study. However, three-quarters of the participants stopped taking their first antipsychotic medication before the end of 18 months. The study investigators recorded why a
participant stopped taking a medication: if the medication did not control symptoms, if the side effects were not tolerable or, if the patient chose to stop treatment for some other reason.

2. Q. What treatments were available in phase 2 of CATIE?

A. Two different treatment pathways were available to the participants who stopped medication for any reason during phase 1 yet wanted to continue with the study. Participants in phase 2 collaborated with their doctors to determine the pathway that was best for them.

- The **efficacy** pathway was designed for participants who discontinued their phase 1 medication because of inadequate symptom control. This pathway examined the question: *if a patient stops taking an atypical antipsychotic because it was not effective enough, what are the benefits of clozapine (Clozaril®) versus another atypical antipsychotic medication as the next treatment?* The efficacy pathway compared clozapine to the other newer atypical antipsychotic medications. Participants who chose this pathway were randomly assigned to receive either clozapine or an atypical antipsychotic (olanzapine, risperidone, or quetiapine) different from the one they took in phase 1.

- The **tolerability** pathway was designed for participants who discontinued their phase 1 medication because of side effects. This pathway examined the question: *if a person with schizophrenia stops taking an atypical antipsychotic because of intolerable side effects, which medication is the best next choice?* The tolerability pathway compared ziprasidone to the other atypical medications. Participants who chose this pathway were randomly assigned to receive either ziprasidone or an atypical medication different from their phase 1 medication.

3. Q. Why was clozapine chosen as the comparison medication for the efficacy pathway?

A. Clozapine is the only antipsychotic medication that has been shown to be more effective than other antipsychotics in controlling psychotic symptoms. Unfortunately, clozapine is associated with serious side effects, including life-threatening blood and heart complications such as agranulocytosis (decreased white blood cell count) and myocarditis (inflammation of the heart); as a result, people who take clozapine must be monitored closely, which includes blood tests. Due to these safety concerns, current practice guidelines limit the use of clozapine for treating people with schizophrenia who have not gotten better on other antipsychotic medications. However, many doctors and patients find clozapine's potential side effects and monitoring requirements too burdensome and are reluctant to consider using clozapine even where it might be helpful.
4. Q. Why was ziprasidone chosen as the comparison medication for the tolerability pathway?

A. Phase 1 demonstrated that the atypical antipsychotics differ considerably in their side effects. However, patients and doctors did not know whether a person who had intolerable side effects with one atypical medication might respond to and tolerate a different atypical antipsychotic medication. When the CATIE study began, ziprasidone was the newest antipsychotic and the least familiar to doctors. It was known that the side effects of ziprasidone were very different from the side effects of the other atypical antipsychotic medications; in particular, ziprasidone was known not to cause weight gain. Therefore, it was important to test whether switching to ziprasidone versus switching to some other atypical antipsychotic medication would be beneficial to participants who stopped taking their first antipsychotic medication due to side effects.

5. Q. How were participants in phase 2 assigned to the two treatment pathways?

A. Participants who discontinued their first antipsychotic medication because of inadequate management of symptoms were encouraged to enter the efficacy (clozapine) pathway, while participants who discontinued their first treatment because of intolerable side effects were encouraged to enter the tolerability (ziprasidone) pathway. However, participants were free to choose either pathway regardless of the reason for discontinuing their initial treatment. This freedom to choose mimics real-world practice where patients might or might not accept a doctor's recommendation of one treatment over another.

Of the 1,052 participants who discontinued phase 1 treatment before 18 months, 509 left the study entirely, 99 participants entered the efficacy (clozapine) pathway, and 444 entered the tolerability pathway. Most of the 99 participants who entered the efficacy pathway (86 percent) had stopped their phase 1 medication because of inadequate symptom management; very few participants who stopped due to side effects chose the efficacy pathway.

There were 184 participants who stopped their phase 1 medication because of inadequate symptom control who did not enter the efficacy pathway but instead entered the tolerability pathway, presumably because they were reluctant to try clozapine. Thus, the 444 participants in the tolerability pathway included a mix of participants: 41 percent discontinued their first treatment due to lack of efficacy, 38 percent discontinued due to intolerable side effects, and 21 percent discontinued for other reasons.

6. Q. Was perphenazine included in phase 2?

A. Perphenazine was not studied in phase 2. Phase 1 found that the older typical antipsychotic medication, perphenazine, generally performed as well as the four newer atypical medications and at the low doses used in CATIE study, perphenazine was just as well tolerated as the atypical medications. The study design did not anticipate this unexpected result that challenged the widely accepted (but never proven) belief that the
newer atypical antipsychotic medications are better than all older antipsychotic medications. Thus, the CATIE study did not evaluate, and therefore cannot answer, whether the older antipsychotic medications, such as perphenazine, would be good treatment choices after discontinuing one of the atypical antipsychotic medications.

7. Q. What are the main results of the efficacy (clozapine) pathway?

A. Most of the participants who chose the efficacy (clozapine) pathway had not benefited from their first phase 1 treatment. Their psychotic symptoms at the start of phase 2 were worse than at the start of phase 1. Furthermore, these participants had worse symptoms than the participants who chose to tolerability pathway.

In this group of very ill patients, clozapine was remarkably effective and was substantially better than all the other atypical medications: 20 out of 45 patients (44 percent) who received clozapine were able to stay on clozapine for the rest of the study, whereas only eight out of 45 patients (18 percent) who received another atypical antipsychotic medication were able to stay on that medication to complete the study. The participants taking clozapine remained on it for an average of 10 months compared to an average of three months for those taking any of the three other medications. Those taking clozapine also had greater symptom reduction than those who took any of the other medications. Only one patient developed agranulocytosis (and was taken off clozapine).

8. Q. What are the main results of the tolerability (ziprasidone) pathway?

A. The tolerability (ziprasidone) pathway of phase 2 studied the same antipsychotic medications as phase 1 of CATIE (except perphenazine was not included). As in phase 1, there was again a high rate (74 percent) of patients who stopped taking their medication for any reason. However, also as in phase 1, there were differences between the four atypical antipsychotic medications. In phase 2, about 35 percent of the participants who took olanzapine or risperidone were able to continue on their medication until the end of the 18 months of the study. This compares to only 23 percent of those who took ziprasidone and 16 percent of those who took quetiapine that were able to continue.

It was important to examine the results in phase 2 separately for those participants who had stopped their phase 1 medication for different reasons. For those who had stopped phase 1 medication due to inadequate management of psychotic symptoms, those taking olanzapine or risperidone in phase 2 stayed on their medication for a significantly longer duration than those taking quetiapine or ziprasidone, results that are similar to the overall results above. However, for the participants who had stopped phase 1 medication due to side effects, there were no significant differences among the four phase 2 medications. Thus, which medication works best depends in large part on why a patient was switched to it.

The main difference between the phase 1 and phase 2 results is that in phase 2, those who took risperidone received similar benefit as those who took olanzapine. In phase 1,
olanzapine's management of symptoms was better than all of the three other atypical medications.

9. Q. How will the results from the two CATIE phase 2 pathways help doctors and people with schizophrenia?

A. Doctors now have more information to guide the selection of the next antipsychotic medication to try in treating people with schizophrenia if treatment with a first antipsychotic is not successful. The results have shown that the reason why the first medication was stopped is an important consideration in choosing the next medication. Specifically, the success of symptom management and side effects experienced by the patient on the first medication may help predict which medication may be more successful next.

The CATIE results show that for patients whose symptoms are not wholly responsive to other antipsychotic medications, clozapine is an effective choice for the next step. Almost half the patients who took clozapine in phase 2 continued on treatment to the end of the study. Clozapine was more effective at preventing discontinuation because of inadequate control of symptoms than the other three atypicals in this phase: olanzapine, risperidone, or quetiapine. It was also shown to be more effective at reducing the actual level of symptoms than two of the atypicals in this phase: risperidone and quetiapine. The evidence confirms that clozapine is an effective medication in schizophrenia and the CATIE study results provide further support for efforts directed at both patients and doctors to increase the use of clozapine in the treatment of schizophrenia.

Even with increased support for the use of clozapine, there will still be numbers of patients who need a medication change because their symptoms are not well managed yet do not want to try clozapine. For those patients, CATIE phase 2 results show that olanzapine and risperidone are more effective than ziprasidone and quetiapine. But side effects must be considered.

For patients who stop their first medication because of side effects, there is no clear evidence for switching to one atypical medication over another. Instead, the patient and doctor will best be guided by the nature of the side effects and will have to balance this with the level of symptom control achieved. Olanzapine was associated with substantial weight gain and metabolic problems, more so than the other medications. Ziprasidone was consistently associated with reduction in weight and improvement in metabolic indicators. Risperidone showed the lowest rate of intolerable side effects.

References


Updated: 10/10/2006


Reducing the burden of mental illness and behavioral disorders through research on mind, brain, and behavior

Press Release

September 19, 2005

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NIMH Study To Guide Treatment Choices for Schizophrenia (Phase 1 Results)

A large study funded by NIH's National Institute of Mental Health (NIMH) provides, for the first time, detailed information comparing the effectiveness and side effects of five medications — both new and older medications — that are currently used to treat people with schizophrenia. Overall, the medications were comparably effective but were associated with high rates of discontinuation due to intolerable side effects or failure to adequately control symptoms. One new medication, olanzapine, was slightly better than the other drugs but also was associated with significant weight-gain and metabolic changes. Surprisingly, the older, less expensive medication used in the study generally performed as well as the newer medications. The study, which included more than 1,400 people, supplies important new information that will help doctors and patients choose the most appropriate medication according to the patients' individual needs. The study results are published in the September 22 issue of the *New England Journal of Medicine*.

"The study has vital public health implications because it provides doctors and patients with much-needed information comparing medication treatment options," said NIMH Director Thomas R. Insel, M.D. "It is the largest, longest, and most comprehensive independent trial ever done to examine existing therapies for this disease."

Schizophrenia, which affects 2.4 million Americans, is a chronic, recurrent mental illness, characterized by hallucinations, delusions, and disordered thinking. The medications used to treat the disorder are called antipsychotics. Previous studies have demonstrated that taking antipsychotic medication is far more effective than taking no medicine, and that taking it consistently is essential to the long-term treatment of this severe, disabling disorder. Although the medications alone are not sufficient to cure the disease, they are necessary to manage it.

In the $42.6 million CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial, researchers directly compared an older medication (perphenazine), available since the 1950s, to four newer medications (olanzapine, quetiapine, risperidone, and ziprasidone), introduced in the 1990s. The purpose of the study was to learn whether there are differences among the newer medications and whether the newer medications hold significant advantages over the older medications; these newer medications known as atypical antipsychotics, cost roughly 10 times as much as the older medications.

The size and scope of the trial, with more than 1,400 participants at 57 sites around the country, its 18-month duration, and its inclusion of a wide range of patients in a variety of treatment settings ensure that the findings are reliable and relevant to the 2.4 million Americans suffering from schizophrenia.

At the beginning of the study, patients were randomly assigned to receive one of the five medications. Almost three quarters of patients switched from their first medication to a
different medication. The patients started on olanzapine were less likely to be hospitalized for a psychotic relapse and tended to stay on the medication longer than patients taking other medications. However, patients on olanzapine also experienced substantially more weight gain and metabolic changes associated with an increased risk of diabetes than those study participants taking the other drugs.

Contrary to expectations, movement side effects (rigidity, stiff movements, tremor, and muscle restlessness) primarily associated with the older medications, were not seen more frequently with perphenazine (the drug used to represent the class of older medications) than with the newer drugs. The older medication was as well tolerated as the newer drugs and was equally effective as three of the newer medications. The advantages of olanzapine — in symptom reduction and duration of treatment — over the older medication were modest and must be weighed against the increased side effects of olanzapine.

Thus, taken as a whole, the newer medications have no substantial advantage over the older medication used in this study. An important issue still to be considered is individual differences in patient response to these drugs.

Several factors, such as adequacy of symptom relief, tolerability of side effects, and treatment cost influence a person's willingness and ability to stay on medication.

"There is considerable variation in the therapeutic and side effects of antipsychotic medications. Doctors and patients must carefully evaluate the tradeoffs between efficacy and side effects in choosing an appropriate medication. What works for one person may not work for another," said Jeffrey Lieberman, M.D., CATIE's Principal Investigator and Chair of The Department of Psychiatry, Columbia University and Director of the New York State Psychiatric Institute.

The CATIE study was led by Lieberman, and co-Principal Investigators Scott Stroup, M.D. (University of North Carolina at Chapel Hill), and Joseph McEvoy, M.D. (Duke University). CATIE was carried out by researchers at 57 sites across the country, including private and public mental health clinics, Veteran's Health Administration Medical Centers, and University Medical Centers, where people with schizophrenia received their usual care.

This New England Journal of Medicine article is the first to report outcomes from the CATIE schizophrenia trial, and addresses many of the primary questions from the study. Future reports will address a multitude of topics (e.g., cost-effectiveness of the medications, quality of life, predictors of response) and will provide a more detailed picture of the interaction between patient characteristics, medication, and outcomes. The information from the CATIE study will inform new approaches for improving outcomes in schizophrenia.
CATIE is part of an overall NIMH effort to conduct "practical" clinical trials that address public health issues important to those persons affected by major mental illnesses in real world settings.

For more information on CATIE, visit http://www.nimh.nih.gov/healthinformation/catie.cfm.

Updated: 03/31/2006