

## *Treatment with Antipsychotic Medication - an Update*

Antipsychotic medications have been available since the mid-1950s when chlorpromazine (Thorazine) was discovered by the French surgeon Henri Laborit while searching for a drug to reduce surgical shock. This accidental discovery led to the development of other medications, including haloperidol, which were highly effective in reducing psychotic symptoms in patients with schizophrenia. These medications made significant improvements in the lives of individuals but brought with them a host of intolerable side effects, primarily in the form of movement disorders.

Beginning in the 1990s, a new group of antipsychotic medications became available with the promise of providing superior symptom relief with fewer movement disorder side effects. Because of their different pharmacological profile, these medications were dubbed 2nd generation or "atypical" and the older dopamine type drugs were called 1st generation or "typical" antipsychotics. It was believed that treatment adherence, which had been a frequent problem with the typicals, would improve with the atypical medications.

Atypical antipsychotic medications, including clozapine\*, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole, and paliperidone, are now among the first line treatment for patients with schizophrenia and are effective in treating psychotic symptoms. These medications have been shown to be effective in controlled clinical trials but are costly when compared to the older medications. In addition, in some cases, these medications bring with them serious metabolic side effects, including substantial weight gain, increased lipids (cholesterol and triglycerides), and increased risk for diabetes, all of which are associated with disability and premature death. Given these issues, many have questioned whether when all factors are considered, atypical antipsychotics are indeed superior to older medication.

### **The CATIE Study, Phase 1**

To address this question, the National Institute of Mental Health (NIMH) conducted a three phase Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, beginning in 2001 and ending in 2004, to find out how four atypical medications and one typical medication work in "real-world" situations. The CATIE study was designed to find out how individuals with or without co-morbid medical and substance abuse disorders tolerated the medication over a long period of time, 18 months. They measured time to discontinuation of medication and cause for discontinuation. Reasons could include failure of the medication to reduce symptoms, intolerable side effects, or other issues such as inconvenience of taking the medication or lack of belief that medications are necessary. This study differed from previous trials in that it was longer in duration and the patient pop-

### **Key Findings**

- ♦ Patients not satisfied with medications
- ♦ Older medications more comparable to newer medications than expected
- ♦ Clozapine was most effective
- ♦ Clozapine underused
- ♦ Metabolic side effects of newer antipsychotics reconfirmed

### ***A MIRECC Study Comparing Risperidone & Olanzapine***

Investigators from the MIRECC including Stephen Marder, M.D. and Shirley Glynn, Ph.D. recently reported on a study that compared risperidone and olanzapine in 107 patients from Los Angeles, California and Manchester, New Hampshire. This was reported at the annual meeting of the American College of Neuropsychopharmacology. Patients were stabilized individuals with schizophrenia who were also participating in supported employment. As in CATIE we measured how long patients remained on their assigned medication without changing it for reasons that included lack of efficacy, lack of tolerability or other reasons. Using this measure, we found no difference between risperidone and olanzapine. We also found that patients in both groups showed improvement in positive and negative symptoms, and we found no difference between the two drugs. Patients in both groups were more likely to remain

on the medication to which they were assigned when compared with CATIE patients. This may be because they were receiving supported employment and they were more stable. Although patients gained more weight on olanzapine than risperidone the amount of weight gain was substantially less than the weight gain on olanzapine in CATIE. In CATIE, patients gained an average of 2 pounds each month on olanzapine. In our study, olanzapine treated patients gained about 6 pounds over two years. In addition, the elevations in triglycerides and cholesterol were lower. This probably occurred because weight and lipids were measured more frequently and patients were removed from the study when these and other side effects occurred. This suggests that careful monitoring of patients may be an effective strategy for managing the metabolic side effects of antipsychotics. ♦

Stephen R. Marder, MD

## Progress with Antipsychotic Medication



Recent large clinical trials from the United States and the United Kingdom have provided valuable information for clinicians, patients, and family members. The largest, called CATIE (Comparative Antipsychotic Trials of Intervention Effectiveness) was an NIMH study that compared the effectiveness and side effect profile of one older and several newer antipsychotic medications on more than 1400 individuals with schizophrenia. The first results were published over a year ago and are somewhat surprising. The surprising part is that perphenazine did as well as most of the other medications in both effectiveness and side effects. Other findings suggested that there was widespread dissatisfaction with antipsychotics since most of the patients switched to another medication within the first few months. In addition, the medication which came out the best with regard to effectiveness, olanzapine, also had serious side effects. Olanzapine-treated patients gained an average of two pounds per month and had elevations in lipids and triglycerides. The study results were widely publicized as indicating that the drug companies had grossly distorted the evidence in order to promote the more expensive newer drugs.

The results of the trial emphasize why the drug treatment of schizophrenia and other psychotic illnesses can be so difficult. Antipsychotic treatment would be relatively easy if the most effective antipsychotic also had the mildest side effects. Phase 1 of CATIE shows that it is just the opposite. This unfortunate trend is also apparent in a Phase 2 study that included patients who discontinued their medications in Phase 1 because of lack of effectiveness. In this study, clozapine was clearly the most effective for this population of patients who were not adequately treated during the first phase. Clozapine was also associated with substantial weight gain and other side effects. A study from the United Kingdom also found that the effectiveness of newer and older antipsychotics was similar and that clozapine was superior in effectiveness.

The study provides valuable information, but can be misinterpreted. First, the patients who were in the study may not be typical of patients who are treated in many settings. These were individuals who had been ill for an average of more than 15 years and had still not found a drug they with which they were pleased. These were patients with illnesses that were only partially responsive to their medications or patients who were sensitive to side effects. If they were doing well, they would not have entered the trial. In addition, the study was too brief to measure whether there were difference in the risk for tardive dyskinesia, a serious side effect that occurs less often on newer drugs.

These studies should not be used as evidence that patients should have fewer antipsychotic choices. The available antipsychotics are not interchangeable since they have different side effect profiles. Although some patients may do well on the older drugs, others will be tormented by discomforting side effects and some may be more likely to develop tardive dyskinesia. The decision which drug to take should probably occur in an environment that permits open discussions about how the patients feels on medication ♦

### **Antipsychotic Update** *(Continued from page 1)*

ulation better represent a typical clinical population who often have been ill for many years and have other medical or substance abuse conditions. In this study, participants had been chronically ill with schizophrenia for an average of 14 years and they often had other mental disorders, substance abuse, or medical conditions. This study also provided a protocol for allowing patients to switch to different medications. This would provide valuable information for clinicians since switching medications is a common occurrence in clinical settings.

The results of Phase I were surprising. Overall, 74 percent (3 out of 4) of participants discontinued their first study medication before the end of 18 months. Furthermore, there was little difference between the older "typical" antipsychotic medication and the newer "atypical" medication in discontinuation rates. The results showed that 1) Most participants discontinued the first study medication on their own meaning that they were not advised to stop taking the medication by their doctors because of side effects or lack of efficacy; 2) Patients randomized to olanzapine stayed on the study medication longer; and 3) Perphenazine and the atypical antipsychotics were similarly effective in reliev-

ing psychotic symptoms. These findings generated a flurry of discussion and further analysis within the psychiatric community.

#### **The CATIE Study, Phase 2**

Patients who stopped taking an atypical antipsychotic for any reason were eligible to participate in Phase 2. If they were receiving inadequate symptom control they were randomly assigned to receive one of four medications: clozapine, olanzapine, quetiapine, or risperidone. We will call this group 1. If they stopped taking their Phase 1 medication because of intolerable side effects or because they told their doctors they wanted to change medications, but didn't want to take clozapine, they took part in a different Phase 2 trial which did not include clozapine. We will call this group 2. Group 2 patients either received ziprasidone, the newest of the atypical medications at the time or one of the other three Phase 1 atypical antipsychotic medications (olanzapine, quetiapine, or risperidone).

The results of group 1 indicated that clozapine was the most effective for relieving psychotic symptoms and was well tolerated. Forty-four percent of patients who changed to clozapine stayed on it for the rest of the 18-month study, *(Continued on Page 3)*

compared with 18 percent of patients who changed to the other medications. On average, patients stayed on clozapine for 10 months, while patients on the other medications stayed on them for only 3 months. In group 2, patients remained on risperidone and olanzapine longer (7 and 6 months respectively) than quetiapine or ziprasidone. Overall results of Phase II of the CATIE study suggest that clozapine is the most effective medication for treatment resistant schizophrenia and that olanzapine and risperidone are superior to quetiapine and ziprasidone in how well they manage symptoms and how they are tolerated for long term use.

**Discussion**

There are important lessons to be learned from the results of this study. First, the high discontinuation rate (74%) shows there is a lot of dissatisfaction with the new medications and there is a need for developing more effective and better tolerated treatments for schizophrenia. Of the three measured causes for discontinuation (lack of efficacy, intolerable side effects, and patient decision) patient decision was the most frequent. This group includes those who may lack insight into the necessity for treatment because of cognitive deficits due to the disorder or other reasons. Perhaps therapies that address other issues involved in this disorder, including cognitive behavioral therapy, might improve medication adherence. Second, we need better training for clinicians on when and how to use clozapine. It was again shown to be superior in effectiveness but continues to be underused in typical clinical settings. There is progress in identifying genetic factors that contribute to vulnerability to clozapine-induced agranulocytosis which may eventually lead to making the use of clozapine easier because it might eliminate the need for close monitoring of individuals who are not genetically disposed to agranulocytosis.

The perceived advantage of olanzapine in this study is controversial. The dosage used in the study was higher than the usual dose in clinical practice whereas the dosages of the other study medications were more in line with typical dosing. This may have skewed the results in favor of olanzapine.

Another analysis of the data looking at whether patients were switching or staying with their old medicine found that there was an advantage to "staying" with current medication and a disadvantage to "switching", no matter which medication was studied. If a person was randomly assigned to a medication that they had been on prior to the study, they were more likely to stay on it. This was the case with olanzapine where a higher percentage of patients were on it prior to the study.

The adverse metabolic effects of atypical antipsychotics, particularly olanzapine and clozapine were clearly observed and

pose a real dilemma for patients and clinicians. Weight, blood pressure and lipids need to be closely monitored and patients educated on nutrition and exercise as a way to counter potential serious side effects of some of the newer medications. Our MIRECC is conducting a study that will provide clinicians with a protocol for monitoring their patients for signs of metabolic side effects and then provide these patients with the opportunity to participate in a wellness program. The goal is that these patients will be better educated and able to take responsibility for lowering their risk for cardio-vascular disease.

The current medications are effective for reducing psychotic symptoms of schizophrenia but they are relatively ineffective for improving the cognitive deficiencies associated with this disorder. MIRECC director Stephen R. Marder, M.D., and Michael F. Green, Ph.D. were co-principal investigators in the NIMH-sponsored program, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). This program developed the MATRICS Consensus Cognitive Battery, a brief battery of tests for measuring several areas of cognition as well as guidelines for clinical trials for potential cognitive-enhancing medications and new approaches for drug discovery. These guidelines are being utilized in the Treatment Units for Research on Neurocognition and Schizophrenia, another NIMH-sponsored initiative headed by Stephen R. Marder, M.D. for finding new medications to improve cognitive abilities in individuals with schizophrenia.

One potential target for cognitive enhancing medication is the glutamate system. Glutamate is a chemical in the brain that is believed to play a role in learning and memory. Nicotine activates the glutamate neurotransmitter system. There is a higher prevalence of smokers among people with schizophrenia than in the general population which may provide a clue for future drug discovery. The challenge may be to find a medication with the cognitive enhancing benefits of nicotine, without its harmful side effects. ♦

Treatment Success vs. Side Effect Profile - Phase I of the CATIE Study						
Longer ↑ Length of treatment ↓ Shorter	How Long Treatment Lasted Before Meds Changed	How Side Effects Related to Stopping Meds				Less ↓ Side Effects ↓ More
		EPS	Weight Gain	Insomnia	Anxiety	
	olanzapine	ziprasidone	perphenazine	olanzapine	olanzapine	
	risperidone	olanzapine	risperidone/ ziprasidone	quetiapine	risperidone	
	quetiapine	quetiapine	quetiapine	risperidone	quetiapine	
	perphenazine	risperidone	olanzapine	perphenazine	perphenazine/ ziprasidone	
	ziprasidone	perphenazine		ziprasidone		

\* Clozapine, the first atypical antipsychotic was first discovered in the 1950s, but not approved for use the US until 1989. It has not received wide usage in the US because it can lead to a dangerous side effect, agranulocytosis, an acute condition involving a dangerously low white blood cell count. Clinicians are reluctant to prescribe clozapine for that reason. Patients on clozapine must have their blood counts closely monitored.

# THE FACES OF MIRECC

## Christopher Reist, M.D., MBA



*Dr. Reist is Associate Director, of the VISN 22 MIRECC and Director of Research at the VA Long Beach Medical Center. He was raised in Western Pennsylvania, received his BS in biology and chemistry at Eastern Mennonite University and his medical training at Virginia Commonwealth University. He completed a psychiatric residency at the University of California, Irvine and earned an MBA at the University of California, Los Angeles. Prior to becoming the Director of Research, he served as the Chief of Mental Health for the Long Beach VA Healthcare System. Dr. Reist is Associate Professor and Vice Chair of Psychiatry and*

*Human Behavior at the University of California, Irvine. Dr. Reist is an "action junkie" spending his free time playing soccer, ice hockey and snowboarding.*

### **Describe your top interest current research project**

I am interested in the broad area of personalized medicine as it applies to psychiatry. Where this has had most relevance is in the area of drug metabolism and transport. Learning more about these systems may lead us to be able to use medications in a more effective and safe manner. A current project is looking at how drug transporters can affect how much medication actually reaches the brain. While these systems serve to protect the brain from environmental toxins at the blood-brain-barrier, they can also work to "pump" medications such as risperidone and olanzapine out of the brain. This may explain some cases of treatment non-response. We are studying approaches to measure how active the drug transport system is in individuals along with ways of modifying its activity.

### **What first interested you in this area?**

It has been known for some time that the activity of certain liver enzymes that metabolize medications can be influenced by genetic and environmental factors. For example, individuals of Asian descent are more likely to have genes that produce a less active version of the CYP2D6 enzyme. This can result in slowed metabolism of certain drugs such as risperidone, codeine and drugs used for treating high blood pressure. Regular use of cigarettes can dramatically "rev up" the CYP1A2 enzyme that metabolizes olanzapine. Consequently smokers require higher doses of olanzapine to achieve the same blood level compared to non-smokers. Physicians are becoming more and more aware of the importance of understanding these variables to maximize the effectiveness of medications in their patients.

An important factor that is promoting interest in this area is that drug companies are having a more difficult time developing "blockbuster" medication. Part of being a "blockbuster" is that the drug needs to be equally safe and effective in all populations. The development of many potentially useful drugs has been abandoned because of differences in metabolism or effectiveness in various subgroups of the population. Through advances in our understanding of pharmacogenetics, the study of genetic variation that gives rise to differing response to drugs, medications can now be developed for use only in populations that have a particular genetic make up. With an absence of "blockbuster" drugs on the horizon, these smaller market drugs are looking more attractive.

### **What are your future research plans?**

Another developing area in the pharmacogenetics is understanding how genetic variations in drug targets such as receptors can impact drug effectiveness. Not only can we optimize drug dose through understanding of an individual's metabolism, the future holds the promise of selecting drug treatments based on genetics. This is already occurring in cancer chemotherapy. I hope to contribute to the development of this approach to bring personalized medicine to psychiatry. ♦

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