SPEAKER NOTES

New Concepts in the Treatment of Psychosis

Summarized by Thomas T. Thomas

Psychosis is a common element of such serious mental illnesses as schizophrenia, bipolar disorder (also known as manic depression), and major depression. A person becomes psychotic when he or she can no longer distinguish between the internal dialogues and fantasies occurring within the mind and external reality. In some people, this loss of the sense of reality can be difficult to control. In his dual positions as professor of psychiatry at UC San Diego and director of the clinical neuropharmacology research program at the University of California San Francisco, the speaker at our January 22 meeting, **S. Craig Risch, MD,** has particular insight into recent research on psychosis.

S. CRAIG RISCH, MD

"It's exciting how far we've come in research on psychosis," Dr. Risch said from his perspective of 30 years in dealing with schizophrenia, bipolar disorder, and depression. "We are now approaching a time when we can subtype these illnesses, based on the fact that different chemical imbalances cause different forms of the disease in different people, and we will soon be able to treat the cause.

"Another exciting development is the contribution of genetics. We are coming close to being able to draw a blood sample and tell what's causing that particular person's illness."

Dr. Risch showed a series of PET (positron emission tomography) scans of the brains of schizophrenics compared with controls. This kind of imaging shows brain activity, and in the brains of schizophrenics there is too much activity on the left temporal side. "That's where the hallucinations come from," he said. "At the same time, there is too little activity in the frontal part of the brain, and that's associated with abstract thinking and other cognitive functions."

The scans, he said, also showed problems in the basal ganglia, which are normally associated with movement, and lowered activity in the cerebellum— which is a kind of second brain— again indicating cognitive impairment.

Work by a team led by Dr. Ralph Hoffman, he said, has been experimenting with transcranial magnetic stimulation— focusing magnetic fields on different parts of the brain. When the field is generated by an alternating current, it yields a pulse. These pulses can stimulate or inhibit activity. Magnetic stimulation may replace electro-convulsive therapy (ECT) in depression and supplement antipsychotic medications in schizophrenia patients who are not responding to medications. For example, inhibiting the left temporal lobe might turn off the hallucinations.

Where there is an abnormal amount of brain activity, Dr. Risch said, that indicates too much of the brain's neurotransmitters: dopamine, serotonin, and

glutamate. These chemicals sometimes work alone and sometimes work in concert, activating or inhibiting each other.

The dopamine hypothesis has long been held to be a key to schizophrenia, where there may be too much of the chemical stimulating the sides of the brain. This may be a pure dopamine problem, Dr. Risch said. Or it may be a problem in the balance between serotonin and dopamine, as serotonin can inhibit dopamine: with too little serotonin, dopamine activity increases. In this case, a serotonin enhancer should block the dopamine activity. However, if the balance between the two chemicals is not the problem, then the patient should not respond.

If a patient is supersensitive to dopamine, as some schizophrenics appear to be, then there is a narrow window of activity in the brain's dopamine receptors. This creates a potential problem because, once the patient starts to get better, the dopamine sensitivity will generally disappear. It may then become difficult to keep the patient well and not begin suffering the side effects of low dopamine activity.

A further complication is the role of glutamate. Low glutamate levels will affect dopamine release. But studies have shown that glutamate is low in some schizophrenics but not in others. A team led by Dr. Carol Tamminga has identified a genetic propensity toward low levels of glutamate. Glutamate activity can also be damaged by substance abuse, such as cocaine, alcohol, and ecstasy. One study has shown that patients with a history of drug abuse can take three times as long to get well as those without such a history. Other studies indicate drug abuse may account for slow response time to medications such as Clozaril (generic: clozapine), Risperdal (risperidone), Zyprexa (olanzapine), and Prolixin (fluphenazine).

One way to measure glutamate response non-invasively is to administer one of the newer, atypical antipsychotics, which increase glutamate levels where the older, typical medications do not. This may be of use in Alzheimer's, AIDS dementia, Huntington's disease, and even sudden infant death syndrome, all of which are linked to low glutamate levels. Coincidentally, the atypical antipsychotic medications can also improve cognition and areas of the brain related to the positive symptoms of schizophrenia.

Acetylcholine is related to glutamate, so medications that remove acetylcholinesterase— the enzyme that mops up acetylcholine— may help improve glutamate levels. Aricept (generic: donepezil hydrochloride) is an inhibitor of this enzyme and is generally used as an Alzheimer's medication. Interestingly, patients who respond to donepezil often have a deficiency in nicotine receptors. Heavy nicotine use is associated with schizophrenia, appearing to calm the symptoms, although the effect diminishes with time.

Another condition associated with schizophrenia is ventricular enlargement. The ventricles are fluid-filled sacs inside the brain that are kept small by the natural pressure in the skull. As brain tissue degenerates through the neuron loss caused by the disease, these sacs grow larger. Medications like Topamax (generic: topiramate) can be added to antipsychotic medications to block this kind of brain damage.

Dr. Risch said that research is only beginning to make use of the new approaches offered by genetics. We know only some of the genes that are involved with brain proteins and their function. Studies in this area suggest that Clozaril and

Risperdal work for a patient because he or she has the genes for the receptors that these medications target.

Amino acids– the building blocks that genes use to make proteins– can also have a direct effect on brain chemistry. Studies have shown that with the amino acid valine present, an enzyme in the brain becomes active and chews up dopamine. Inhibitors of the cell's cytolysin-mediated translocation (CMT) receptor can block this action.

These different findings suggest that we can start to subtype various kinds of psychoses around certain neurotransmitters– dopamine, serotonin, and glutamate– and their associated receptors. In addition, some of the medications mentioned above can be used to supplement the traditional antipsychotic medications.

Dr. Risch noted that 80 percent of schizophrenia patients have some form of cognitive impairment, compared to 40 percent of bipolar patients. But the schizophrenic impairments have no common theme: some patients have problems with attention, others with memory or with verbal fluency. Different drugs have different effects on these impairments. His research group is now engaged– along with 50 other centers around the country– on a controlled effectiveness study of the atypical antipsychotic medications. Although it is double blinded, there is no placebo. The patients are placed on a medication and, if they do well, stay on it for three years. If there is no effect, they are assigned a different medication. The patients are assessed monthly and their condition reported. In another study, his UCSF research group is working with the acetylcholinesterase inhibitor Aricept.

After his presentation, Dr. Risch answered questions from the audience.

Has there been any study on taking Haldol and Zyprexa at the same time?

Yes, there has been some clinical experience with this. Should you combine them? Optimally, no– but sometimes yes. Haldol blocks dopamine and controls hallucinations, while the other new, atypical medications can improve cognition. However, mixing them should be the exception, not the norm.

Can these studies be applied to bipolar disorder and depression?

Virtually all of them, but specifically the PET imaging, cholinesterase inhibitor, and cognitive studies. The path of physiology may be different in schizophrenia, bipolar, and depression, but the imaging tools are the same. A broken leg is a broken leg, regardless of how you broke it.

A new study has shown that the brain makes new neurons from stem cells every day– something we once thought did not happen. This process can have an effect on degenerative diseases like Parkinson's and Alzheimer's. Interestingly, when people get depressed, their brains stop making neurons. And when they get antidepressant medication, their brains start making them again.

As a consumer and a schizophrenic, I can say that nicotine works for me. It quiets the noises.

Not everyone experiences the diminishment of effect over time. But smoking is still bad for you, and the newer medications work better and don't diminish. Also, cigarettes do nothing to improve cognitive function.

If a medication turns off the serotonin receptors, does that exacerbate depression?

Apparently not. The medications seem to lower serotonin in the areas that affect dopamine reception, but not generally throughout the brain.

According to the San Francisco Chronicle, autism is increasing due to vaccinations. Is there a similar increase in schizophrenia and bipolar disorder?

There is no evidence of that. In fact, there is evidence that schizophrenia and bipolar are decreasing. As these conditions are apparently related to prenatal conditions, the recent improvements in prenatal care may be lowering the incidence of these illnesses. And all the literature does not support the link between autism and vaccines, although some people would dispute that.

Are any psychiatrists now prescribing cholinesterase inhibitors as a supplement?

This use is still in the research stage. However, there is some off-label clinical use in treating Alzheimer's and other conditions.

Have you heard of Abilify?

This medication (generic: aripiprazole) is very good. It and the atypical antipsychotic Geodon (ziprasidone) are two of my favorite medications because their side-effects profiles are so good. In trials, the side effects were virtually indistinguishable from those of the placebo.

What is the half-life of Geodon and Abilify?

Geodon is short: you administer it twice a day, although a double dosage can be given once a day. Abilify lasts longer in the body, about three days.

Can you add Depakote to Clozaril?

If the Clozaril isn't working, you can add it. It does not hurt.

Can you take antipsychotic medications with lithium?

We used to think that lithium could damage the brain, but now you can use it with the atypical antipsychotics to improve cognition.

Do the antipsychotic medications lose effectiveness over time?

Many of these medications have not been around long enough to find out. Most studies run three to six months. Some have gone three to five years. That is not a long time in the life of a patient.