Clinical News

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Update from the ACNP Meeting

Williams Syndrome – Schizophrenia in Reverse?

As we go to press, the 46th annual meeting of the American College of Neuropsychopharmacology is occurring in Boca Raton, Florida, where Karen Berman from the NIMH reports on her very interesting work with children who suffer from Williams syndrome. Williams syndrome is a rare disorder caused by deletion on chromosome 7. It has long intrigued neuroscientists as it presents with a picture of hypersociability with characteristic neurocognitive deficits. Most children with Williams syndrome have similar facial features including a small upturned nose, long philtrum (upper lip length), wide mouth, full lips, small chin, and puffiness around the eyes. Blue- and green-eyed children with Williams syndrome can have a prominent "starburst" or white lacy pattern on their iris. Facial features become more apparent with age. The majority of individuals with Williams syndrome have some type of heart or blood vessel problem. Typically, there is narrowing in the aorta or narrowing in the pulmonary arteries. Most children with Williams syndrome have a low birthweight and low weight gain, especially during the first several years of life. Slightly small, widely spaced teeth are also common in children with Williams syndrome.

Most interesting to psychiatry, individuals with Williams syndrome have a very endearing personality. They have a unique strength in their expressive language skills and are extremely polite. They are typically unafraid of strangers and show a greater interest in contact with adults than with their peers. Most people with Williams syndrome have some degree of intellectual handicap. Young children with Williams syndrome often experience developmental delays; milestones such as walking, talking and toilet training are often achieved somewhat later than is considered normal. Distractibility is a common problem in midchildhood, which appears to get better as the children grow older. Older children and adults with Williams syndrome often demonstrate intellectual "strengths and weaknesses." There are some intellectual areas (such as speech, long-term memory, and social skills) in which performance is quite strong, while other intellectual areas (such as fine motor and spatial relations) are significantly deficient. Clinically, these people often seem to have the "reverse" of schizophrenia in that, although they have similar cognitive deficits, their increased social cognition often allows them to be much more socially functional than expected. Dr. Berman's group has now been able to show that the changes in social cognition in this disorder are associated with changes in frontal cortex and amygdale. This may lead to phenotypic models of brain function that allow us to understand and develop treatments in the area of social affiliation, a major problem in psychotic disorders.

Meyer-Lindenberg A, Mervis CB, Berman KF. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. Nat Rev Neurosci 2006;7(5):380-393.

New Drugs on the Horizon

Vanda Pharmaceuticals announced on November 27, 2007 that the U.S. Food and Drug Administration (FDA) has officially accepted the New Drug Application (NDA) for iloperidone, an investigational antipsychotic for the treatment of schizophrenia. Acceptance of the NDA confirms that the application is sufficiently complete for FDA review. This drug has been studied for a long time without ever being marketed. Hoechst Marion Roussel first conducted studies with the drug. However, in May 1996, Hoechst discontinued research, and in June 1997 gave the research rights to Titan Pharmaceuticals. Titan then handed over worldwide development, manufacturing and marketing rights to Novartis in August 1998. On June 9, 2004, Titan Pharmaceuticals announced that the Phase III development rights had been acquired by Vanda Pharmaceuticals from Novartis.

Iloperidone acts on both dopamine and serotonin receptors like many other currently marketed antipsychotics. It appears to work in animal studies, as it reverses behaviors induced by PCP, apomorphine, and cirazoline. Clinical studies have shown that some patients treated with iloperidone suffer from extrapyramidal symptoms and weight gain. Phase II testing has shown that effectiveness in humans is possible with as low as 8 mg per day, and is tolerable up to 32 mg per day. Phase III trials are currently completed involving over 3,300 patients. It will be interesting to see if this long-studied medication can come to the market with evidence of specific benefits that warrants its specific use in treating psychosis, or if it will be another "me-too" agent.

The FDA has also accepted Schering-Plough's new drug application for asenapine as a possible treatment for schizophrenia and acute mania or mixed episodes associated with bipolar 1 disorder. The clinical program consisted of schizophrenia and bipolar mania trials involving approximately

3,000 patients. Asenapine was shown to be effective and well tolerated in patients with acute schizophrenia, according to a six-week study recently published in the *Journal of Clinical Psychiatry.*

In the study, 174 patients were randomized to a twice-daily, 5-mg dose of asenapine; a twice-daily, 3-mg dose of risperidone; or placebo for six weeks. Asenapine was more effective than placebo in improving both positive and negative symptoms associated with schizophrenia. Schering-Plough acquired asenapine from Organon BioSciences, which, until recently, had been developing this drug with Pfizer. The same interest and questions apply to this drug as to iloperidone – will it really be an important addition to our pharmacopeia?

Further away from final FDA review is the drug RG2417. Repligen Corporation reported positive results from a Phase IIa clinical trial of RG2417, an oral formulation of uridine, in patients with bipolar disorder. In the multicenter study, eighty-four patients received either RG2417 or placebo twice daily for six weeks. The objective of the study was to assess the safety and efficacy of RG2417 on the symptoms of bipolar depression as measured by the Montgomery-Asberg Depression Rating Scale (MADRS). Over the six-week treatment period, patients on RG2417 experienced significant improvement in the symptoms of depression when compared with those taking placebo on the MADRS. This study is also interesting in that it represents a collaboration between a biotech company and the Stanley Medical Research Institute.

Also in earlier review is the drug TS-032. Japan's Taisho Pharmaceutical and Pfizer have signed a letter of intent with regard to TS-032, a new schizophrenia drug candidate discovered by Taisho. The drug, which is in the preclinical stage, is a novel metabotropic glutamate receptor agonist that may offer an option for central nervous system disorders. This may have some similar actions to the new Lilly compound targeting glutamate receptors reported in last issue's ***Clinical News.*** Under the agreement, Taisho will grant exclusive development and commercialization rights outside Japan to Pfizer.

Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. J Clin Psychiatry 2007;68(10):1492-1500.

Jain KK. An assessment of iloperidone for the treatment of schizophrenia. Expert Opin Investig Drugs 2000;9(12):2935-2943.

Intravenous Haloperidol Associated with Sudden Death

Haloperidol is still one of the commonly used antipsychotics, particularly in the acute setting. It is often used in high doses and also intravenously, both of which are outside of the package labeling. Injectable haloperidol is only labeled for IM administration. This September, Johnson and Johnson and the FDA informed healthcare professionals that the "Warnings" section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection stating that cases of sudden death, QT prolongation and Torsades de Pointes (TdP), have been seen in patients treated with haloperidol, especially when given intravenously, or at doses higher than recommended. There is considerable evidence that the intravenous administration of haloperidol is a relatively common off-label clinical practice. We need to take extra care and consideration in how and when to use this effective, but not always safe, medication. (http://www.fda.gov/medwatch/safety/2007/safety07.htm#Haloperidol)

Rimonabant is Associated with Severe Adverse Psychiatric Events

Patients given the weight-loss drug rimonabant are at increased risk of severe psychiatric events, according to new work recently reported in *The Lancet.* The prevalence of obesity continues to increase worldwide and is particularly severe in people with psychosis. Rimonabant is not approved in the U.S. as yet, but is used in over forty other countries and is advertised on-line to people in the U.S. Arne Astrup and colleagues did a meta-analysis of four double-blind, randomized controlled trials with a total of 4,105 subjects. They found that patients given rimonabant had a 4.7 kg greater weight reduction after one year than did those given placebo. However, patients given rimonabant were at 40% higher risk of having adverse events or serious adverse events. Patients given rimonabant were 2.5 times more likely to discontinue treatment because of depressive disorders than were those given placebo, and three times more likely to discontinue treatment due to anxiety. Suppression of appetite drive by rimonabant increased the risk of psychiatric events, such as depressed mood disorders and anxiety, despite depressed mood being an exclusion criterion in the trials. There are a number of drugs similar to rimonabant in Phase II or III development. We will need to understand their safety carefully before they are commonly used in the U.S.

Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonobant: a meta-analysis of randomized trials. Lancet 2007;370(9600):1706-1713.