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Clinical Schizophrenia & Related Psychoses

New Drugs

Quetiapine Sustained Release Studied in the Treatment of Schizophrenia

Quetiapine is one of the most commonly used antipsychotics. AstraZeneca just presented clinical trial data for quetiapine fumarate sustained release at the European Congress of Psychiatry (ECP) in Madrid in March 2007. The data demonstrated that quetiapine fumarate sustained release administered once daily was safe and effective when administered through a three-step dose initiation aimed at reaching the effective dose range on the second day of treatment in people with schizophrenia. This formulation is currently under review by regulatory authorities around the world for the treatment of schizophrenia and has not been approved in any market. Statistical significance on the primary endpoint was seen at doses between 400 and 800 mg/day and patients achieved that range within two days of starting treatment. This dosage formulation is theoretically advantageous over the immediate release quetiapine, where the initial dose escalation is more complex and the dosing interval is more frequent. It will be interesting to see if this new formulation is a useful addition, as there is a great deal of speculation that the short half-life, as well as the low affinity of quetiapine to dopamine receptors, is critical to the clinical benefits of this drug (1).

Acadia Schizophrenia Drug Effect in Phase II Studies

Acadia Pharmaceuticals Inc., in a press release dated March 19, 2007, stated its drug for psychosis, a potent and selective serotonin (5-HT_{2A}) inverse agonist, met its goal in a recent Phase II trial. Drugs in this phase of research, if successful, are still usually three to five years away from being marketed. The drug, now called ACP-103, showed a statistically significant level of effectiveness when used in conjunction with marketed antipsychotics (both haloperidol and risperidone). The company hopes that the use of ACP-103 in co-therapy with risperidone or other antipsychotics may result in enhanced efficacy and an improved side-effect profile. This would be the basis of a new strategy for bringing antipsychotics to the market, not as stand-alone drugs, but rather as adjunct agents. Antipsychotics are now seen as drugs that can be highly profitable to drug companies. Likely, because of this news, Acadia's stock price soared on that day by 87.6% in trading on the Nasdaq Stock Market. Let's hope that the efficacy of this drug truly mirrors the advance expectations.

Paliperidone Released to the Market

Paliperidone, the active metabolite of risperidone (9-OH-risperidone), has been released to the market. It is only available as an extended release form (ER), which uses the patented "OROS" technology that releases the drug into the bloodstream steadily over a 24-hour period. This formulation technology has been used successfully in the recent past in a long-acting form of methylphenidate. Paliperidone ER is marketed in the United States by Janssen, L.P., a wholly owned subsidiary of Johnson & Johnson. The trade name is Invega. A tolerability profile similar to risperidone was seen in the clinical trials of this drug, specifically, prolactin elevation and dose-related extrapyramidal effects. A relapse prevention study in people with schizophrenia showed evidence of superiority of paliperidone over placebo in the maintenance of response similar to other antipsychotics. There are no published studies available directly comparing paliperidone to other antipsychotics, including risperidone. With the impending availability of oral risperidone as a generic medication, one of the most prescribed antipsychotics in use today, it will be important to see what advantages this drug formulation has over risperidone as its long-term usefulness is determined.

Vaccines for Addictions?

Many people with schizophrenia smoke, are obese, and/or abuse drugs. There may soon be clinical vaccines for all of these conditions. Vaccines that may actually change behaviors will provide an interesting, but ethically and medically challenging treatment option. They seem to be on the way. In regard to smoking, it remains the leading cause of preventable death worldwide and is responsible for much of the excess mortality associated with serious mental illness. Despite the development of a number of

drugs for smoking cessation, overall efficacy of these substances is limited. Vaccines against nicotine work by inducing nicotine-specific antibodies, causing nicotine to be sequestered in the blood, prevented from crossing the blood/brain barrier. In this way, the addictive properties of cigarettes are reduced, and smokers attempting to quit might be able to have minor relapses without becoming addicted again. Recent research with vaccines against nicotine has clearly demonstrated in animals that antibodies can interfere with the addictive properties of nicotine in different settings (2). The first Phase II clinical trial has confirmed the validity of the concept and shown that a vaccine against nicotine was efficacious for enhancing the likelihood of smoking cessation in humans provided anti-nicotine antibody levels are sufficiently high. Similar studies with a vaccine against cocaine (3) have shown promise. Ghrelin, an obesity-related hormone, has been successfully targeted in a vaccine developed in studies with obese rats, but has not yet been developed in humans (4).

Clinical News on the Horizon

A Fix for Fatty Livers?

People with schizophrenia and serious mental illness are also at risk for metabolic disorders. Diabetes, obesity, and heart disease are common problems in this group, but there are other disorders in this spectrum that deserve attention. This includes nonalcoholic steatohepatitis (NASH), which is characterized by liver inflammation and formation of scar tissue in the organ. People with schizophrenia have a high incidence of liver disease as they age (5), have frequent liver abnormalities associated with the use of antipsychotics (6), and have a high incidence of viral hepatitis (7,8). Some of this vulnerability is likely caused by NASH. Overall, NASH affects about 10 million U.S. adults. At this time, weight loss is the only treatment for this condition, but this may soon change. One commonly used oral hypoglycemic drug, pioglitazone, has been shown to decrease fat deposition in the liver compared to placebo in adults with NASH (9). This was found despite the drug being associated with weight gain. There is also evidence that metformin and other oral hypoglycemic drugs may be useful for this condition, but there is a great need for more clinical trials in this area (10). As we develop more holistic treatment for people with serious mental disorders, we will need to attend many medical sequelae of these disorders. This new information will help.

Autism and Schizophrenia: Genetic Risk May be Related

Why do people inherit a vulnerability to mental illness? Is there a "schizophrenia gene?" As we further study the neurobiology of serious mental illness, we will likely find the conditions we consider as separate mental illnesses may not be so separate after all.

Inheritance of a common variant of a gene that influences immunity, gastrointestinal repair, and brain growth substantially raises the chances of developing autism, at least in families with more than one child diagnosed with the severe brain disorder. Based on neurobiological findings and location within a chromosome 7q31 autism candidate gene region, researchers analyzed the gene encoding the pleiotropic MET receptor tyrosine kinase in a family-based study of autism including 1,231 cases (11). MET signaling participates in neocortical and cerebellar growth and maturation, immune function, and gastrointestinal repair, consistent with reported medical complications in some children with autism. They demonstrated a genetic association ($p=0.0005$) of a common C allele in the promoter region of the MET gene in 204 autism families. Study participants who carried two copies of a specific MET variant displayed autism substantially more often than the others did. These results could help explain reports that people with autism often have immune and gastrointestinal problems. About 47% of the population carries at least one copy of the autism-associated MET variant.

It has long been thought that abnormalities in the tyrosine kinase physiology are associated with schizophrenia risk. HOPA (MED12) is an X-chromosome gene that codes for a critical member of the Mediator Complex, which influences tyrosine kinase pathways. Researchers have shown that the presence of an evolutionarily conserved insertional polymorphism is associated with increased risk for an endophenotype of schizophrenia (12). They now report that the presence of the HOPA (12bp) polymorphism is associated with increased risk for schizophrenia in subjects of European ancestry. In light of this new study and the prior wealth of clinical and basic science data, they conclude that the HOPA (12bp) allele is a risk factor for schizophrenia in subjects of European ancestry and suggest that further studies to define the endophenotype and mechanisms of illness associated with this polymorphism are indicated. New associational studies between these disorders are also warranted.

Why Do Our Patients Gain Weight?

The development of animal models for the probable association between serious mental illness and metabolic disturbances is critical. We know that a stressful fetal environment can lead to an increased risk for mental illness. Now a new study, reported in *Science News* (13), suggests that, in mice, being either over- or undernourished before birth can lead to obesity during adulthood, possibly from altered gene activity. This finding could lead to more-tailored treatments for obesity. To determine whether fetal changes in gene activity could be associated with adult obesity, Frederick vom Saal of the University of Missouri-Columbia and his colleagues removed a single ovary from female mice (14). When these

mice became pregnant, the eight or so fetuses that typically occupy both tubes of the mothers' uteruses crowded into a single tube.

Vessels that feed into both ends of each tube of a mouse uterus supply it with the mother's blood. Therefore, in the experiment, fetuses stuffed into the middle of the single uterine tube received less nourishment than fetuses at either end did. Those at either end of the tube were unusually heavy at birth, and those in the center of the tube were unusually light. Fetuses located at intermediate positions were born at normal weights.

As the mice matured, the normal-weight pups typically became normal-weight adults and the obese pups became obese adults. However, those pups born underweight quickly became as heavy as the obese pups and remained so into adulthood. This research was reported at the annual meeting of the American Association for the Advancement of Science in San Francisco this February 2007 (15).

When the researchers analyzed gene activity in fat samples from the adult obese mice, they found 435 genes that were more active in one of the groups of obese mice than in the other. In most cases, these genes controlled metabolic activities, such as creating fat cells or regulating the cells' uptake of energy-storing lipid molecules. The results suggest that the amount of nutrition that the fetuses received permanently affected how their genes functioned. Differing gene activity between the low- and high-birth weight groups suggests that their obesity stemmed from separate mechanisms.

It is known that exposure to stress during gestation in rats also induces marked changes in the behavior of the offspring. Koenig and colleagues in 2005 (16) observed the offspring of pregnant female Sprague-Dawley rats who were exposed to a variable stress paradigm during either the second or third week of gestation. Behavioral and neuroendocrinological consequences of the prenatal stress exposure were evaluated in the male offspring on postnatal day 35 or 56. Prenatal stress exposure caused the adult male rats to exhibit prolonged elevation in plasma glucocorticoid levels following acute exposure to restraint stress indicative, thus these rats were relatively stress intolerant. They also were obese and tended to easily become habituated to alcohol. Similarly, they had an enhanced locomotor response to the psychomotor stimulant amphetamine on postnatal day 56, but not on postnatal day 35, which is a similar response to other rat models of schizophrenia.

Examining the consequences of prenatal stress may prove useful in understanding more about the origins of schizophrenia and related disorders, including substance abuse and metabolic disorders. These disorders may frequently occur together because they all can arise from similar fetal insults. Prenatal stress can change many facets of adult mammalian behavior. Our patients may have lifelong co-occurring vulnerabilities that all need active, continual attention and therapy.

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