Clinical News

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New Indications for Antipsychotic Use in Adolescents

Schizophrenia and related psychoses are chronic debilitating disorders. Early and appropriate treatment with antipsychotics is an important strategy for patients with first-episode schizophrenia, and this often means treating adolescents. However, many possible safety issues should be considered and properly addressed. Safety concerns are paramount in young patients as they are starting antipsychotic treatment that is likely to last for the remainder of their lives. All antipsychotics used today appear to offer similar efficacy for amelioration of positive psychotic symptoms in young people with a short duration of illness; side effects are the limiting factor in treatment. Conditions such as extrapyramidal symptoms (EPS), tardive dyskinesia, and prolactin-associated side effects were common with older antipsychotics. Newer antipsychotic medications tend to cause weight gain, metabolic disturbances, and sexual dysfunction.

Bristol-Myers Squibb and Otsuka reported at this year's 160th annual meeting of the American Psychiatric Association a successful clinical trial treating teenagers with schizophrenia with aripiprazole. Based on this data, the U.S. Food and Drug Administration (FDA) is conducting a priority (six-month target) review of the supplemental new drug application for the use of this drug in this patient population. The six-week study enrolled 302 ethnically diverse adolescents ages thirteen to seventeen with primary diagnoses of schizophrenia. It was the largest study to date to investigate the treatment for schizophrenia in adolescents, and it showed that the drug was effective at 10 mg and 30 mg doses by six weeks and was generally well tolerated. Approximately eighty-five percent of the patients completed the randomized, double-blind, placebo-controlled study, which was conducted at a hundred and one sites in thirteen countries. The overall rate of study discontinuation due to adverse events was 4.3%. The most common adverse events associated with aripiprazole were extrapyramidal disorder, somnolence, and tremor. There were no significant differences between aripiprazole and placebo in measures of akathisia (restlessness) or tardive dyskinesia. At six weeks, the mean change in weight from baseline was a loss of 0.8 kg (1.8 pounds) in the placebo group, no change in weight in the 10 mg aripiprazole group, and a gain of 0.2 kg (0.4 pounds) in the 30 mg aripiprazole group. Among all patients, the average prolactin levels decreased relative to baseline. The EPS seen in this study is a concern, and it will be important to assess if this drug carries more risk for tardive dyskinesia in this group over the long term. The apparent mild effects on weight and lack of prolactin effect are encouraging.

In a related item, Johnson & Johnson Pharmaceutical Research & Development (JJPRD) announced it has received an approvable letter from the FDA for risperidone's treatment of schizophrenia in those aged thirteen to seventeen years and for the short-term treatment of mania associated with bipolar I disorder in those aged ten to seventeen years. The FDA has not asked for any additional studies. JJPRD is currently reviewing the letter and looks forward to finalizing the label with the agency. It is important to monitor the use of this drug closely in the young and to closely attend to correct dosing.

Personalized Psychoactive Drugs?

An article in *The New York Times* by Dr. Richard Friedman published June 19, 2007 notes that there may soon be a test that will predict with good sensitivity if a person will improve with an antidepressant within four to six weeks. Instead of the current haphazard approach we must use in the clinic, pharmacogenetic blood testing may soon help a psychiatrist to biologically personalize treatments. For example, depressed patients who have abnormally low levels of serotonin seem to respond to Selective Serotonin Reuptake Inhibitors (SSRIs), which relieve depression, in part, by flooding the brain with serotonin. Other depressed patients may have an abnormality in other neurotransmitters that regulate mood, like norepinephrine or dopamine, and may not respond to SSRIs.

In the October 6, 2006 issue of the journal *Science*, Francis Lee of Weill Cornell Medical College and colleagues identified a genetic mutation that could potentially predict patients' responses to an entire class of antidepressants. A common single-nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) gene, a methionine (Met) substitution for va-

line (Val), is associated with alterations in brain anatomy and memory, but its relevance to clinical disorders was unclear. Lee's group generated a variant BDNF mouse (BDNF [Met/Met]), which reproduced the phenotypic hallmarks in humans with the variant allele. BDNF (Met) was expressed in brain at normal levels, but its secretion from neurons was defective. When placed in stressful settings, BDNF (Met/Met) mice exhibited increased anxiety-related behaviors that were not normalized by the antidepressant, fluoxetine. The implication is that people with this variant will not be able to respond to SSRIs, which require normal neurotrophic-factor function to work. A psychiatrist could identify this genetic variant, and then steer his patient to a different class of antidepressants.

My colleagues, Ganshyam Pandey and Yogesh Dwivedi from the University of Illinois, and I have reported on biochemical variances in young people who have committed suicide. These include abnormalities in both adenylyl cyclase (AC) and phosphoinositide (PI) signaling systems. Cyclic AMP response element-binding protein (CREB) is a transcription factor that may help control both AC and PI signaling systems. CREB is involved in the transcription of many neuronally expressed genes that have been implicated in the pathophysiology of depression and suicide. Since we observed abnormalities of both AC and PI in the postmortem brain of teenage suicide victims, we examined if these abnormalities are also associated with abnormalities of CREB. We observed a lowered amount of DNA signal for CREB and less CREB protein made in the brains of teenage suicide victims compared with controls. These findings were specific on brain regions associated with depression. There are also a number of new findings in the area of pharmacogenomics which may allow us to predict which drugs might produce toxic side effects or higher plasma levels in certain patients. Nearly all drugs are metabolized by a group of enzymes that vary greatly in activity from person to person. If patients have a genetic mutation that results in either deficient enzyme activity or none, they would be likely to have serious side effects if exposed to the drug that is metabolized by the enzyme. For example, data presented at the 2007 American Psychiatric Association meeting has shown that genotyping may facilitate individualized prediction of response to the antipsychotic iloperidone, an agent that is currently in Phase III clinical trials.

Within a few years, patients could be routinely screened for these genetic variations, which will tell a clinician which drugs to use or avoid. We are in great need of better markers of likely outcome and toxicity when we prescribe psychoactive medications. Drug prescription based on an individual's biological profile is beginning to transform some areas of medicine, such as oncology, and hopefully will soon reach psychiatry.

Psychotherapy is an Effective Treatment for Borderline Personality

Borderline personality disorder is a vexing chronic condition. It afflicts an estimated 1.3 percent of U.S. adults. Symptoms include intense fear of abandonment, frequent displays of anger, unstable and intense personal relationships, impulsive acts, feelings of emptiness, suicidal threats or acts, and self-mutilation. People with this condition often experience symptoms that are alleviated by antipsychotics, but medications alone are not very effective in the long-term treatment of this condition. A new study indicates that some types of psychotherapy may cause substantial improvement in people with this disorder. Psychotherapy that centers on emotional themes arising in the interaction between patient and therapist, known as transference-focused therapy, stimulates the most change in people with borderline personality disorder. Dialectical behavior therapy, a currently popular brand of psychotherapy that teaches patients how to control and alter their emotional reactions, also produced good responses, as did supportive psychotherapy that provides basic advice on dealing with daily challenges. These finding were reported in the June 2007 *American Journal of Psychiatry* from a team led by psychologist John F. Clarkin.

Clarkin's group randomly assigned each of ninety outpatients diagnosed with borderline personality disorder, most of them women, to one of the three psychotherapies. For one year, each participant attended one or two weekly sessions with a seasoned therapist. Overall, patients in each group displayed notable one-year improvements on measures of depression, anxiety, social adjustment, and overall ability to function in daily life. No one fully recovered, however. Other measures of success varied across treatments. For example, only transference-focused and dialectical behavior therapy yielded declines in suicide threats and attempts, while only transference-focused and supportive therapy reduced anger and impulsiveness. Moreover, only transference-focused therapy led to fewer instances of verbal and physical assaults on others and increased patients' abilities to reflect on their own motivations and those of others.

Other recent findings question whether transference-focused therapy is the best available treatment for borderline personality disorder. An example is a study, published in the June 2006 *Archives of General Psychiatry*, directed by psychologist Arnoud Arntz. Arntz and his coworkers studied eighty-eight patients randomly assigned to transference-focused therapy or to schema-focused therapy, which addresses feelings related to past traumatic experiences, as well as the patient's current relationship with the therapist. After three years of twice-weekly sessions, patients in both groups displayed fewer symptoms of borderline personality disorder and reported quality-of-life improvements. Schema-focused therapy yielded bigger changes than transference-focused therapy. It appears, overall, that the use of a well-thought-out technique by an experienced worker may be more important to a person's likelihood of improvement than the use of one particular technique. This is not surprising and does not diminish the work. Many drugs with apparently different mechanisms of action often have therapeutic benefit in the same area. Why should this also not be true for "talk therapy?" As we attempt to improve treatments for mental disorders, it is crucial that we understand and use effective techniques. There are too few well-done studies of psychotherapy in serious mental disorders, and this work is a great help in our field.

The Search for Relief of Cognitive Disorders in Schizophrenia Continues

Memory Pharmaceuticals announced that it plans to commence a proof-of-concept Phase IIa study of MEM 3454 for the treatment of cognitive impairment associated with schizophrenia. MEM 3454 is a partial agonist of the nicotinic alpha7 receptor (alpha7 nAChR), a highly specialized receptor found in the central nervous system. Selective alpha7 nAChR agonists have been developed as potential candidates for the treatment of schizophrenia, cognitive disorders (including Alzheimer's disease), and inflammation. A Phase I clinical trial program of MEM 3454 showed that it was safe and generally well tolerated up to and including a dose of 450 mg. In addition, cognition data demonstrated that a 15 milligram dose of MEM 3454, administered once daily for a period of thirteen days, showed a statistically significant effect on the Quality of Episodic Secondary Memory (QESM). QESM is a composite score derived from memory tests, which measures the efficiency with which study participants are able to remember words and pictures. It appears the positive effects of MEM 3454 are only apparent at lower doses, a common finding with partial agonists. This often makes prescribing these drugs complex.

In general, neuronal nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels, which have very broad distribution and structural heterogeneity. They are involved in a wide variety of neuronal processes and have generated great interest as targets for therapeutic intervention in a number of neuropathological conditions and diseases. It is clinically important to use ligands that only selectively interact with distinct receptor subtypes in such a way as to maximize the therapeutic effect and minimize the adverse effects. The alpha7 nAChR has been the most intensively studied nAChR in recent years. There remain concerns that the rapid desensitization property of the alpha7 nAChR will limit the therapeutic potential of these compounds. However, several, including MEM 3454, have already been advanced to clinical trials. Further work is needed to see if these exciting new compounds have a true therapeutic potential.

Weight Gain Associated with Antipsychotics

There have been a number of breaking news items in the area of weight gain with antipsychotics. First, Eli Lilly has stated that the company has reached settlement agreements, resolving approximately nine hundred lawsuits related to Lilly's schizophrenia and bipolar disorder drug olanzapine (Zyprexa), four of which were scheduled for trial in July. At the beginning of January, Eli Lilly stated that as much as $500 million might be spent to resolve most of the remaining product liability claims over olanzapine. The company estimated then that more than 18,000 claimants had settled, leaving approximately 1,200 claims outstanding. It appears this most recent action settles most, but not all, of these claims. Lilly is also claiming that legal advertisements regarding olanzapine are hurting patients. The company asserts that a recent study showed that patients using olanzapine were more likely to abruptly stop taking the drug once they were exposed to legal advertising that highlighted olanzapine's harmful side effects. The study, which Lilly sponsored, surveyed 402 patients. While Lilly agrees that patients should never stop a medication without first consulting their own physicians, many plaintiff attorneys dispute Lilly's claims. Despite the controversy surrounding olanzapine, the FDA still has not required Eli Lilly to publish medication guidelines for the drug. It is clear

the legal advertising decried by Lilly has become a new bellwether for drug danger. Legal advertisement itself may be the first indicator to a patient that the drug he is taking may be doing more harm than good. We, as a field, need to do better in warning our patients of likely drug side effects, and consider what we can do if the drug side effects occur.

One choice, that appeared to be close to the clinic, is now much further away. A drug once viewed as a possible magic bullet against obesity was rejected for approval on June 13 by an advisory panel to the FDA because of worries that it causes neurological and psychiatric problems and increases the risk of suicide. The drug, rimonabant, is already marketed in thirty-seven countries; it is now very unlikely that the FDA will approve its sale in the United States without additional safety data. The advisory panel voted unanimously, 14 to 0, against recommending the drug, noting that it indeed was associated with weight loss but there was inadequate evidence of its safety. The FDA is not required to follow the advice of such panels, but it typically does. Sanofi-Aventis, the company that makes the drug, had expressed hope that the drug would be a leading seller, with much of that market in the United States, a country with a growing obesity problem. In a statement issued after the panel's vote, the company said it would continue to work with the FDA to address the panel's concerns, which included worries about a high drop-out rate in clinical studies of the drug.

Rimonabant works on the brain's endocannabinoid system. The system was discovered through research into marijuana, which often makes users hungry. By inhibiting those receptors, rimonabant is thought to curb hunger. This is critical for people who have gained weight after taking antipsychotics, as there is evidence the antipsychotics themselves may induce weight gain by influencing the endocannabinoid system as well. However, this same brain system also modulates depression, phobias, anxiety, and post-traumatic stress disorder. Data suggested that rimonabant use increased such dysphoria and suicidal thoughts. The advisory panel's vote that there was not enough safety data to approve the drug came after being presented with data that indicated the drug doubled the risk of anxiety, depression, aggression, and psychosis compared to placebo. In a presentation to the panel, representatives of Sanofi-Aventis recommended a special screening of prospective patients to measure their risk for psychiatric symptoms. However, it was correctly noted that pre-existing psychiatric conditions did not predict risk when taking this drug. Indeed, psychiatric patients may have less risk than others in regard to developing dysphoria. This ruling likely benefited the psychiatric community, as Sanofi-Aventis essentially proposed to rule out the use of rimonabant in the mentally ill, instead of presenting data on how to use the drug safely. Sanofi-Aventis had first petitioned the FDA in 2005 to approve the drug. Its work is not done. Drugs like rimonabant may soon become an important addition to the pharmacopoeia, but we must first know how to use them correctly in order to avoid the very common problem of inappropriate use secondary to lack of adequate data regarding safe use.

A New Technique to Treat Brain Disease with Medication

The blood-brain barrier is critical to normal health, but is a major impediment to the delivery of medications to the brain. Now, for the first time, a team from Harvard, headed by Dr. Manjunath Swamy, has developed a method to selectively ferry a drug across the blood-brain barrier to treat a neurological disease in mice. The new method could eventually make new treatments possible for a wide range of brain disorders. The team exploited a trick that some viruses use, including rabies, to cross the blood-brain barrier. They have molecules that trick the barrier into allowing them to pass. The research team attached a molecule from the rabies virus to a drug and demonstrated that the coupled molecules got through the capillary walls and into the brain. A drug delivered in this way kept eighty percent of mice infected with Japanese encephalitis alive for at least thirty days, while all of the experiment's untreated mice died, the scientists report online and in June 17, 2007 *Nature*.

The molecule from the rabies virus binds to nicotinic acetylcholine receptors on the surfaces of the capillary walls. When drug-ligand complex interacts with the receptor it moves through the wall carrying the drug with it. The drug molecule used by the researchers was a type of RNA that can block the activity of a gene. These RNAs, called short-interfering RNAs (siRNAs), can be custom tailored to target virtually any disease-causing gene or protein. Scientists are developing siRNAs to treat Alzheimer's, Huntington's, and Parkinson's diseases, among others. Many questions remain before the new technique can be used on people, such as whether some regions of the brain receive more of the drug than others, and whether the human immune system might neutralize the molecule. However, this is a very exciting new lead.