Phase 1 Results of New Putative Antipsychotic RP5063 Reported

Results were presented at the recent New Clinical Drug Evaluation Unit (NCDEU) Conference on a Phase 1 study of a putative antipsychotic RP5063 in 55 subjects. The agent was found to have antipsychotic effects on positive symptoms of psychosis and appeared to be well tolerated. A Phase 2 study is now under development. RP5063 is an agent with selective partial agonist effects on dopamine D2 and serotonin SHT1A, as well as dopamine antagonism at D3 and D4 dopamine receptors. More information available at www.revivapharma.com.

Intramuscular Aripiprazole: New Data

We have previously highlighted in CS the development of an intramuscular (IM) formulation of aripiprazole. A double-blind, placebo-controlled study of 710 patients with schizophrenia that was conducted over four phases with a total study duration of one year found that intramuscular aripiprazole was effective in reducing the time to (“impending”) relapse (10% in IM group versus 39.6% in placebo group). Symptoms also improved on intramuscular aripiprazole compared with placebo, and there was also a statistically greater improvement in social functioning in patients receiving aripiprazole. Intramuscular aripiprazole was generally well received, with weight gain observed in 6.4% of patients versus 5.2% of patients receiving placebo. Injection site pain was recorded during the maintenance-treatment phase among 3% of patients receiving intramuscular aripiprazole and among 3.7% of patients receiving placebo (“during”) injections.

Antipsychotic Use in Anorexia Nervosa: Mouse Model Provides New Evidence

Klenotich and colleagues recently provided an elegant series of studies in rodents to address and explain the potential benefit of antipsychotics—in this instance olanzapine—in the treatment of anorexia nervosa. Although this is very clearly an off-label use of these drugs, antipsychotics have long been used as an adjunct for recalcitrant anorexia nervosa. It has been considered that their potential benefit is not just to “put on weight” in these patients. This study created an animal model of anorexia—Activity-Based Anorexia (ABA)—and optimized its expression through food access. The authors report that olanzapine given over time reduces ABA in mice, an effect that was not seen with fluoxetine. The authors did not find that this effect could be explained through sedation or hyperphagia. They concluded that neurochemical changes related either to dopamine and reward circuits, or related to alterations in hypothalamic pituitary-adrenal (HPA) axis activity during chronic therapy. Of course, the study could not address whether mood-related changes with antipsychotic therapy might also help in controlling symptoms of anorexia nervosa.

Study of Zonisamide for Antipsychotic-Related Weight Gain

Susan McElroy and colleagues have recently provided us with a thoughtful study that evaluates the potential of zonisamide—an anti-epileptic drug that has also been used (importantly, in an off-label, non-FDA approved approach) in treating mood disorders—to ameliorate antipsychotic-related weight gain. This group had previously studied topiramate in a similar manner. In this study, they assessed zonisamide versus placebo add-on to olanzapine over 16 weeks of therapy in 40 patients. There was overall less weight gain on zonisamide, although patients receiving this drug also experienced more cognitive impairment (25% of patients versus 0% in the placebo group). This is, of course, a “hot” area of research in the psychopharmacology of schizophrenia.

Staccato Loxapine under Continued Review by the FDA

In previous issues of CS we have highlighted the delivery system as well as key findings from clinical trials of the putative antipsychotic staccato loxapine—an inhalant form of loxapine. The U.S. Food and Drug Administration (FDA) has recently requested some clarification from the pharmaceutical company, although no clinically substantive issues were brought forward by the FDA at this time. Staccato loxapine has been shown in clinical trials to be effective for the treatment of acute agitation in psychotic patients. More information available at www.alexza.com.
Can Antipsychotic-Related Weight Gain be Genotyped?

A very recent multicenter, international study by Malhotra and colleagues conducted a pharmacogenetic analysis of susceptibility to antipsychotic-related weight gain in a combined sample of 344 subjects who were treated with various second-generation antipsychotic medications (SGAs). The duration of treatment was between 6 and 12 weeks (maximum) for all patients. The study showed an association—through a genome-wide association study (GWAS) examining polymorphisms—of the melanocortin 4 receptor (MC4R) gene and weight gain liability. This was also extended to metabolic measures such as insulin and lipid. The rs489693 genotype pattern of expression was also replicated in all of the cohorts in this study. It is also important, however, to appreciate that while the MC4R gene was implicated in this study, the specific single-nucleotide polymorphisms (SNPs) of rs489693 was less prominent than other SNPs associated with weight gain in the general population.


Polypharmacy in Schizophrenia: Relationships to Suicide and Non-Suicidal Deaths

The practice of polypharmacy is common—if not ubiquitous—in the treatment of people with schizophrenia. The extent to which such practices improve outcomes—reduced relapse, improved symptoms—is debated amidst a highly variable literature that points to largely idiosyncratic effects. The adverse effect profile and long-term risks of such augmentation strategies is of course “the flip side of the coin.” A recent study by Tiihonen and colleagues cites no difference in mortality between patients receiving two antipsychotics and those treated with antipsychotic monotherapy. The same result was observed for patients who also received concomitant antidepressant medications. On the contrary, however, patients receiving benzodiazepines had higher mortality rates, both from suicide and from non-suicidal causes of death. This is an important study and further informs the ongoing concern regarding premature death among people with serious mental illness.

Tiihonen J, Suokas J, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry 2012;69(5):476-483.

German Multicenter Study of Relapse in Schizophrenia

Schennach and colleagues recently examined the course of illness in the first year following hospital discharge in 200 patients with schizophrenia. At the end of this year, 25% of patients were on treatment with first-generation antipsychotic (FGA) medications while 65% of patients received second-generation antipsychotic medications. The study also illustrates how people traverse in their illness over time between relapse, remission, and recovery. It also highlights that patients who relapsed over time were more likely to be receiving FGA medications, to have a poor attitude toward medication compliance, and to be unemployed.


Is Childhood Adversity a Risk Factor for Schizophrenia?

We have previously highlighted literature that addresses this fundamental issue: can childhood trauma (and, if so, what types of trauma) bring on schizophrenia? Bentall and colleagues have carefully culled the literature from several complimentary vantage points to clarify this potential relationship. They too found an over representation of later development of schizophrenia in children who have had some sort of trauma before 16 years of age. They also report that the effect of different sources of trauma may impact the symptom profile—with childhood physical and sexual abuse more associated with auditory hallucinations while paranoia is associated with childhood neglect/institutionalization. The association between childhood rape and hallucinations appeared quite robust (observed ratio 8.9). The study also reports “dose response relationships” for each trauma. These findings are both interesting and provocative, although there are several limitations to this study including diagnosis, symptom capture, and reliance/over interpretation of questionnaire data.


Readers wishing to know more about the details of individual studies cited in Clinical News should consult directly the pharmaceutical company who sponsored the study and/or www.clinicaltrials.gov.