Clinical News

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Staccato Loxapine Resubmitted to FDA

In a previous issue of ***CS*** we described the profile and some initial registration trial study results for the putative antipsychotic investigational drug Staccato Loxapine. The drug is being developed for use in schizophrenia and mania where there is agitation. The drug has a novel delivery system as an inhalant. Initial study results have been encouraging. Alexza Pharmaceuticals submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) last year and received review and formal feedback by the FDA last fall. The company has now resubmitted the revised NDA.

Update on Putative Cognitive Enhancing Agents as a Novel Therapeutic Strategy for Schizophrenia

In past issues of ***CS*** we highlighted early efforts in drug development of putative cognitive enhancing medication for schizophrenia. We have previously mentioned the agent EVP-6124, which is a selective alpha-7 agonist drug. The company making this drug—EnVivo Pharmaceuticals—has announced initial findings from an early phase study (Phase 2b) of EVP-6124, which showed positive improvements over placebo in cognitive and psychotic features over a 3-month exploratory trial. More detailed results will be forthcoming from the company.

Study on Once-Monthly Investigational Antipsychotic Drug

Another pharmaceutical company—Alkermes, Inc.—has reported initial results from an early phase trial of their agent ALKS 9070. The drug has two unique features that are incorporated into its clinical drug development profile. Firstly, it may be developed as a once-monthly oral dosing medication. Secondly, it is biodegraded in the blood to aripiprazole. Thus, the hope is that this novel approach may combine the potential for better medication adherence with the already established efficacy of aripiprazole. In a 20-week, early-phase, placebo-controlled trial, ALKS 9070 was well-tolerated and without serious side effects among 32 patients with schizophrenia who received one of three dosing regimens. Further studies of this agent are anticipated.

International Collaborative Molecular Study Reveals Core Enzymatic Deficit in Schizophrenia

Researchers in the Department of Neuroscience at King's College London teamed up with experts at the University of Magdeburg, Germany, to examine the molecular infrastructure of cyclin-dependent kinase 5, an enzymatic system that is putatively indicated in cognition (Engmann et al., 2011). In a study of post mortem brains from both institutions, these researchers found a reduction in the enzyme subunit p35 in both the frontal cortex and hippocampus of patients with schizophrenia. This deficit was quite pronounced, in the order of a 50% reduction in p35 overall.

In parallel, the group conducted a series of molecular and behavioral studies in mice to elucidate the biochemical and biobehavioral correlates of this deficit. Using a knockout mouse strategy, the authors found that mice deficient in p35 exhibited several changes in synaptic proteins that are key to neural integration. These mice also exhibited prepulse inhibition deficits and social isolation behaviors that are often considered to be "animal correlates" of the manifestations of schizophrenia in humans. These are an interesting series of studies, conducted with exemplary methodology. Another novel agent aspect of their work was the use of a putative anticancer drug—MS-275—in their studies. When given to mice, MS-275 appeared to reverse the inhibition of histone acetylation that may be associated with genes that regulate synaptic plasticity. When MS-275 was administered to these p35 knockout mice, the effects on synaptic proteins that were observed earlier—as well as their apparent behavioral correlates—were reversed. These studies have implications for more novel approaches to enhancing cognition in schizophrenia.

Engmann O, Hortobagyi T, Pidsley R, Troakes C, Bernstein HG, Kreutz MR, et al. Schizophrenia is associated with dysregulation of a Cdk5 activator that regulates synaptic protein expression and cognition. Brain 2011;134(Pt 8):2408-2421.

Stanford Group Examines Neurobiology of Social Deficits

Stanford University was home to Dr. Fritz Redlich, a pre-eminent schizophrenia researcher who in the 1940s–

1950s proposed the "social deficit hypothesis" of schizophrenia— that is, people who developed schizophrenia were unable to sustain social integration, "slipped into psychosis," and declined in social status as the illness took effect. Now, psychiatry and bioengineering researchers at Stanford (Yizhar et al., 2011) have teamed up to test another social deficit hypothesis. They sought to test an "excitation-inhibition hypothesis" of overarousal to external stimuli as a result of an imbalance in the "toning" of either inhibitory or excitatory brain cells (E/I balance). Yizhar et al. tested this hypothesis in an elegant series of studies wherein they selectively bioengineered distinct nerve cells to be either hyper- or hyporesponsive to light. They then examined neurobiological and biobehavioral parameters against varying frequencies of light—in this way, toning "up or down" the selective neural cells in their transgenic mouse model. They found that raised—but not reduced—E/I balance selectively in the medial prefrontal cortex produced a marked dysfunction in information processing along with high-frequency, "EEG-like" brain activity changes and social isolation behaviors in the mouse. These abnormalities are thought to resemble both social and neurobiological correlates of autism and schizophrenia.

Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 2011;477(7363):171-178.

Major New Study on the Merits of Antipsychotic Medications as Antimanic Treatments

Several years ago, Professor John Geddes published a provocative and informative study in the *British Medical Journal* suggesting that the efficacy of second-generation antipsychotic medications had been "hyped" and that first-generation antipsychotics (in this instance, chlorpromazine) were just as good, especially if they were used judiciously and used at lower doses that minimized the risks of extrapyramidal side effects. Now Dr. Geddes and colleagues have published in *The Lancet* another key paper on the comparative efficacy and tolerability of antipsychotics, this time focusing on their role in the therapeutic armamentarium for treating acute mania (Cipriani et al., 2011). The authors meticulously extracted and examined information from 68 acute, randomized, controlled clinical trials of various putative mood stabilizing drugs. The studies included the period from 1980 to 2010. The results are well-summarized in the paper's abstract: "Overall, antipsychotic drugs were significantly more effective than mood stabilizers. Risperidone, olanzapine, and haloperidol should be considered as among the best of the available options for the treatment of manic episodes." The study also provides evidence for the use of haloperidol as potentially a first-line antimanic drug, although the authors acknowledge that this finding may in part be influenced by its being the most frequently chosen comparator drug in these randomized clinical trials. On the other hand, the study reports that lamotrigine, gabapentin, and topiramate were no better than placebo as acute antimanic agents. In discussing haloperidol's outcome, as well as the other drugs' profiles as acute antimanic agents, the authors caution us that "all statements comparing the merits of one medicine with another must be tempered by the potential biases and uncertainties that result from choice of drug and choice of patients." This, of course, holds true for psychopharmacology in general.

Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011. Published online August 17, 2011.

Antipsychotics and Posttraumatic Stress Disorder

John Krystal and colleagues have recently published the results of an important randomized trial of risperidone in patients with posttraumatic stress disorder (PTSD). In this VA cooperative study involving 23 facilities nationally, 267 patients with chronic PTSD were treated for 6 months with either risperidone or placebo. The patient sample had high rates of comorbid depression and substance abuse. Patients treated with risperidone received an average of 2.74 mg/day. Both groups showed a similar but modest improvement in symptoms over time. Patients receiving risperidone had more side effects. Apart from weight gain (observed in 15.3% of risperidone-treated patients compared with 5.3% of the placebo group), side effects were generally tolerable and, overall, not serious. The study is important because of the clinical, off-label use of antipsychotics to treat recalcitrant anxiety symptoms (as well as "pseudo-hallucinations") in patients with PTSD. The results of this study may be surprising to some clinicians, although, of course, aspects of the study sample (in particular, the comorbidity) may have contributed to these findings. The role of other antipsychotic drugs deserves similar meticulous study.

Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA 2011;306(5):493-502.

Study Shows Insufficient Monitoring for Metabolic Side Effects of Antipsychotic Medications

Mitchell and colleagues (2011) have conducted a comprehensive meta-analysis of studies dated between 2007 and 2011 that examined physician habits in monitoring for

metabolic side effects among their patients who are being treated with antipsychotic medications. The researchers identified 48 studies stretching across 5 countries, including the United States. Cholesterol, glucose, and weight monitoring occurred overall in less than half of instances. Lipids and hemoglobin A1C were evaluated less than 25%. Only blood pressure monitoring and assessment of triglycerides exceeded 50%. Evaluation patterns were generally similar between studies in the United States and studies of care in England. The study tried to measure the impact of guidelines on rates of monitoring and found that monitoring did improve in the wake of relevant guidelines for that country. The overall results are not surprising in the absolute sense—in that, inadequate monitoring could be anticipated for a variety of reasons. However, the extent of low monitoring is surprising.

Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, DeHert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. Psychol Med 2011:1-23. Published online August 10, 2011.

European College of Neuropsychopharmacology Produces Position Paper on Psychiatry Drug Development

The European College of Neuropsychopharmacology (ECNP) held a summit earlier this year involving a diverse group of leaders in psychopharmacology. The recently published report of that ECNP summit is an excellent read as it provides a comprehensive, yet concise, appraisal of the state of drug development for psychiatry. The issues raised in the report are inordinately complex and span from scientific entrepreneurism to political/social indolence regarding mental disorders. It is well worth a read.

Nutt D, Goodwin G. ECNP Summit on the future of CNS drug research in Europe 2011: report prepared for ECNP by Davit Nutt and Guy Goodwin. Eur Neuropsychopharmacol 2011;21(7):6495-6499.

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.*