Clinical News … updates on new putative antipsychotics, antipsychotic effects in young children and adolescents with psychosis, novel pharmacologic approaches to negative symptoms and cognitive impairment in schizophrenia …

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Updates on New Putative Antipsychotic Agents

We previously highlighted the development of the putative dopamine-serotonin stabilizer RP5063. Recent results have become available from a large Phase 2 study (n=234 schizophrenia patients) comparing three doses of RP5063 with either placebo or aripiprazole. The study shows that RP5063 had antipsychotic efficacy. The putative antipsychotic also demonstrated a favorable adverse effect profile.

ALKS 3831, a putative mu opioid receptor modulator in combination with olanzapine, has been described before. A Phase 2 clinical trial is starting to evaluate the efficacy—as well as tolerability—compared with olanzapine monotherapy in patients with schizophrenia. Four hundred patients are anticipated to enroll in this study.

New Study of First- and Second-Generation Antipsychotic Medications

Stefan Leucht and colleagues have published another important, high-level, meta-analytic review of the comparative efficacy and tolerability of antipsychotic medications. Drawing from 212 acute-treatment, placebo-controlled clinical trials, the authors describe in comparative terms the profile of fifteen antipsychotics. In terms of efficacy, clozapine, amisulpride, and olanzapine (in that order) stand out as the three most powerful antipsychotics. Haloperidol was the worst drug for extrapyramidal side effects, though the best drug for weight gain. There were differences between the second-generation antipsychotics. However, importantly, this comprehensive review did not find that pharmaceutical sponsorship, year of publication, or other sources of potential bias have influenced the results overall.

Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013:S0140-6736(13)60733-3. [Epub ahead of print.]

Antipsychotic Effects in Young Children and Adolescents with Psychosis

In previous issues of ***CS*** we have highlighted the widespread public and professional concern about the use of antipsychotic medications in children and adolescents—especially when these powerful drugs are prescribed for non-psychotic, unapproved clinical situations. A team of Spanish investigators (Noguera et al., 2013), which includes one of our ***CS*** Editorial Board members (Celso Arango, MD), provides important information from their longitudinal, first-episode psychosis study on the effect of antipsychotic exposure among 110 patients aged between 9 and 12 years. The authors report a high rate of medication discontinuation over time: 45% at 6 months, 59% at one year and 70% at two years. The main reason for discontinuation was insufficient clinical response and then various adverse effects. However, while there were adverse effects on weight and muscular function at six months, these did not persist and were not observed at either the one-year or two-year follow-up assessments. In contrast to the other second-generation antipsychotics, there was a low discontinuation rate in young patients who received clozapine and, in these patients, the adverse effect profile over time also mirrored that observed in adult patients who are on clozapine as a maintenance treatment.

As highlighted in previous ***CS*** issues, there is continued and progressive public concern about the use and cost of antipsychotic medications in children and adolescents. The U.S. Department of Health and Human Services is investigating the use of these medications in this population in the five largest states with Medicaid prescriptions for these drugs.

In addition to cost concerns, there is concern about risk exposure in this population to weight gain and metabolic liabilities of antipsychotic medications. A recent Medicaid analysis (Bobo et al., 2013) among almost 29,000 patients exposed to antipsychotics showed a threefold increase in diabetes risk in this large sample of 6 to 17 year olds.

Noguera A, Ballesta P, Baeza I, Arango C, de la Serna E, Gonzalez-Pinto A, et al. Twenty-four months of antipsychotic treatment in children and adolescents with first psychotic episode: discontinuation and tolerability. J Clin Psychopharmacol 2013;33(4):463-471.

Bobo WV, Cooper WO, Stein CM, Olfson M, Graham D, Daugherty J, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry 2013 Aug 21. doi: 10.1001/jamapsychiatry.2013.2053. [Epub ahead of print.]

MRI Study Provides Complex Answers to Role of Relapse and Antipsychotic Medication in Progressive Neurodegeneration in Schizophrenia

Our esteemed ***CS*** Editorial Board member, Dr. Nancy Andreasen, and colleagues from the University of Iowa published an important longitudinal MRI study assessing the

brain changes over time in relation to relapses and medication among 202 patients with schizophrenia. Their results confirm the deleterious effect of relapses upon brain structures, pointing to frontal lobe decrements in particular. Paradoxically, while it is readily acknowledged that medications help to reduce the risk of relapses over time, the authors also found that the greater extent of medication exposure was associated with more diffuse (but less pronounced) tissue loss than relapse itself. The results provide a complex message for clinicians, and the study—while provocative—is largely cross-sectional and driven by complex analyses such that it does not represent the final word on these aspects.

Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. Am J Psychiatry 2013;170(6):609-615.

Novel Pharmacologic Approach to Negative Symptoms in Schizophrenia

Both clozapine and olanzapine are noteworthy by their pleomorphic binding to various neuroreceptors, an observation that has catalyzed many explanations as to how these drugs work in comparison with other second-generation antipsychotic medications. Both clozapine and olanzapine bind preferentially and strongly to histamine (H2) receptors, and this effect is generally considered to result in the sedative properties of these drugs—more so than being an explanation for their efficacy. That said, there is evidence for histamine (especially H1) receptor dysfunction in schizophrenia.

In an elegant, double-blind, placebo-controlled clinical trial study from Finland, Meskanen and colleagues (2013) found a robust effect of the H2 antagonist famotidine on negative symptoms in patients with schizophrenia. The authors also noted an improvement in general functioning, although positive symptoms and other symptoms were unaffected. While this is a small add-on study (n=30) and with heterogeneity among patients, the results are provocative.

Meskanen K, Ekelund H, Laitinen J, Neuvonen PJ, Haukka J, Panula P, et al. A randomized clinical trial of histamine 2 receptor antagonism in treatment-resistant schizophrenia. J Clin Psychopharmacol 2013;33(4):472-478.

Novel Pharmacologic Approach to Cognitive Impairment in Schizophrenia

Prasad and colleagues (2013)—including ***CS*** Editorial Board member Matcheri Keshavan, MD—report on a very interesting and innovative trial of an antiherpes virus drug valacyclovir (the prodrug of acyclovir) as an adjunctive treatment for cognitive dysfunction in schizophrenia. In a double-blind, placebo-controlled, 18-week study, they found modest improvements in memory (working and immediate recall verbal memory) and visual affect learning among valacyclovir-treated patients. Both patient groups improved in symptoms, with no advantage for the vaccine-treated group. Importantly, valacyclovir was well tolerated with no noteworthy side effects. This innovative study, funded by the Stanley Foundation, which has a longstanding interest in supporting "proof-of-concept" studies of novel pharmacologic approaches, has its rationale in a body of basic neuroscience and epidemiological studies which shows evidence for prenatal viral infections in schizophrenia. As reported in prior issues of ***CS***, there is great interest in novel approaches to treating the cognitive deficits associated with schizophrenia.

Prasad KM, Eack SM, Keshavan MS, Yolken RH, Iyengar S, Nimgaonkar VL. Antiherpes virus-specific treatment and cognition in schizophrenia: a test-of-concept randomized double-blind placebo-controlled trial. Schizophr Bull 2013;39(4):857-866.

Statin Use Similar among Patients with Schizophrenia and Nonpsychotic Patients

Mansi and colleagues (2013) report a surprising observation—that runs counter to many prior studies in schizophrenia—that patients prescribed statins had similar rates of schizophrenia and related psychoses than patients who were not receiving statins. The study is from Texas and is based upon military claims data; likely accordingly, then, the rates of mental illness are unrepresentative in this sample.

Mansi I, Frei CR, Pugh MJ, Mortensen EM. Psychologic disorders and statin use: a propensity score-matched analysis. Pharmacotherapy 2013;33(6):615-626.

Sudden Death and Schizophrenia: A Link with the Neuregulin Gene?

The neuregulin gene is one of several neurodevelopmental genes that has been associated with schizophrenia. Interestingly, a recent study from a large (n=682) observational study of sudden death that examined 17 single nucleotide polymorphisms (SNPs) found an over representation of the neuregulin 1 gene in patients who had sudden death. This was also confirmed by the authors (Huertas-Vazquez et al., 2013) in a second, independent dataset. Neuregulin regulates cell-cell interactions and may influence the prolonged QT syndrome that is both associated with sudden death, as well as being proposed as a pathogenic mechanism to explain the higher rate of unexplained sudden death in patients with schizophrenia. That said, the study did not focus on patients with schizophrenia and the study sample was not broadly representative. Nevertheless, it does point to the potential of molecular genetics to unify and explain longstanding brain-body abnormalities in schizophrenia.

Huertas-Vazquez A, Teodorescu C, Reinier K, Uy-Evanado A, Chugh H, Jerger K, et al. A common missense variant in the neuregulin 1 gene is associated with both schizophrenia and sudden cardiac death. Heart Rhythm 2013;10(7):994-998.

Gene Tests Going Viral? Implications for Psychosis

Earlier this year, the American College of Medical Genetics and Genomics (ACMG) recommended that when gene sequencing is being performed, laboratories now have an obligation to track down any incidental findings with an analysis—and reporting out—of 57 genes. This set of recommendations has brought attention—and controversy—to the clinical role of gene sequencing as well as the true meaning of "incidental findings." The implications of these ACMG recommendations for patients with psychosis and their families are not yet clear. To the extent that the complex genetic profile of schizophrenia gets unraveled by the current series of high-throughput genetic studies, this could influence—as well as propel forward—the emergence of genetic testing for patients with psychosis. In previous issues of ***CS*** we have highlighted genetics findings as well as a critical assessment of the role of genetic counseling.

Ross LF, Rothstein MA, Clayton EW. Mandatory extended searches in all genome sequencing: "incidental findings," patient autonomy, and shared decision making. JAMA 2013;310(4):367-368.

Green RC, Lupski JR, Biesecker LG. Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. JAMA 2013:310(4):365-366.

Klitzman R, Appelbaum PS, Chung W. Return of secondary genomic findings vs patient autonomy: implications for medicine care. JAMA 2013:310(4):369-370.

Cognitive Remediation for Schizophrenia Gaining Momentum?

Dr. Sacks and colleagues reported interesting results on cognitive remediation (CR) in a recent issue of ***CS*** (Volume 7, Number 2). There is an accruing literature that this approach might be a useful adjunct to treatment. Potentially, if the data holds up, this approach could be tailored to each patient's needs—even potentially tailored to suit the patient's daily schedule. Saperstein and Kurtz (2013) provide a comprehensive and "easy-to-read" overview of this emergent field. They also highlight the potential with CR to advance personalized treatment for schizophrenia. They also show appropriate caution regarding generalizability of CR research findings to clinical settings. Time will tell.

Saperstein AM, Kurtz MM. Current trends in the empirical study of cognitive remediation for schizophrenia. Can J Psychiatry 2013;58(6):311-318.

Nosological Significance of a Major Depression with Psychotic Features: An Important "Counterpoint" to *DSM-5* Categorizations

Owoeye and colleagues (2013) provide important findings on the similarity of outcomes—yet potentially subtle pathobiological differences—in an Irish longitudinal study of psychoses between patients with schizophrenia (n=73), with bipolar disorder (n=73), and with major depressive disorder with psychosis (n=77). Patients with psychotic depression exhibited a prominence of negative symptoms, neurological soft signs, cognitive dysfunction and premorbid impairment that better resembled patients with schizophrenia than bipolar disorder. As Dr. Tandon highlighted in his recent review of *DSM-5* in ***CS*** (Volume 7, Number 1), the distinctions drawn between mood disorders and schizophrenia focused largely on schizoaffective disorder and on bipolar disorder. This study suggests that the connection of major depression with psychotic features to other psychoses may have been overlooked somewhat. Moreover, additional study of the neurobiological features of major depression with psychotic features might also be informative regarding schizophrenia.

Owoeye O, Kingston T, Scully PJ, Baldwin P, Browne D, Kinsella A, et al. Epidemiological and clinical characterization following a first psychotic episode in major depressive disorder: comparisons with schizophrenia and bipolar I disorder in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). Schizophr Bull 2013;39(4):756-765.

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, or go directly to the journal that published this work.*