Clinical News … a beautiful mind … genetics of autism … putative antipsychotics … non-psychotic pediatric conditions … inflammation and the brain … neural networks and deficit schizophrenia … precision medicine … antipsychotics and PTSD …

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Update on Antipsychotic Drug Development

Neurocrine Biosciences, Inc. is conducting a Phase 3, double-blind, placebo-controlled, 2-week trial testing a novel putative antipsychotic NBI-98854. This trial includes 240 patients with schizophrenia and related mood disorders who also have tardive dyskinesia. The compound—NBI-98854—is of particular interest because of its novel mechanism of action as a Vesicular Mono-Amine Transporter 2 (VMAT2) inhibitor, wherein it selectively affects dopamine neurotransition and modulates its release, an effect that may be of benefit to patients with tardive dyskinesia. This compound is also being studied in Tourette syndrome.

Intra-Cellular Therapies, Inc. is conducting another Phase 3 clinical trial of its compound ITI-007. Enrollment of 500 patients with schizophrenia is anticipated into a 6-week study, with randomization to this compound, risperidone, or placebo.

Aripiprazole extended-release injectable (Abilify Maintena) is now also approved by the U.S. Food and Drug Administration (FDA) for delivery to the deltoid muscle in the arm as well as the already FDA-approved route of administration to the gluteal muscle.

The FDA has also approved a new atypical antipsychotic to treat bipolar I disorder and schizophrenia. Cariprazine, a once-daily capsule marketed as Vraylar, is indicated for adults. The drug reduced symptoms of bipolar disorder in three 3-week trials of some 1,000 patients, and symptoms of schizophrenia in three 6-week trials of about 1,800 patients. Like other bipolar and schizophrenia drugs, cariprazine is not approved for older patients with dementia-related psychosis. It will contain a boxed warning about the increased risk for death in this patient group. Akathisia, drowsiness, dyspepsia, extrapyramidal symptoms, restlessness, and vomiting are among the most common side effects.

The REPRIEVE (Relapse prevention study in patients with schizophrenia) clinical study was recently presented and showed a 79.6% relapse-free rate in patients receiving iloperidone compared with 36.6% of patients in the placebo-control group.

The results from the Optimize Trial, aptly named to evaluate the most effective dose of lurasidone, found that 20 mg of lurasidone was not effective while 40 mg/day was effective. Moreover, among patients with inadequate response following a higher dose of lurasidone for 2 weeks (80 mg/day), there was some additional improvement in those patients whose doses were increased to 160 mg/day.

We have highlighted in previous issues of ***Clinical News*** the novel antipsychotic brexpiprazole (Rexulti). This agent is now FDA-approved for the treatment of adults with schizophrenia and also as an adjunctive treatment for antidepressant therapy in adults with major depressive disorder.

FORUM Pharmaceuticals Inc. has completed enrollment of patients into two Phase 3 clinical trials of its putative "precognitive" agent encenicline. Results will be forthcoming in due course. The FDA has approved "Fast Track" designation for consideration of encenicline, which is an alpha-7 nicotinic receptor agonist.

Lessons Learnt from the Genetics of Autism Spectrum Disorders?

Yuen and colleagues (2015) have published in *Nature Medicine* the results of an important whole genome sequencing (WGS) study of autism spectrum disorder (ASD) that has relevance for schizophrenia research and clinical diagnostics. In an analysis of phenotypic expression among 85 families that were comprised of both parents and two ASD-affected siblings, they found that 64% of affected siblings had different mutations that were relevant to those already described in earlier, smaller studies. They also noted the marked genetic and clinical heterogeneity in this large patient sample.

Yuen RK, Thiruvahindrapuram B, Merico D, Walker S, Tammimies K, Hoang N, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Med 2015;21(2):185-191.

Inflammation and the Brain: New Provocative Findings

Dr. Jonathan Kipnis, a neuroscientist at the University of Virginia School of Medicine, has made an important and provocative discovery that is very relevant to the burgeoning interest in neuroinflammation and schizophrenia. Essentially, Kipnis discovered that there are tiny vessels that interface between the brain and its vascular system, such that there is a conduit for direct release of immune proteins and markers into the brain. The paper, based upon observations and microdissection of the meningeal tissues and interface in the brains of mice, is complicated and a terse read but it sure is provocative stuff!

Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015;523(7560):337-341.

Neural Networks and Deficit Schizophrenia

Wheeler and colleagues (2015) report a fascinating and novel analysis—a connectomics approach—of MRI brain imaging data from patients with schizophrenia (divided into those with and without the deficit syndrome), patients with bipolar disorder, and healthy control subjects. Patients with deficit syndrome have frontoparietal cortical altered neural network interconnections, which distinguishes this patient group from the other three samples. The article is a very interesting read.

Wheeler AL, Wessa M, Szeszko PR, Foussias G, Chakravarty MM, Lerch JP, et al. Further neuroimaging evidence for the deficit subtype of schizophrenia: a cortical connectomics analysis. JAMA Psychiatry 2015;72(5):446-455.

Thoughtful Viewpoint on Precision Medicine

Hawgood and colleagues (2015) provide a clear and comprehensive—yet brief—appraisal of the current "state-of-play" of precision medicine. They describe that our field is now at a key inflection point that will proceed to more sophisticated use of integrated, personalized data from multiple sources.

Hawgood S, Hook-Barnard IG, O'Brien TC, Yamamoto KR. Precision medicine: beyond the inflection point. Sci Transl Med 2015;7(300):300ps17.

Substantial Use of Antipsychotic Medications for Non-Psychotic Pediatric Conditions

Olfson and colleagues (2015) provide a provocative analysis on the use of antipsychotic medications in children and adolescents (up to age 24), based upon a retrospective review of prescriptions from 2006–2010. Comparing 2006 and 2010, antipsychotics were prescribed to 0.14% (2006) and 0.11% (2010) of kids aged 1–6 years, 0.85% and 0.8% of kids aged 7–12 years, 1.1% and 1.19% of adolescents aged 13–18 years, and 0.6% and 0.84% of young adults aged 19–24 years. The most common diagnosis in these children was attention deficit hyperactivity disorder, depression, bipolar disorder, and anxiety. Overwhelmingly (96.7%), prescriptions were for second-generation antipsychotics. While claims data analysis is notoriously weak for understanding the clinical context of individual treatment, these data show low—yet sustained—use of drugs for non-psychotic conditions in pediatric populations.

Olfson M, King M, Schoenbaum M. Treatment of young people with antipsychotic medications in the United States. JAMA Psychiatry 2015;72(9):867-874.

Use of Antipsychotic Medications in Posttraumatic Stress Disorder

It is known that antipsychotic medications are sometimes used to treat recalcitrant posttraumatic stress disorder (PTSD) symptoms. Cohen and colleagues (2015) report an interesting analysis among veterans from Iraq and Iran who had PTSD diagnoses but no schizophrenia or bipolar diagnoses. Almost 19% of the patients were receiving antipsychotics and these patients were more likely to have other psychiatric comorbidities (personality disorder, alcohol use disorder, drug use disorder) and they were more likely (over 4 times more likely) to be suicidal. While direct causality cannot be concluded from this pharmacoepidemiological study, it does highlight the continued frequent use of antipsychotics in VA patients, specifically now among those who have returned from Iraq-Afghanistan wars.

Cohen BE, Shi Y, Neylan TC, Maguen S, Seal KH. Antipsychotic prescriptions in Iraq and Afghanistan veterans with posttraumatic stress disorder in Department of Veterans Affairs healthcare, 2007–2012. J Clin Psychiatry 2015;76(4):406-412.

Use of Risperidone in Obsessive-Compulsive Disorder

It is estimated that about one-third of patients with obsessive-compulsive disorder (OCD) will show some response when antipsychotic medications are given in conjunction with standard treatments for OCD. In this 6-month maintenance study of exposure and response prevention compared with risperidone augmentation, the behavioral treatment was superior over time in maintaining symptom gains.

Foa EB, Simpson HB, Rosenfield D, Liebowitz MR, Cahill SP, Huppert JD, et al. Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and response prevention or risperidone in adults with obsessive-compulsive disorder. J Clin Psychiatry 2015;76(4):440-446.

Antipsychotic Use in Elderly Population

Antipsychotics are frequently used to manage behavioral disturbances in elderly patients with dementia. Prior FDA black box warnings about cardiovascular safety, combined with less than compelling efficacy results from well-conducted, large clinical trials, has prompted a reconsideration of the relative merit of using antipsychotics in the elderly population. Maust and colleagues (2015) address this issue by examining mortality statistics and number-needed-to-harm (NNH: number of patients exposed to drug to be associated with premature death) in a Veterans Affairs' database between 1998–2009. Haloperidol was the drug with the greatest mortality risk, with a 3.8% increased mortality and an NNH of 26. Corresponding mortality risk and NNH rates for other drugs were 3.7% and 27 for risperidone, 2.5% and 40 for olanzapine, and 2.0% and 50 for quetiapine. An increase in risk was observed with higher doses of antipsychotics. These are important findings.

Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry 2015;72(5):438-445.

A Beautiful Mind … and a Beautiful Story

Our ***CS*** distinguished Editorial Board member, Dr. Nancy Andreasen, provides a poignant account of noted mathematician, Nobel Laureate, and person with schizophrenia—John Nash—and the joys and anguish he and his wife Alicia shared through their great marriage. Dr. Andreasen's account is, itself, beautifully written and she reminds us of the perplexing relationship between creativity and serious mental illness. It's a great read and a wonderful tribute to a remarkable couple.

Andreasen NC. John and Alicia Nash: a beautiful love story. Am J Psychiatry 2015;172(8):710-713.

*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.*