Clinical News … update on putative antipsychotics … boundaries of psychosis … copy number variants … cerebrospinal fluid analysis … cannabis and schizophrenia … precision medicine and schizophrenia … suicide and early detection in first-episode psychosis …

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Update on Putative Antipsychotics

Results have become available for an important study—titled Enlighten 2—which is sponsored by Alkermes plc and has been described before in ***CS***. This is a 6-month, double-blind, comparative study of a putative novel antipsychotic ALKS 3831, which is a combination of olanzapine and samidorphan, versus just olanzapine. Some 29% of olanzapine-treated patients gained 10% or more of their baseline weight compared to 17% of ALKS 3831-treated patients. There was a similar completion rate among both groups, with the common side effects among ALKS 3831 being dry mouth, weight gain, and sleepiness.

Minerva Neurosciences determined, in an early-stage trial in healthy volunteers, the cardiovascular safety margin and dosing of a novel, putative antipsychotic roluperidone (MIN-101). The results favor an expanded therapeutic window and will also inform the outcome and context of an ongoing 12-week study of 32 mg and 64 mg of roluperidone in patients with schizophrenia.

Cariprazine, an FDA-approved drug for the treatment of schizophrenia, has also been studied as a potential treatment for bipolar depression. Allergan, the pharmaceutical company that launched cariprazine, has submitted to the FDA a supplemental New Drug Application based upon data from three studies in patients with bipolar depression.

Lumateperone (ITI-007), a new putative novel antipsychotic developed by Intra-Cellular Therapies, Inc., is now under consideration by the FDA, based upon a New Drug Application covering some twenty clinical trials. Lumateperone has a novel mechanism of action as a dopamine receptor phosphoprotein modulator.

If Only Kraepelin Knew What We Do Now … Or Maybe He Did?!

Ken Kendler, luminary in the fields of psychiatric genetics and psychiatric nosology, provides a simply fascinating account—in essence, a kind of "retrospective"—on the writings of Emil Kraepelin regarding psychosis. In an erudite historical review and timeline, Dr. Kendler walks us through Kraepelin's diagnostic and conceptual approaches to nonaffective delusional psychoses from the first to the sixth edition of his seminal textbook. Dr. Kendler notes that Kraepelin seemed to sense—but could not find—some organic brain disease, especially in the more severe psychoses. He also illustrates that Kraepelin was intrigued by the difference between delusional thinking which arises/is contemporaneous with hallucinations and delusional thinking which has a more environmental referential framework. As Kendler highlights, Kraepelin intuitively understood the need for longitudinal study of the trajectory of psychoses. A fascinating read.

Kendler KS. The development of Kraepelin's mature diagnostic concepts of paranoia (die verrücktheit) and paranoid dementia praecox (dementia paranoides): a close reading of his textbooks from 1887 to 1899. JAMA Psychiatry 2018;75(12):1280-1288.

Psychiatry-Neurology Dichotomy Affirmed While Diagnosed Boundaries Within Psychiatry are Blurred

The Brainstorm Consortium (Anttila et al., 2018) is an international group that has contributed a pivotal analysis of the genetic overlap—based upon a large genome-wide association study—among 25 psychiatric and neurological disorders. In accordance with earlier analysis, the group reports strong genetic convergence among the psychiatric conditions, with schizophrenia and bipolar disorder being central to this. In contrast, there was conspicuously little convergence between psychiatric and neurobiological disorders. Moreover, there was a curious lack of genetic association across neurological conditions (e.g., multiple sclerosis) that are considered to have a potential neuro-inflammatory basis.

Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, et al. Analysis of shared heritability in common disorders of the brain. Science 2018;(360)6395:1-12.

Coming Together or Coming Apart

In a previous issue of ***CS***, we reviewed a seminal study by Gandal and colleagues that showed genetic overlap across several psychiatric disorders, with the notable exception of alcoholism. Another article from this large collaborative group (Gandal et al., 2018) drills down on the transcriptome analysis, doing an RNA seq-analysis, also clarifying distinct cellular morphology, and genetic network expression across the same 5 disorders: schizophrenia, bipolar disorder, depression, autism, and alcoholism. These additional findings, delivered in a terse yet fascinating article in *Science*, are confirmatory of the molecular and architectural convergence across major psychiatric disorders.

Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science 2018;359(6376):693-697.

Copy Number Variants (CNVs) in Neurodevelopment Disorders

In previous issues of ***CS***, we have highlighted the small yet significant presence of copy number variants (CNVs). In an interesting study by Thygesen and colleagues (2018), the authors found that 13% of adults with intellectual disabilities had CNVs. Among the some 600 adults with intellectual disabilities, higher rates of CNVs were skewed in the comorbid conditions of schizophrenia and autism spectrum disorder. All that said, the phenotypic presentation among CNV subjects was highly variable.

Thygesen JH, Wolfe K, McQuillin A, Viñas-Jornet M, Baena N, Brison N, et al. Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders. Br J Psychiatry 2018;212(5):287-294.

Are Copy Number Variants (CNVs) Independent or Additive to Polygenetic Risk in Schizophrenia?

Previously in ***CS***, we highlighted how genetic "microdeletion" and/or "microadditions" called copy number variants (CNVs) are overrepresented in schizophrenia. In a large (almost 22,000 schizophrenia subjects) study drawn from the international Psychiatric Genomics Consortium (PGC), Bergen and colleagues (2018) found that the presence of CNVs was inversely related to polygenic risk in this sample. In modeling, however, the investigators report interactive and additive contributions of CNVs and single-nucleotide polymorphisms (SNPs). This study extends our understanding of the interactions between/among rare and common genetic changes as risk factors for schizophrenia.

Bergen SE, Ploner A, Howrigan D, CNV Analysis Group and the Schizophrenia Working Group of the Psychiatric Genomics Consortium, O'Donovan MC, Smoller JW, et al. Joint contributions of rare copy number variants and common SNPs to risk for schizophrenia. Am J Psychiatry 2018 Nov 5:appiajp201817040467. doi: 10.1176/appi.ajp.2018.17040467. [Epub ahead of print]

"Seq-Analysis" of Schizophrenia Cell Typology

Skene and colleagues (2018) have conducted an interesting analysis concerning cell types and their etiological relevance to schizophrenia. They performed a "scRNA-seq"—single cell RNA sequencing—of cell types and then related these to known genome-wide association studies "hits" in schizophrenia. The cell samples and "seq-analysis" was performed at the Karolinska Institute in Sweden, a premiere center globally for neuroscience research. They found a strong overlap between the cell types and genes implicated in schizophrenia, suggesting a more selective (rather than generalized) neurobiology of schizophrenia.

Skene NG, Bryois J, Bakken TE, Breen G, Crowley JJ, Gaspar HA, et al. Genetic identification of brain cell types underlying schizophrenia. Nat Genet 2018;50(6):825-833.

Cerebrospinal Fluid Analysis for Schizophrenia?

Previously, we have highlighted information from preclinical and clinical studies that are suggestive of a neuroinflammatory component to the etiology of schizophrenia(s). This perspective was propelled by the dramatic and public descriptions of autoimmune encephalitis (AIE), begging the question that perhaps this is a more frequent cause of psychosis than heretofore considered. To that end, Oviedo-Salcedo and colleagues (2018) conducted a retrospective analysis of cerebrospinal fluid (CSF) antibodies in 81 patients who underwent antineuronal antibody analysis from a naturalistic group of patients with schizophrenia. There were no cases of AIE, and less than 4% of patients had even any to albeit very low, positive titre. This is certainly not any endorsement for CSF analysis in schizophrenia.

Oviedo-Salcedo T, de Witte L, Kumpfel T, Kahn RS, Falkai P, Eichhorn P, et al. Absence of cerebrospinal fluid antineuronal antibodies in schizophrenia spectrum disorders. Br J Psychiatry 2018;212(5):318-320.

Cannabis does not Cause Schizophrenia: A Provocative Study

An important and provocative genome-wide associa-

tion study (GWAS) contributes a new and different perspective that does not endorse the association between cannabis and schizophrenia. The study is based upon a large sample of 183,000 people from around the world, reportedly the largest study to date on cannabis. The study suggests significant eight associations with 35 genes involved in these "hits." While the authors report an association between cannabis and schizophrenia, a more selective "Mendelian randomization" showed a weak causal relationship. However, this analysis was based upon a subset of genes.

Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci 2018;21(9):1161-1170.

Stem-Cells and Drug Development: Opportunities for "Precision Medicine" in Schizophrenia

Stem-cells—from neural progenitor cells (NPCs)—have been explored in combating Parkinson's disease and other neurodegenerative disorders. In a fascinating (albeit though quite terse) article by Readhead and colleagues (2018), NPC cells from 12 patients with schizophrenia and 12 normal controls were derived and used to better understand the impact of multiple drug doses upon the human transcriptome. Surprisingly, the drug effects were more pronounced in schizophrenia patients. That said, more of the drugs were antipsychotics. This study is of exemplary methodology and is likely to presage a wave of new transcriptome research in schizophrenia. While still in its infancy, this sophisticated line of scientific enquiry might advance the promise of precision medicine and selective drug discovery for schizophrenia.

Readhead B, Hartley BJ, Eastwood BJ, Collier DA, Evans D, Farias R, et al. Expression-based drug screening of neural progenitor cells from individuals with schizophrenia. Nat Commun 2018;9(1):4412.

Precision Medicine and Treatment Response in Schizophrenia

The "trial-and-error" nature of treatment response to antipsychotic medications has been a major drawback in improving outcomes in schizophrenia. This dilemma underlies the search for biomarkers for schizophrenia. Obviously, this also underlies the increasingly diverse pharmacodynamics conceptualizations of antipsychotic drug development, leaving behind the previously "monochromatic" over reliance on dopamine receptor blockade as a unifying feather of antipsychotics' mechanism of action. A large Chinese neuroimaging study of response to risperidone therapy in first-episode patients offers a new approach here. In this functional MRI study, the application of machine learning differentiation of cerebral connectivity predicted response to treatment with an accuracy of 82.5%. We can look forward to this—and related other artificial intelligence (AI) technologies—making their way into schizophrenia research. This is welcome, given the enormous amount of data that need to be analyzed —and integrated—in current day neurobiological research on schizophrenia.

Cao B, Cho RY, Chen D, Xiu M, Wang L, Soares JC, et al. Treatment response prediction and individualized identification of first-episode drug-naïve schizophrenia using brain functional connectivity. Mol Psychiatry 2018 Jun 19. doi: 10.1038/s41380-018-0106-5. [Epub ahead of print]

European Treatment Study: Algorithms for First-Episode Schizophrenia?

Rene Kahn and colleagues (2018) published an important study called "OPTiMiSE" (optimization of treatment and management of schizophrenia in Europe), which endowed 27 premier treatment centers from 14 European countries that enrolled almost 450 first-episode schizophrenia patients who received up to 800 mg/day of amisulpride (a European dopamine D2 antagonist antipsychotic)—Phase 1. Those who did not respond by 4 weeks received either a further 6 weeks of amisulpride or as much as 20 mg of olanzapine—Phase 2. For those who turned out to be refractory, they were put on clozapine for a further 3 months—Phase 3. Only 56% of patients remitted during Phase 1, and equal amounts of patients on amisulpride (45%) or olanzapine (44%) remitted in Phase 2. Of 18 patients who completed Phase 3, 28% remitted. Taking "drop out" of patients into account, some 76% of first-episode patients achieved remission. The study will be influential since its conclusion was that Phase 2 (longer continuation of treatment or switching to another medication) was a redundant step and essentially, after first failure, a trial of clozapine should be considered. This provocative recommendation—based upon a first-episode schizophrenia population—is in contradiction to the dwindling and restricted use of clozapine in clinical practice. It is also noteworthy that 44% of patients gained weight (more than 7% baseline weight) over the course of 12 weeks of clozapine therapy.

Kahn RS, Winter van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. Lancet Psychiatry 2018;5(10):797-807.

Suicide and Early Detection in First-Episode Psychosis

Simon and colleagues (2018) provide a compelling analysis of the early risk of suicide among first episode of psychosis (PEP) patients. In a 3-year comparison of mortality among PEP patients, patients with depression, and a general outpatient care recipients cohort, the relative risk of death from suicide was 34.0 in the PEP group compared to 4.7 in the outpatient control group. This rate declined over the 3 years. Surprisingly, also, mortality risk rates were low and similar between the PEP and control groups. These robust findings underscore the heightened risk of suicide early in the course of schizophrenia as opposed to the pattern that is associated with illness chronicity for depression, alcoholism, anorexia, and other mental conditions.

Simon GE, Stewart C, Yarborough BJ, Lynch F, Coleman KJ, Beck A, et al. Mortality rates after the first diagnosis of psychotic disorder in adolescents and young adults. JAMA Psychiatry 2018;75(3):254-260.

What Influences Treatment Decision-Making Capacity in People with Schizophrenia

It is important for clinicians to better understand what features impact negatively on a patient's ability to collaborate in shared decision making with his clinician about treatment. Impaired cognition and lack of insight are two obvious examples. In a comprehensive meta-analysis, Larkin and Hutton (2017) evaluated clinical associations with decision making based upon clinical studies, which ultimately included some 23 studies. There was wide variability across aspects and, surprisingly, depression did not impact decision making. The length of time in education was a major consideration, and people could retain judgement if they had inadequate education. The authors also emphasize ongoing patient assessment and make the point that continuously assessing is needed in both research trials as well as in clinical practice.

Larkin A, Hutton P. Systematic review and meta-analysis of factors that help or hinder treatment decision-making capacity in psychosis. Br J Psychiatry 2017;211(4):205-215.

*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.*