Clinical News … putative antipsychotics … developmental trajectories … schizophrenia-mood continuum and neurobiological constructs … novel treatments … weight gain …

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Update of Putative Antipsychotics

The U.S. Food & Drug Administration (FDA) has approved ARISTADA INITIO for the initiation of ARISTADA (aripiprazole lauroxil), a long-acting injectable atypical antipsychotic for the treatment of schizophrenia in adults. ARISTADA INITIO—in combination with a single 30-mg dose of oral aripiprazole—provides an alternative regimen to initiate patients onto any dose of ARISTADA on day one.

Intra-Cellular Therapies Inc. has active clinical trials on a novel compound ITI-007—called lumateperone—for the treatment of schizophrenia. Lumateperone has a very interesting pharmacologic profile—it is a dopamine receptor phosphoprotein modulator (DPPM), which confers combined agonist-antagonist properties at pre-and post-synoptic D2 receptors, respectively. Additionally, this putative agent also has effects at serotonin and glutamate receptors. Presently, the agent is under investigation as a potential treatment for schizophrenia in a drug development program that includes a switching trial as well as double-blind, placebo-controlled trials. Note: as we went to press, Intra-Cellular announced initiation of a rolling submission of its New Drug Application with the FDA for lumateperone for the treatment of schizophrenia.

Neurocrine Biosciences, Inc., which developed the new anti-tardive dyskinesia (TD) drug valbenazine (licensed as Ingrezza), has completed a large pragmatic trial (called RE-KINECT) evaluating the risk and presence of TD in patients taking antipsychotic medications. As previously highlighted in ***CS***, valbenazine is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor. Teva Pharmaceutical Industries Ltd. has also provided new data on long-term outcomes of TD in patients treated with deutetrabenazine (called Austedo). Deutetrabenazine is another VMAT2 inhibitor.

New data on lurasidone (called Latuda) developed by Sunovion Pharmaceuticals Inc. provide information on the use of the drug in adolescents with schizophrenia or with bipolar disorder. Allergan plc has completed studies of cariprazine (called Vraylar) in patients with bipolar depression. There are now two pivotal studies of cariprazine that demonstrate efficacy of this novel drug in bipolar depression.

Finally, results are expected shortly from the second study (ENLIGHTEN-2) of antipsychotic ALKS 3831, evaluating the weight profile of this agent in comparison with olanzapine. The ENLIGHTEN 1 study, developed by Alkermes plc, showed that ALKS 3831—a combination of olanzapine plus samidorphan—was an effective antipsychotic over the four-week study.

Differential Cognitive Trajectories Across the Developmental Child-Adult Period

Based upon the British Longitudinal study of children followed sequentially from 1991–1992 up until age 18 years, Mollon and colleagues (2018) reported interesting findings with respect to adolescents with psychotic disorders, "prepsychotic" states, and childhood depression. Children/adolescents with psychosis showed broad developmental delays in several cognitive processes, while the children with depression had less pronounced and circumscribed deficits early on, while overall there were little sustained deficits in depressive and "prepsychotic state" groups.

Mollon J, David AS, Zammit S, Lewis G, Reichenberg A. Course of cognitive development from infancy to early adulthood in the psychosis spectrum. JAMA Psychiatry 2018;75(3):270-279.

Should First-Episode Psychosis Patients Receive an MRI as Part of Assessment?

Falkenberg and colleagues (2017) address the thorny issue as to whether it is worthwhile doing an MRI brain scan as part of the "work-up" evaluation of first-episode psychosis patients. The study is pertinent because it includes both clinical and research samples. The authors found abnormalities

in MRI scans among 15% of the clinical group and 6% of the research group. That said, the abnormalities were not serious and did not alter their clinical management. The authors still support the need to evaluate patients using MRI.

Falkenberg I, Benetti S, Raffin M, Wuyts P, Pettersson-Yeo W, Dazzan P, et al. Clinical utility of magnetic resonance imaging in first-episode psychosis. Br J Psychiatry 2017;211(4):231-237.

Neuroscience of Genetic Phenocopies of Attention-Deficit/Hyperactivity Disorder: Implications for Schizophrenia

We have previously highlighted phenotypic studies of the biology of schizophrenia, including the biotypes in schizophrenia of intermediate phenotypes (BSNIP). A landmark schizophrenia study, previously cited in ***Clinical News***, demonstrated 108 genetic associations based upon the large psychiatric genetics consortium (PGC). Nigg and colleagues (2018) examined the genetic associations with five proposed cognitive domains in attention-deficit-hyperactivity disorder (ADHD) that included memory, temporal processing, output speed, arousal-attention, and inhibition. The study sample comprised some 650 children with ADHD, between ages 7 and 11 years and then another 20,000 ADHD subjects and 35,000 normal subjects from the PGC study. Based upon analysis of polygenic risk scores and structural equation modeling, the authors' main effects resided in working memory and in arousal-attention. There were not associations between genes and the ADHD cognitive domains of temporal processing, output speed, or inhibition. These results demonstrate potential genetic scaffolding for ADHD, using approaches that are similar to studies in schizophrenia research.

Nigg JT, Gustafsson HC, Karalunas SL, Ryabinin P, McWeeney SK, Faraone SV, et al. Working memory and vigilance as multivariate endophenotypes related to common genetic risk for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2018;57(3):175-182.

More on Biotypes for Psychosis

Sophia Frangou and colleagues at Mount Sinai NYC (2018) provide additional important data on the neurobiological heterogeneity of psychosis. They conducted MRI imaging among 100 patients with schizophrenia, 40 bipolar patients, and 50 normal control patients. In addition to structural MRI measures, the authors examined functional and cognitive measures. Interestingly, imaging and non-imaging data were highly interrelated, thus not driven by either diagnosis. Substance use was related to lower subcortical volumes and white matter fractional anisotropy. Positive symptoms were associated with global tissue loss and reduced cortical thickness, in contrast to the subcortical tissue loss seen with negative symptoms. Depressive symptoms were also associated with white matter fractional anisotropy.

Moser DA, Doucet GE, Lee WH, Rasgon A, Krinsky H, Leibu E, et al. Multivariate associations among behavioral, clinical, and multimodal imaging phenotypes in patients with psychosis. JAMA Psychiatry 2018;75(4):386-395.

Depression and Negative Symptoms in Schizophrenia: Separate Dimensions or Overlapping Constructs?

The relationship between negative symptoms of schizophrenia and comorbid depression has been a longstanding source of ambiguity, both with respect to assessment and treatment. Krynicki and colleagues (2018) provide us with a modern day current appraisal of this enigmatic relationship, based upon their thorough review of some 27 articles selected from an original post of over 2,200 articles. They conclude that the greatest area of overlap and, therefore ripe for therapeutic uncertainty, resides in the three features of anhedonia, anergia and avolition. Alternatively, blunted affect and alogia were more specific to negative symptoms while depressed mood, hopelessness, and suicidality were more specific to depression. All that said, these constellations can overlap in the same patient and current formal assessment instruments/clinical interviews do not adequately discriminate between these symptoms in such circumstances. There is an urgent need to tease out one's heterogeneity of symptoms in order to tailor specific treatments to selective patient groups.

Krynicki CR, Upthegrove R, Deakin JFW, Barnes TRE. The relationship between negative symptoms of depression in schizophrenia: a systemic review. Acta Psychiatr Scand 2018;137(5):380-390.

MicroRNA Biomarkers for Schizophrenia?

MicroRNAs (mRNAs) are components of RNA that turn on/off the expression of selective proteins. Since mRNAs relate to distinct alleles, they might be explored as another heuristic biomarker to tease out the etiological heterogeneity of schizophrenia. To that end, Manley and colleagues (2018) from Canada conducted a mRNA analysis of 24 multiplex families focusing on an histone gene. The group describes a strong association between a specific mRNA and a selective (G) allele. This work builds upon previous work from this excellent research team focusing on chromosome 17, as well as the seminal Psychiatric Genomics Consortium (PGC) finding of 10 genetics "hits," including on chromosome 17.

Manley W, Moreau MP, Azaro M, Siecinski SK, Davis G, Buyske S, et al. Validation of a microRNA target site polymorphism in H3F3B that is potentially associated with a broad schizophrenia phenotype. PLoS One 2018;13(3):e0194233.

Genetic and Molecular Convergence Across Psychiatric Diagnoses—Einpsychoses Revisited?

Early in the last century, the German phenomenologist Kleist suggested the notion of a "unitary psychosis" ("Einpsychoses"), where the boundaries between schizophrenia and mood disorders were lost. A contemporary and likely-to-be highly influential paper in *Science* by Gandal and colleagues (2018) offers a similar conclusion. These colleagues experienced the genetic and messenger RNA transcriptome patterns in the post mortem cerebral cortex samples from patients with schizophrenia (SZ), autism (ASD), alcoholism, bipolar disorder (BD), and major depressive disorder (MDD).

They observed statistically robust transcriptome correlations across all diagnoses—except alcoholism (itself very interesting for substance abuse research). The convergence had strongest correlations between SZ-BD (r=0.75), followed by ASD-SZ (0.48), ASD-BD (0.38), and SZ-MDD (0.25). Equally surprising, the weakest correlation was between BD-MDD (0.17).

These findings do not uphold the notion of schizophrenia as a singular disorder or even the proposed schizophrenia-mood disorders continuum. Rather, they suggest a more diffuse and interrelated neurobiological architecture among psychiatric disorders, which today are largely distinguished between each other in phenomenology.

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.

Formal Thought Disorder: Convergent Science

Kircher and colleagues (2018) provide a thoughtful appraisal of both the nosology and neuroscience of formal thought disorder—a cordial (historically, a Schneiderian first-rank) feature of schizophrenia. They illustrate the validity of current rating scales assessments, the prediction and associations between cognitive impairments and formal thought disorder, and neurological findings. The latter include structural brain correlates—often related to superior temporal gyrus gray matter loss—and functional MRI changes. It is suggested that glutamatergic dysfunction is related to formal thought disorder. It is less clear that these constellations define formal thought disorder as a symptomatic correlate or a distinct neurobiological substrate.

Kircher T, Bröhl H, Meier F, Engelen J. Formal thought disorders: from phenomenology to neurobiology. Lancet Psychiatry 2018;5(6):515-526.

Breast Cancer and Schizophrenia

Zhuo and Triplett (2018) provide us with important, yet nevertheless conflicting, information on the putative relationship between breast cancer and schizophrenia. Twelve studies, totaling almost 126,000 female patients with schizophrenia, were evaluated and, overall, the results are mixed. In the aggregate, there is a heightened risk of breast cancer among females with schizophrenia. On the other hand, there is a wide variance across these studies, including several which showed a similar breast cancer rate as that of the general population. This is not an inconsequential issue, especially given the health access difficulties that patients with schizophrenia report and how they receive care later for their conditions. Moreover, there is a longstanding concern (not validated by incontrovertible research) that hyperprolactinemia in schizophrenia might be associated with a heightened risk for breast cancer.

Zhuo C, Triplett PT. Association of schizophrenia with the risk of breast cancer incidence: a meta-analysis. JAMA Psychiatry 2018;75(4):363-369.

Current Stimulation for Schizophrenia: Old Wine in a New Bottle?

We know that a sizeable minority of patients with schizophrenia continue to experience auditory hallucination even when pharmacotherapy—either as monotherapy or strategic polypharmacy—is optimized. About two decades ago, Ralph Hoffman showed that repetitive transcranial magnetic resonance (rTMS) was an effective and well-tolerated treatment for persistent auditory hallucinations in patients with schizophrenia who were recalcitrant to pharmacotherapy. As a modification of rTMS, transcranial direct current stimulation (tDCS) is a lower cost, portable, and potentially more direct approach to stimulation and this has recently been applied in direct and alternating forms (tACS-transcranial alternating current stimulation) to 22 patients with schizophrenia (Mellin et al., 2018). In a five-day study of tACS and tDCS versus sham stimulation, tACS showed the strongest effect on reducing hallucinations (1.31 size effects for tACS, 1.06 for sham and 0.17 for tDCS). The authors conducted a methodologically robust study, which turns out to be the first published study of tACS in schizophrenia. The procedure was safe and well tolerated. If confirmed in further studies of larger size and longer treatment—and observation—this approach could emerge as another option for patients with persistent auditory hallucinations.

Mellin JM, Alagapan S, Lustenberger C, Lugo CE, Alexander ML, Gilmore JH, et al. Randomized trial of transcranial alternating current stimulation for treatment of auditory hallucinations in schizophrenia. Eur Psychiatry 2018;51:25-33.

Provocative Stories Carry Weight

Haracz and colleagues (2018) provide a chilling account of females with schizophrenia, grappling with the distress of gaining weight while in treatment. While this qualitative study focused on (just) eleven women with schizophrenia/schizophrenia spectrum disorders, it still is compelling because it brings the experience of weight gain and consequences thereupon "to life." The findings are aggregated into two broad headings: "piling on the weight" and "its impact on my health." Components/experiences related to "piling on the weight" include: 1) gaining a lot of weight quickly, how quickly it came on, especially when there was not an antecedent weight problem; 2) the impact of drugs and the robust association of weight gain with most of these medications; 3) the impact of comfort eating to aggravate weight gain; and, 4) identifying the occurrence of weight gain.

The components/experiences related to "its impact on my health" include: 1) physical illness and the foreshadowing risk of diabetes; 2) reduced daily activities and energy level; 3) poor self-esteem; and, 4) stigma associated with weight gain. There's a ton (pun intended) of evidence showing the heightened rate and risks of obesity in people with schizophrenia and detailing the figures and trajectories thereupon. This compelling article is short on data yet powerful on human substance and experiences.

Haracz K, Hazelton M, James C. The "double whammy": women's experiences of weight gain after diagnosis and treatment for schizophrenia spectrum disorders. J Nerv Ment Dis 2018;206(5):303-309.

Genetic Predictions of Treatment Response in Schizophrenia

The understanding continues to grow of human conditioning to antipsychotic treatment, with respect to both antipsychotic response and adverse effects. Zai and colleagues (2018) review the field and point to advances in the prediction of treatment-related movement disorders and glutamate-related alleles and antipsychotic response. In a separate and large genome-wide association (GWAS) study, Yu and colleagues (2018) describe pharmacogenetic testing between two Chinese populations comprised of over 2,400 patients and 1,370 patients who were being treated over eight weeks with either risperidone, haloperidol, quetiapine, aripiprazole, or ziprasidone. Overall, five allele loci were found to be associated with treatment response, as evaluated on the PANSS rating scale. There was also evidence of selective alleles that were associated with treatment response to individual antipsychotic medications.

Zai CC, Tiwari AK, Zai GC, Maes MS, Kennedy JL. New findings in pharmacogenetics of schizophrenia. Curr Opin Psychiatry 2018;31(3):200-212.

Yu H, Yan H, Wang L, Li J, Tan L, Deng W, Chinese Antipsychotics Pharmacogenomics Consortium, et al. Five novel loci associated with antipsychotic treatment response in patients with schizophrenia: a genome-wide association study. Lancet Psychiatry 2018;5(4):327-338.

*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.*