Clinical News … putative antipsychotics … bipolar disorder and schizophrenia … cannabis and psychosis … genetics continuum … neurogenesis and schizophrenia … treatment-refractory schizophrenia … stigma …

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Update on Putative Antipsychotics

We have previously described the pharmacology and development of MIN-101, a putative antipsychotic (now bearing the name Roluperidone) without dopamine receptor binding while with marked affinity for serotonin 5-HT2A and sigma-2 receptors. Results of a 12-week study of Roluperidone for cognitive dysfunction in schizophrenia are now available online (see *Journal of Clinical Psychiatry*, online) and show a modest benefit in verbal fluency measure in patients receiving 32 mg of Roluperidone. This drug is under development through the clinical trials program of the biopharmaceutical company Minerva Neuroscience Inc.

Intra-Cellular Therapies Inc. (ITCI) is developing a putative antipsychotic, Lumateperone (ITI-007), which is a neuromodulator of dopamine (as a phosphoprotein modulator, with presynaptic partial agonism and postsynaptic antagonism at D2 receptors), serotonin, and glutamate receptors. ITCI is developing this agent as a potential treatment for several neuropsychiatric conditions beyond schizophrenia. Three studies in schizophrenia suggest efficacy and favorable tolerability of Lumateperone.

Brexpiprazole, approved for the treatment of schizophrenia and an adjunctive treatment for major depression, is also being considered in clinical trials as a potential agent to treatment agitation in patients with Alzheimer's disease. A 12-week clinical trial is now underway.

Neurocrine Biosciences has developed Valbenazine (known as Ingrezza) in the U.S. for the treatment of tardive dyskinesia. The biopharmaceutical company has also developed another agent Opicapone (known in Europe as Ongentys), which is available in Europe for the treatment of Parkinson's disease. It is noteworthy to observe this resurgence of drug development in movement disorders, as well as in their neuropsychiatric manifestations, including psychosis.

Risperidone is an established antipsychotic medication, available now in various formulations. The latest formulation of Risperidone as a long-acting injectable is an oral monthly drug (known as PERSERIS) delivered by subcutaneous route. This formulation was developed by the biopharmaceutical company Indivior. This formulation has been approved by the U.S. Food and Drug Administration based upon Phase 3 clinical trials in patients with schizophrenia.

Autism Spectrum Disorder and Maternal Nutritional Health: Implications of Schizophrenia

It is estimated that 1 in 5 mothers of offspring who later develop schizophrenia have experienced an obstetric complication during that pregnancy. Moreover, low folic acid and vitamin D deficiency in utero have been proposed as risk factors for schizophrenia. Given that context, the recent case-controlled Israeli short study of some 45,000 children by Levine and colleagues (2018) is noteworthy and illustrative. Maternal nutritional health with adequate folic acid and multivitamin supplementation were associated with a lower risk of later expression of autism spectrum disorder. This is an important observation with substantial public health implications.

Levine SZ, Kodesh A, Viktorin A, Smith L, Uher R, Reichenberg A, et al. Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring. JAMA Psychiatry 2018;75(2):176-184.

Bipolar Disorder and Schizophrenia: Coming Together or Coming Apart?

Among a remarkable array of genetic experts in serious mental illness, Ruderfer and colleagues (2018) utilized

a pooled database of some 54,000 patients in a case control design of the genetic interface between schizophrenia and bipolar disorder. Some 114 loci were highlighted in this large genome-wide association study (GWAS), with several points of convergence and with more distinct portfolio for bipolar disorder with psychotic features. This study is intriguing because it simultaneously upholds the proposition of a shared genetic profile between schizophrenia and bipolar disorder, as well as a distinction of genetic contribution across these conditions.

Ruderfer D, Ripke S, McQuillin A, Boocock J, Stahl EA, Pavlides JMW, et al. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell 2018;173(7):1705-1715.

Genetic Associations for Major Depressive Disorder: Implications for Schizophrenia

Howard and colleagues (2018) report 17 independent loci that were identified in a large (300,000 plus) genome-wide association study (GWAS) of depression from a British sample that includes broad and more constructed definitions of depression. Interestingly with respect to schizophrenia research, there is a marked similarity (to the untrained eye) between the Manhattan plot of this large GWAS in depression and the 108 loci Manhattan plot reported for schizophrenia. Also noteworthy were the genetic correlations between depression and schizophrenia, depression and bipolar disorder, as well as depression and attention deficit hyperactivity disorder. In contrast, there were no relationships identified between depression and autism spectrum disorder.

Howard DM, Adams MJ, Shirali M, Clarke TK, Marioni RE, Davies G, et al. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat Commun 2018;9(1):1470.

Genes and Birth: Additive Bed Fellows

Ursini and colleagues (2018) from the Lieber Institute report an overall 12-fold increased risk of schizophrenia among 5 genetic samples. The identified genes are related to placental function and are highly expressed in placenta from individuals that come from pregnancies with birth complications. This is an interesting and provocative finding that reminds us of the synergistic effect of individual risk factors for schizophrenia.

Ursini G, Punzi G, Chen Q, Marenco S, Robinson JF, Porcelli A, et al. Convergence of placenta biology and genetic risk for schizophrenia. Nat Med 2018;24(6):792-801.

Neurogenesis and Schizophrenia

Earlier basic science studies raised optimism that *ingesting* antipsychotic drugs—and lithium for bipolar disorders and antidepressants for depression—stimulates new cell growth. Liu and Howard review the literature and express optimism for future treatments, albeit as they add it is difficult to demonstrate directly that neurogenesis has/is occurring.

Liu KY, Howard R. Why has adult hippocampal neurogenesis had so little impact on psychiatry? Br J Psychiatry 2018;212(4):193-194.

Cannabis Use: A Gateway to Later Opioid Use and Psychosis Risk?

Convergent lines of evidence point to a higher rate of later psychosis among cannabis users. To some extent, this point has been lost politically since both medical marijuana and general cannabis use has become increasingly legalized across the U.S. A recent report by Olfson and colleagues (2018) adds to another dimension to this consideration, namely the relationship between cannabis use and later opioid addiction. In the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), three-year prospective longitudinal assessments show higher rates of opioid use (observed: expected rate of 5.87 at year one) among those with cannabis use, especially so among those with pain difficulties (observed: expected rate of 2.99). A very compelling report.

Olfson M, Wall MM, Liu SM, Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. Am J Psychiatry 2018;175(1):47-53.

Predictive Association Between Adolescent Cannabis Use and Subsequent Psychosis

The Northern Finland Birth Cohort of 1986 was used to track cannabis use, prodromal symptoms, and the emergence of florid psychosis in a large sample (over 7,300) initially evaluated at age 15–16 years and followed up to age 30 years. There was a powerful effect on cannabis use increasing the risk of psychosis by 6.5 times. This robust effect remained even with potential confounds of prodromal features (timing effect), parental psychosis (genetic effect), or other substance abuse (illicit drug effect). This is yet another confirmatory study of the risk of psychosis among individuals who use/misuse cannabis. Interestingly, there was a "dose response" effect between the extent of cannabis use and occurrence of psychosis.

Mustonen A, Niemela S, Nordstrom T, Murray GK, Maki P, Jaaskelainen E, et al. Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. Br J Psychiatry 2018;212(4):227-233.

Cannabis and Psychosis

Colizzi and Murray (2018) make a passionate plea for thoughtful deliberation on public policies on cannabis concerning emergent use of cannabidiol which may have non-addictive—as well as healing—properties. This article also nicely summarizes the current "state-of-play" of cannabis research.

Colizzi M, Murray R. Cannabis and psychosis: what do we know and what should we do? Br J Psychiatry 2018;212(4):195-196.

Cannabidiol and Schizophrenia: An Unlikely Treatment Option?

There is overwhelming evidence that cannabis use is associated with a higher rate of psychosis. Evidence of this association is derived from epidemiological and clinical studies, including follow-up of high-risk populations and direct pharmacological probe studies with functional neuroimaging. In this British study, McGuire and colleagues (2018) "buck" conventional wisdom and explore the impact of cannabidiol oil (cannabidiol without active THC) in patients with schizophrenia. In a well-conducted Phase 2, 8-week, placebo-controlled trial, the investigators did not detect harmful effects of cannabidiol oil and actually found some modest improvements especially in positive symptoms. While the results are interesting and one magnitude of potential effects are small (including trends toward improvements in cognition and overall functioning), this is an intriguing and highly innovative approach to augmenting antipsychotic efficacy in schizophrenia.

McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry 2018;175(3):225-231.

Cannabidiol Treatment for Schizophrenia

Boggs and colleagues (2018) report an interesting placebo-controlled, double-blind study of cannabidiol oil (dosed at 600 mg/day) in 41 people with schizophrenia over 6 weeks. In contrast to another earlier study by McGuire and colleagues reported above in ***CS***, this small yet meticulously conducted trial did not show efficacy in either positive or negative symptoms. This is an important and emerging perspective that will also inform a broader societal stance on the place of marijuana and its related compounds.

Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia: a randomized placebo controlled trial. Psychopharmacology (Berl) 2018;235(7):1923-1932.

Treatment-Resistant Depression: Definition, Detailing, and Implications for Refractory Schizophrenia

Anderson (2018) provides a thoughtful, clinically oriented review of the nosology of treatment-resistant depression (TRD), as well as treatment implications thereupon. While placebo effect is higher in depression, clinical trials methodology, duration, and number of medication trials are aspects of consideration similar to treatment-refractory schizophrenia. Interestingly, McAllister and colleagues (2018) go one step further to articulate another group of refractory patients—multiple-therapy-resistant major depressive disorder (MTR-MDD)—as a watershed to implement more "aggressive" and alternative therapies. This seems analogous to defining either clozapine eligibility or perhaps even the group of patients (ill defined) who turn out to be resistant to clozapine therapy. Time will tell whether the provocative nomenclature of MTR-MDD takes hold.

Anderson IM. We all know what we mean by treatment-resistant depression—don't we? Br J Psychiatry 2018;212(5):259-261.

Vulnerability of People with Schizophrenia to Being Victims of Violence

Dean and colleagues (2018) have conducted an important study with "stigma-busting" potential and messages that to some extent counteract the prevailing public opinion that people with schizophrenia are more likely to be perpetrators (rather than victims) of violence. This study, based upon a longitudinal register linked to police data on some 20 million people from Denmark between 2001 and 2013, calculated incidence rate ratios (IRRs) for being a victim of violence (criminal) event after the onset of mental illness. Overall, IRRs were 1.49 for males and 1.64 for females with any mental illness. The most compelling associations were for substance abuse and personality disorders, with schizophrenia having an IRR of 1.46. The IRR for schizophrenia in relationship to violent crime was higher at 1.76. While one can always question the generalizability of these Danish findings to U.S. society, the message is powerful.

Dean K, Laursen TM, Pedersen CB, Webb RT, Mortensen RB, Agerbo E, et al. Risk of being subject to crime, including violent crime, after onset of mental illness: a Danish National Registry Study using police data. JAMA Psychiatry 2018;75(7):689-696.

Stigma and Schizophrenia

Morris and colleagues (2018) report on the development of a 30-item (and shorter 10-item) scale to evaluate the experiences of stigma among the relatives of people with serious mental illness who had been ill for an average of 18 years. The scale taps into the following constructs that drive stigma among relatives: stereotyping, separation (isolation, exclusion), devaluation (feeling one's worth has been diminished because of mental illness), culpability (feeling self-guilt, blame), and status loss/discrimination (feeling of decline in social status, leading to inequalities).

Morris E, Hippman C, Murray G, Michalak EE, Boyd JE, Livingston J, et al. Self-stigma in relatives of people with Mental Illness scale: development and validation. Br J Psychiatry 2018;212(3):169-174.

*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.*