Clinical News … novel drugs and deliveries … Star Wars biotechnology … convergence science … neurobiology of Parkinson's disease … neurodevelopmental effects of cannabis … cell dormancy … bipolar and schizophrenia comorbidities … e-cigarettes … long-acting injectable antipsychotics …

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Novel Drugs and Deliveries

This issue of ***Clinical News*** highlights several innovations in the delivery of antipsychotic medications. Aripiprazole—an established antipsychotic—has now been approved by the U.S. Food and Drug Administration (FDA) as part of a novel formulation that should greatly aid the detection of medication adherence as well as inform biomarker development in schizophrenia. Otsuka Pharmaceutical has teamed up with Proteus Digital Health to develop a highly innovative tablet-sensor system that will be marketed as "Abilify MyCite." This combines the aripiprazole tablet, a wearable sensor as a patch, a tailored smart phone application, and a web-based portal. This system can detect and display—to patients, providers and relatives as needed—the in-vivo pharmacokinetic signal on aripiprazole once it has been taken orally by the patient. This is the first FDA-approved digital medicine system and this approach will likely have broad applicability throughout medicine.

Alkermes, the maker of aripiprazole lauroxil, has filed a New Drug Application (NDA) with the FDA regarding a nanocrystal dispersion product that would be given in conjunction with the first dose of intramuscular aripiprazole lauroxil. If deemed effective, this novel formulation would replace the current approach of initial oral supplementation of aripiprazole over the first three weeks of intramuscular drug therapy.

Indivior has filed an NDA for an investigational drug—RBP-7000—which is an extended-release system for the subcutaneous delivery of risperidone, given once a month, for the treatment of schizophrenia. Results of a Phase 3 study demonstrated efficacy for RBP-7000, with an adverse effect profile broadly similar to the intramuscular formulation of risperidone.

Cariprazine is now FDA approved as a maintenance treatment for schizophrenia. In a placebo-controlled trial of 72 weeks duration, 29.7% of cariprazine-treated patients relapsed compared to 49.5% of patients who were receiving a placebo.

Lurasidone was shown to be effective in children and adolescents with bipolar depression, based upon analysis from three pivotal studies.

Valbenazine was shown to sustain its moderating effect on tardive dyskinesia throughout the 42-week, double-blind, extension phase of a pivotal study of almost 200 patients receiving valbenazine. Valbenazine is a highly selective vesicular monoamine transporter 2 (VMAT-2) inhibitor, with negligible effects on other neurotransmitters. It is FDA approved for the treatment of tardive dyskinesia.

Lumateperone (ITI-007) is a postsynaptic dopamine D2 receptor antagonist and a presynaptic dopamine D2 partial agonist currently under investigation. It has an anti-inflammatory effect in rat brain, based upon preclinical studies. Additionally, in an initial six-week, open-label trial of lumateperone patients who were switched to this investigational drug fared well and the drug was well tolerated. Additional research on lumateperone is "in the works."

Reviva Pharmaceuticals is developing an investigational compound—RP5063—which may have benefit for cognitive impairment in schizophrenia. This investigational drug has a unique mixed agonist-antagonist profile centered on both dopamine and serotonin neuroreceptors. Its proposed pharmacologic selectivity might translate into a clinical selective effect of improving memory deficits in schizophrenia. Time will tell.

Star Wars Biotechnology Comes to Schizophrenia Research

Soliman and colleagues (2017) address a highly innovative and promising area of neuroscience—the potential of

stem cell research for schizophrenia. This article is a comprehensive overview of the science, the processes and procedures for cell culture and differentiation, and the application to distinct and current questions in schizophrenia research. The article also addresses the potential of this approach for other mental conditions. Regarding limitations, the article is less critical and does not convey the enormous investment of technical effort, as well as the considerable time (on average about four months) required to generate a cell line. It also requires highly specialized research personnel for this work. All that said, pluripotent stem cell research was advanced in several other areas (especially spinal cord regenerative medicine, cardiac regenerative medicine), and we have barely "scratched the surface" of this "star wars" biotechnology for schizophrenia research. Examples include doing drug screening, cell therapy, drug therapy response prediction, personalized medicine, and teasing out the pathobiology of schizophrenia.

Soliman MA, Aboharb F, Zeltner N, Studer L. Pluripotent stem cells in neuropsychiatric disorders. Mol Psychiatry 2017;22(9):1241-1249. doi: 10.1038/mp.2017.40.

Computational Medicine and Schizophrenia Research

The National Academy of Medicine has emphasized the need for us as scientists to adopt an ever more broad view and expertise for tackling chronic conditions. To that end, there is a convergence of science that increasingly brings together neuroscientists, biomechanical engineers, statisticians, informaticists, and other skilled people to address major problems in a concerted, synergistic manner. Krystal and colleagues (2017) espouse a similar convergence with the application of computational science to schizophrenia research. To a good extent, we have already been applying sophisticated computational approaches to neuroimaging and to EEG studies in schizophrenia. In prior issues of ***CS*** we have emphasized the application of computational approaches to study disease boundaries between schizophrenia and mood disorders. This is an interesting read.

Krystal JH, Murray JD, Chekroud AM, Corlett PR, Yang G, Wang XJ, et al. Computational psychiatry and the challenge of schizophrenia. Schizophr Bull 2017;43(3):473-475. doi: 10.1093/schbul/sbx025.

Neurodevelopmental Effects of Cannabis: Evidence from Rat Model

Several clinical studies suggest a critical effect and timing of cannabis use on the emergence of psychosis. Moreover, human imaging studies suggest longitudinal effects on gray and white matter based upon chronic exposure to cannabis. In this rat model, animals at various stages of brain development were exposed to a CB1 cannabinoid receptor stimulant. No effects were observed in late adolescence or adulthood. Prefrontal disinhibition was evident in rats sampled during early and mid-adolescence. Normalization studies thereafter implicated a function decline in GABAergic transmission that likely relates to pyramidal cell damage selectively during early adolescence with cannabinoid receptor stimulation. This elegant study has clear implications for our understanding of the effects and risks of cannabis use in humans.

Cass DK, Flores-Barrera E, Thomases DR, Vital WF, Caballero A, Tseng KY. CB1 cannabinoid receptor stimulation during adolescence impairs the maturation of GABA function in the adult rat prefrontal cortex. Mol Psychiatry 2014;19(5):536-543. doi: 10.1038/mp.2014.14.

Tumor Dormancy and Relapse: Implications for Neuroinflammation and Schizophrenia

The journey of understanding and discovery of immunological therapies for cancer also holds great hope for other medical conditions. Manjili (2017) demonstrates another area of immuno-oncology—tumor dormancy—that might be pertinent to our evolution of the immunological hypothesis of schizophrenia. Tumor dormancy represents the interplay between genetic risk, potential for mutations, and epigenetic changes over time that causes a shift from tumor dormancy to cancer relapse. These concepts have parallels in the apparently long "dormancy" of risk of psychosis/high risk of prodromal state to first onset of psychosis and subsequent relapse. This also provides a model for considering the role of neuroinflammation in the pathogenesis of schizophrenia.

Manjili MH. Tumor dormancy and relapse: from a natural byproduct of evolution to a disease state. Cancer Res 2017;77(10):2564-2569. doi: 10.1158/0008-5472.CAN-17-0068.

Dopamine, Parkinson's Disease and Schizophrenia

Parkinson's disease (PD) is an important and debilitating condition of direct relevance to schizophrenia, both because of the high comorbidity of hallucinations with frank psychosis and, most recently, the FDA approval of pimavanserin as the first-ever targeted antipsychotic for psychosis in PD. At neurochemical and biomarker development levels, there are also many similarities and opportunities for greater

understanding. In a provocative report by Zhong and colleagues (2017), midbrain neurons from pluripotent stem cells of PD patients showed in-vitro electrical firing activities as compared to a lack of firing in similar stem cells from normal subjects. The sensitivity of this test is intriguing and opens the door for a muscular biomarker for early detection of PD in advance of the clinical appearance of the historic features of PD. There are also several ongoing, early stem cell studies in schizophrenia. This is an encouraging research strategy. More to follow.

Zhong P, Hu Z, Jiang H, Yan Z, Feng J. Dopamine induces oscillatory activities in human midbrain neurons with parkin mutations. Cell Rep 2017;19(5):1033-1044. doi:10.1016/j.celrep.2017.04.023.

Parkinson's Disease: Prodromal Detection?

Oertel (2017) provides an authoritative review of the neurobiology and treatment of Parkinson's disease (PD). It is encouraging that several approaches—including rapid eye movement analysis—are under investigation to detect PD early, ideally in a presymptomatic state. The genetics of PD point to an important mutation in the gene for alpha-synuclein as a mechanism toward PD, leading to a "two-hit" mechanism and the Braak hypothesis that opens the door to consider biomarkers and prodromal PD. This has broadened approaches to the treatment of PD—from "standard" (yet ever-increasingly refined) dopaminergic drugs, active and passive immunization approaches, alpha-synuclein aggregation modulators and alpha-synuclein autophagia enhancers.

Oertel WH. Recent advances in treating Parkinson's disease. F1000Res 2017;6:260. doi: 10.12688/f1000research.10100.1.

The Bipolar Enigma

Hibar and colleagues (2017) report on a major, international collaborative study of brain morphology in over 6,500 people with bipolar disorder (mostly with bipolar I disorder). This is a huge undertaking involving 28 groups across the U.S., Europe and South America that have collated data from co-registered MRI scans over the past seven years. The results of this paper showed widespread cortical thinning that was strongly associated with longer duration of illness, though was not related to any subtype of bipolar disorder. Provocatively, the investigators also found increased cortical surface area with first-generation antipsychotics, in contrast with reduced surface area with second-generation antipsychotics. Antidepressant treatment was unrelated to cortical surface area size, while lithium therapy was associated with increased cortical thickness and antiepileptic medications were associated with reduced cortical surface area. Additionally, there was a prominent age x diagnosis effect, with greater age-related loss among older patients. Interestingly, younger, female patients had better preserved cortical tissue. This is a superb study with several important implications for early intervention and (judicious) use of medications in bipolar disorder.

Hibar D, Westive L, Doan N, Jahanshad N, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry 2017. doi: 10.1038/mp.2017.73. (Epub ahead of print)

Substance Abuse Comparison Between Homeless with Schizophrenia and Bipolar Disorder

Maremmani and colleagues (2017) report on the pattern of substance abuse among over 200 people from Canada with bipolar disorders and 94 with schizophrenia spectrum conditions. Abuse of the following drugs was greater among bipolar patients: cocaine (66% in bipolar patients [BP], 31% in schizophrenia spectrum patients [SS]), amphetamines (33% BP, 12% SS), opiates (42% BP, 12% SS), hallucinogens (20% BP, 4% SS), and tranquilizers (14% BP, 3% SS). There were similar rates of cannabinoids use, alcohol use, and very low rates of inhalants use between both groups. These are informative results, bearing in mind they are based upon self-reporting and are without any biological/laboratory confirmation.

Maremanni AG, Bacciardi S, Gehring ND, Cambioli L, Schutz C, Jang K, et al. Substance use among homeless individuals with schizophrenia and bipolar disorder. J Nerv Ment Dis 2017;205(3):173-177. doi: 10.1097/NMD.0000000000000462.

Smoking, Craving, and Antipsychotic Medications

Wehring and colleagues (2017) produced a provocative finding that patients on first-generation antipsychotics had lower rates of craving than patients on either clozapine or other second-generation antipsychotics. These results are surprising given the literature—albeit based largely on pragmatic studies—suggesting that newer antipsychotics might reduce craving and substance abuse among patients with schizophrenia.

Wehring HJ, Heishman SJ, McMahon RP, Liu F, Feldman S, Raley H, et al. Antipsychotic treatment and tobacco craving in people with schizophrenia. J Dual Diagn 2017;13(1):36-42. doi: 10.1080/15504263.2017.1288946.

E-Cigarettes: More or Less for Mental Health?

Gaznick and Anthenelli (2017) provide a comprehensive overview of the use patterns, risks and potential benefits of e-cigarettes among people with mental illness. This is a great need, covering also the "mechanics" and epidemiology of e-cigarettes, with about 4% of general adults in 2014 using e-cigarettes. There is, as yet, only modest evidence that e-cigarettes are a beneficial cessation strategy for nicotine addiction, and there is very scant information to date in patients with mental illness. Additionally, the risk profile among patients with mental illness has not yet been established.

Gaznick NV, Anthenelli RM. E-cigarettes and vapes: Do they work for smoking cessation and should we be recommending their use? Current Psychiatry 2017;16(5):30-34, 36-39.

Treatment of Schizoaffective Disorder with Long-Acting Injectable Antipsychotic

Bossie and colleagues (2017) report on a comparative analysis of once-monthly paliperidone palmitate in over 600 patients with schizoaffective disorder; 206 of whom were in the recent onset of their illness (≤5 years since first psychiatric diagnosis) and 461 patients with chronic schizoaffective disorder (>5 years). Both groups showed comparable reductions in relapse (30% in placebo group of chronic onset; 10% in medicated group of chronic onset; 35% vs. 18% in the recent-onset groups). Interestingly, the profile of adverse effects was similar between both groups.

Bossie CA, Turkoz I, Alphs L, Mahalchick L, Fu DJ. Paliperidone palmitate once-monthly treatment in recent onset and chronic illness patients with schizoaffective disorder. J Nerv Ment Dis 2017;205(4):324-328. doi: 10.1097/NMD.0000000000000646.

*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.*