Clinical News … biomarkers … OMICS … "cave fish" and schizophrenia … marijuana and psychosis … premature death and schizophrenia … mortality rates and schizophrenia … PRIDE study … weight loss drugs …

Peter F. Buckley, MD
Editor-in-Chief

New Drug Update …

Neurocrine Biosciences, Inc. has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for once-daily dosing of valbenazine (NBI-98854) in treating tardive dyskinesia. Valbenazine is a novel, highly selective inhibitor of one protein—VMAT2—that modulates dopamine release during nerve communication, showing little or no affinity for VMAT1, other receptors, transporters and ion channels. Neurocrine has received Breakthrough Therapy Designation from the FDA for valbenazine in the treatment of tardive dyskinesia.

Based on results from a long-term randomized withdrawal trial in adults with schizophrenia aged 18 to 65 years, the FDA has approved the labeling update of brexpiprazole (Rexulti) to reflect clinical data for maintenance treatment of schizophrenia.

Biotypes for Schizophrenia

Clementz and colleagues (2016) give a fascinating account of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP) research project, which we have highlighted before in ***Clinical News***. This primary paper describes the assessments and biomarker statistical analyses related to 711 patients with psychosis, 883 first-degree relatives, and 278 healthy control subjects. Given the comprehensive biomarker battery and complex multivariate statistics, the authors delineate three distinct neurobiologically derived clusters ("Biotypes") that are *not* reflective of traditional, symptom-based diagnostic categories. This is an important and provocative paper. Replication and extension of the biomarker profile will be essential.

Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, et al. Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry 2016;173(4):373-384.

"OMICS" Comes of Age

Delude (2015) provides a thoughtful overview of deep, genetic and "omics-based" phenotyping at a cellular level to understand diseases and disease processes. It is not specific to mental illnesses and schizophrenia, although the author clearly describes the great advances possible in mental health.

Delude CM. Deep phenotyping: the details of disease. Nature 2015;527(7576):S14-15.

Kraepelin Recasted?

Engstrom and Kendler (2015) produced a fascinating retrospective on Kraepelin's contribution to psychiatry. Parenthetically, they suggest that Kraepelin was less dogmatic about the position that mental illnesses are brain disorders and, apparently, he held up the importance of psychological factors. They also suggest that Kraepelin based his iconic distinctions in clinical nosology ("dementia praecox," "manic-depressive insanity") research solely on his clinical observations and that Kraepelin himself was self-effacing in recognizing this as a drawback. An interesting read.

Engstrom EJ, Kendler KS. Emil Kraepelin: icon and reality. Am J Psychiatry 2015;172(12):1190-1196.

What do "Cave Fish" Tell Us about Schizophrenia?

An interesting article in *Science* suggests that studying fish—specifically cave fish—might be useful for schizophrenia given the high genetic overlap between these fish and humans. Believe it or not, this article also details critical studies giving fluoxetine and even clozapine to these fish! Wow. Available at: www.sciencemag.org/news/2016/06/antisocial-cave-fish-may-hold-clues-schizophrenia-autism?utm_campaign=news_weekly_2016-06-24&et_rid=17042848&et_cid=584788

Visual and Sensory Electrophysiological Measurements as a Potential Biomarker for Schizophrenia

Andrade and colleagues (2016) report that a complex electrophysiological marker of visual adaption correctly determined group assignment in 13 of 15 patients with schizophrenia and 11 of 15 normal subjects. This is an impressive result. The paper is an interesting read. However, as previously emphasized, it is unlikely that any biomarker would have enough discriminatory power on its own to be clinically useful in detecting/diagnosing schizophrenia.

Andrade GN, Butler JS, Peters GA, Molholm S, Foxe JJ. Atypical visual and somatosensory adaptation in schizophrenia-spectrum disorders. Transl Psychiatry 2016 May 10;e804. doi: 10/1038/tp.2016.63.

Slaves to *DSM*: A Thoughtful Critique

Ken Kendler provides an erudite and provocative account of how, as mental health professionals, we have reified the criteria and concept of the *Diagnostic and Statistical Manual* (*DSM*). The paper is a great read and chronicles historical accounts of depression and the dissonance between these and the *DSM* criteria. As a byproduct, Kendler suggests that our profession has accepted the (erroneous) assumption that psychiatric diagnoses are actually synonymous with the *DSM* diagnostic criteria. While the article focuses on depression, the issues are very relevant to schizophrenia and related psychosis.

Kendler KS. The phenomenology of major depression and the representativeness and nature of DSM criteria. Am J Psychiatry 2016;173(8):771-780.

Brief Genetics Overview: "Forest from the Trees"

Michael O'Donovan provides a very nice overview of recent genetics findings—not just in schizophrenia—and the progress toward personalized medicine while it is focused on a "mega study:" Psychiatric Genomics Consortium (PGC). This is a succinct summary of where the field is at.

O'Donovan M. What have we learned from the Psychiatric Genomics Consortium. World Psychiatry 2015;14(3):291-293.

Differences between a Biomarker for Risk and one for Disease …

This is an interesting report of zeroing in on cell configuration and differential dysfunction among a subgroup of cells in the hippocampal of patients with Alzheimer's disease. It is also proposed to relate to genetic APOE hereditary risk.

Kunz L, Schröder TN, Lee H, Montag C, Lachmann B, Sariyska R, et al. Reduced grid-cell-like representations in adults at genetic risk for Alzheimer's disease. Science 2015;350(6259):430-433.

"Nonelderly Adults with Schizophrenia … Die at Approximately 3.5 Times the Rate of the General Population"

The title in quotations above is taken from Olfson and colleagues' paper (2015) that examined premature mortality in a Medicaid database between 2001–2007. Schizophrenia patients died prematurely from cardiovascular disease, from cancer (especially lung cancer), from respiratory infections and COPD, from suicide and from accidents (likely some of these were misclassified and were actually suicides). These findings, while always compelling, are not new, although the thoroughness and relative recency of the database analysis is noteworthy. The findings underscore the need to redouble efforts at targeted suicide prevention in schizophrenia and, especially, our efforts at medical management of cardiovascular and respiratory comorbidities in patients with schizophrenia.

Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015;72(12):1172-1181.

Is Metabolic Syndrome Disease or Geographically Specific?

Vancampfort and colleagues (2015) examine this distribution of metabolic syndrome (MS). The overall prevalence of MS was 32–36% across mental health conditions, with no significant difference in rates among patients with schizophrenia or bipolar disorder in extant studies. Geographical rates of MS varied from 25.4% in Brazil to 50.2% in Australia and New Zealand. In alignment with prior studies of rates of MS across patients receiving different antipsychotics, the highest rates were seen with clozapine and olanzapine therapy and the lowest rates comparative with aripiprazole with respect to first-generation antipsychotics.

Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 2015;14(3):339-347.

Marijuana and Psychosis: Converging Evidence and Public Policy

Two important papers—one a policy/scientific review and the other a fascinating study of marijuana's effect on dopamine receptor sensitivity—authored by Volkow and colleagues inform us about cannabis and the brain. The papers judiciously, yet firmly, juxtapose science and public policy as the debate about legalizing cannabis rages on. Very interesting reads.

Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry 2016;73(3):292-297.

Volkow ND, Wang GJ, Telang F, Fowler JS, Alexoff D, Logan J, et al. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proc Natl Acad Sci U S A 2014;111(30):E3149-3156.

PRIDE Study, Relapse and Reincarceration

Alphs and colleagues (2016) provide a further analysis of the PRIDE (paliperidone palmitate research in demonstrating effectiveness) study, a 15-month, open-label pragmatic trial of paliperidone palmitate compared with oral antipsychotics among 442 patients with schizophrenia. Paliperidone palmitate reduced relapse, hospitalization, and reincarceration among this relative population, which was characterized by recent criminal justice system involvement.

Alphs L, Mao L, Lynn Starr H, Benson C. A pragmatic analysis comparing once-monthly paliperidone palmitate versus daily oral antipsychotic treatment in patients with schizophrenia. Schizophr Res 2016;170(2-3):259-264.

Weight Loss Drugs: Implications for Schizophrenia

Khera and colleagues (2016) conducted an important meta analysis of 28 general population clinical trials of drugs—orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, liraglutide—that are FDA approved for obesity. The study revealed a median 23% of placebo participants achieving at least a 5% weight loss compared with 44% to 75% of individuals receiving one of the anti-obesity drugs. There was a high dropout rate (30%–45%), in part driven by adverse effects. The combined phentermine-topiramate option fared best. This new information gives context to our efforts with schizophrenia patients to manage weight gain.

Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA 2016;315(22):2424-2434.

*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.*