Clinical News … antipsychotic drug developments … new clozapine monitoring program … antipsychotic use in dementia … antipsychotic exposure during pregnancy … omega-3 … mental illness and premature death … biomarkers … RAISE study … smart phones for schizophrenia …

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Antipsychotic Drug Development Update

Reviva Pharmaceuticals reported cognitive improvements in mice studies testing the new putative drug RP5063.

Otsuka and Proteus Digital Health received a positive response from the U.S. Food and Drug Administration (FDA) for marketing a novel formulation of aripiprazole that is encased in an ingestible sensor that emits a signal once the tablet is digested. This innovation represents a potentially important step in advancing medication adherence in schizophrenia.

Vanda Pharmaceuticals has submitted to the FDA a supplemental New Drug Application (sNDA) for Fanapt (iloperidone) as a maintenance treatment of schizophrenia for adults—based upon the REPRIEVE relapse prevention study, which was previously highlighted in ***Clinical News***.

Acadia Pharmaceuticals submitted an NDA to the FDA in consideration of pimavanserin (Nuplazid) as a treatment for psychosis in Parkinson's disease. This agent was already designated by the FDA as a breakthrough therapy for Parkinson's psychosis, and so it is possible that the FDA review might be of shorter duration.

In the last ***Clinical News***, we highlighted a vesicular monoamine 2 transporter (VMAT2) inhibitor NBI-98854. Neurocrine Biosciences reported positive results of reduction in abnormal involuntary movements from a Phase 3, 6-week trial of this VMAT2. Additionally, Teva is studying another VMAT2 inhibitor, SD-809 (deutetrabenazine). This putative treatment for tardive dyskinesia (TD) was FDA-designated as a breakthrough therapy for TD.

New Monitoring Program for Clozapine Therapy

The FDA has collated all six clozapine register monitoring programs under a single new system—a shared risk evaluation and mitigation strategy (REMS) clozapine program. In addition to enhanced monitoring, the management of neutropenia is better clarified, including explicit recognition of use of—and monitoring of—clozapine in patients with benign ethnic neutropenia.

FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Safety announcement. September 15, 2015.

Antipsychotic Use in Dementia: Authoritative Review

Kales and colleagues (2015) provide a "tour de force" review of the treatment of persons with dementia, with a critical appraisal of the role of antipsychotics in the management of agitation. Importantly, they emphasize the greater effect of non-pharmacologic treatments than medications for psychological symptoms of dementia. That said, they review current information for each second-generation antipsychotic (SGA) and provide a synopsis of findings from the major CATIE-AD study. Additionally, other drugs under investigation include prazosin, brexpiprazole, scyllo-inositol, dextromethorphan, melatonin agonists, and even delta-9-tetrahydrocannabinol. Although still speculative, other options beyond SGAs are being sought, and there remains concern about antipsychotics in this population.

This overview by Kales and colleagues sits nicely with another important study examining mortality among patients with dementia by Maust and colleagues (2015). Their analysis is based upon Veterans Health Administration data between 2008 and 2009. Antipsychotic usage was associated with a higher mortality rate. The excess of mortality is reported as different by drug, at an expected-over-observed mortality risk of 3.8% for haloperidol, 3.7% for risperidone, 2.5% for olanzapine, and 2.0% for quetiapine. Interestingly, valproic acid had the highest association, with a 4.1% mortality risk. That said, these relationships are not necessarily causal and it could even be that those patients who are sicker—and most agitated—are the patients who are consequently treated with haloperidol or other agents.

Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015;350:h369. doi: 10.1136/bmj.h369.

Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry 2015;72(5):438-445.

Side Effects of Antipsychotic Medications—A Comprehensive Review

Correll and colleagues (2015) provided an authoritative review—augmented by information from several meta-analytic studies—of the interface between physical

conditions (especially diabetes, metabolic syndrome, and obesity) and antipsychotic medications. The review also covers the adverse effects of antidepressants and mood stabilizing drugs; good information to have on all of these drug classes all in the same, yet comprehensive, publication—especially since many of our patients are being treated simultaneously with these drugs. The list of current citations in this reference paper is also particularly helpful to readers.

Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14(2):119-136.

Antipsychotic Exposure during Pregnancy

Cohen and colleagues (2015) provide a detailed description of the National Pregnancy Registry for Atypical Antipsychotics (NPRAA). This important database was created at Massachusetts General Hospital in 2008 and presently has data on over 428 patients. The data are prospective and collected during the pregnancy. It will serve as an invaluable source to both clinicians and researchers to help better understand the risk-benefit profile of using antipsychotic medications during pregnancy.

In another complementary study, Sutter-Dallay and colleagues (2015) reported on a French study of over 1,000 pregnant women and found that risk of neonatal hospitalization was increased by exposure to antipsychotics during the pregnancy.

Cohen LS, Viguera AC, McInerney KA, Kwiatkowski MA, Murphy SK, Lemon EL, et al. Establishment of the National Pregnancy Registry for Atypical Antipsychotics. J Clin Psychiatry 2015;76(7):986-989.

Sutter-Dallay AL, Bales M, Pambrun E, Glangeaud-Freudenthal NM, Wisner KL, Verdoux H, et al. Impact of prenatal exposure to psychotropic drugs on neonatal outcome in infants of mothers with serious psychiatric illnesses. J Clin Psychiatry 2015;76(7):967-973.

Skunk and Schizophrenia: "Dirty Pot" Might be Riskier?

Di Forti and colleagues (2015) have done a fascinating and timely analysis from the British first episode of psychosis study. In England, especially London, marijuana is typically sold on the streets in many forms, including highly-contaminated high delta-9-tetrahydrocannabinol (THC). Among 410 patients between 2005–2011, use of high THC—contaminated marijuana ("dirty pot" that is colloquially called "skunk" in England)—was associated with a 5.4 times higher risk of psychotic disorders. Additionally, in this British catchment area study, there appeared to be a higher overall rate of psychosis. This is a very important and smart study that adds significantly to the public health issue and risks of legalizing marijuana use.

Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2015;2(3):233-238.

Omega-3 Can Ward Off Schizophrenia?

Pat McGorry and his colleagues in Melbourne, Australia have truly been trailblazers in the rapidly evolving area of early intervention in psychosis. Here again, they lead our field with a very interesting study … a follow-up over 6.7 years of subjects enrolled in a 12-week, placebo-controlled trial of omega-3 fatty acid for prodromal symptoms. Over the 6.7 year follow-up, just 4 of the 40 subjects receiving omega-3 treatment became psychotic, compared with 16 subjects among the others (n=40) who received placebo. The apparent effect of omega-3 on other psychotic symptoms and overall functioning was also evident among those patients who did not experience a psychotic break during the follow-up period. While it is hard to attribute "cause and effect" of a 12-week intervention over the subsequent seven years, the results are nevertheless provocative.

Moreover, in contrast to the Melbourne group's initial treatment study of antipsychotics in prodromal patients—which raised contentious "risk-benefit" considerations for our field in identifying and treating with powerful drugs a group of people of whom only a minority will become psychotic over the first three years—this study highlights an agent which is readily attainable and is of low risk. This is a key study and others will be completed shortly to further inform our field toward the most appropriate early interventions for psychosis.

Amminger GP, Schäfer MR, Schlögelhofer M, Klier CM, McGorry PD. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. Nature Communications 2015 Aug 11;6:7934. doi: 10.1038/ncomms8934.

Schizophrenia and Measles … What's Up?

In previous issues of ***Clinical News***, we have highlighted information on the rates of transition to psychosis of young people who present with prodromal features. Dr. Fusar-Poli gives a futuristic view of the current field and future opportunities in research to better delineate how we could truly prognosticate who would go on to develop florid psychosis. Dr. Fusar-Poli smartly draws the analogy between Koplik spots for measles (a pathognomonic early sign that the person has contracted measles and will shortly display florid symptoms of measles) and our search for a biological sign of incipient psychosis. The review cites two studies, each with approximately 8% rates of transition to psychosis, which is actually surprisingly low and is lower than reported in other

studies, including Dr. Fusar-Poli and colleagues' prior meta-analysis. Hence, the plea for "Koplik spots for psychosis."

Fusar-Poli P. The enduring search for the Koplik spots of psychosis. JAMA Psychiatry 2015;72(9):863-864.

Meta-Analysis of Mortality of Mental Illness Emphasizes Schizophrenia Premature Death

Walker and colleagues (2015) have conducted a comprehensive meta-analysis of 135 published studies on mortality in mental illness. At a macro level, the results highlight the greater mortality—estimated at a staggering 8 million people a year worldwide (14% of deaths worldwide) with attributable risk due to mental illness. The majority of deaths (67%) were due to natural causes, although 17.5% of deaths were attributable to unnatural (e.g., suicide, violence) causes. The highest mortality risk was observed for schizophrenia.

Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications. JAMA Psychiatry 2015;72(4):334-341.

Infections are Risky for Schizophrenia

We have previously highlighted studies showing a heightened risk of bacterial and viral infections in people with schizophrenia, observations that are congruent with evidence from other studies of immunological deficiencies in schizophrenia … that may, thereupon, predispose people to infections. This Danish registry study by Ribe and colleagues (2015) provides another complimentary vantage point on infections and schizophrenia, in that patients who had serious mental illness were at higher risk of death (52% higher) in the 30 days after an infection than individuals without mental illness. As in other such studies, it is a population, registry-based analysis and so causation cannot be derived from the association observed in this study.

Ribe AR, Vestergaard M, Katon W, Charles M, Benros ME, Vanderlip E, et al. Thirty-day mortality after infection among persons with severe mental illness: a population-based cohort study in Denmark. Am J Psychiatry 2015;172(8):776-783.

Are We Getting Our Biggest "Bang for the Buck"?

Bowen and Casadevall (2015) have produced a provocative analysis of research productivity, federal funding, and improved overall life expectancy between 1965 and 2014. The results are sobering, and have already caught the eye of federal policy makers and academicians alike. We have apparently been relatively stagnant in our progress to improve life expectancy, despite increases in resources and a voluminous increase in scientific publications. While "tying" life expectancy (also affected by a myriad of other variables, mostly social and behavioral) to federal research funding and scientific innovation might be "unfair," it is nevertheless a sobering report.

Bowen A, Casadevall A. Increasing disparities between resource inputs and outcomes, as measured by certain health deliverables, in biomedical research. Proc Natl Acad Sci U S A 2015;112(36):11335-11340.

Biomarkers … Call to Action

Two provocative viewpoints by Paulus, Pine and Leibenluft (2015) deny the need for more mechanistic approaches to biomarker development in mental health. These are interesting reads.

Paulus MP. Pragmatism instead of mechanism: a call for impactful biological psychiatry. JAMA Psychiatry 2015;72(7):631-632.

Pine DS, Leibenluft E. Biomarkers with a mechanistic focus. JAMA Psychiatry 2015;72(7):633-634.

Biomarker-Based Diagnosis for Schizophrenia?

We have highlighted a previous similar study in ***Clinical News***. Now this large collaborative group has coalesced data from several (actually quite dissimilar) studies which applied largely similar biological indexes—these indexes are broad biological measures that charted into 26 variables. The authors (Chan et al., 2015) arrive at a detection rate of 0.97 (area under the curve; AUC analysis) for schizophrenia and, of course, lower detection rate (AUC) of 0.82 in high-risk prodromal subjects, which increases to 0.90 (AUC) when prodromal symptoms are also added to the analysis. These findings are provocative and highlight the promise of personalized medicine for schizophrenia … time will tell.

Chan MK, Krebs MO, Cox D, Guest PC, Yolken RH, Rahmoune H, et al. Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset. Transl Psychiatry 2015 Jul 14;5:e601. doi: 10.1038/tp.2015.91.

"RAISE" Study Raises Treatment Expectations

The publication of two-year outcomes from the National Institute of Mental Health (NIMH) first episode of psychosis "RAISE" (Recovery after an Initial Schizophrenia Episode) program (Kane et al., 2015) has generated much interest and enthusiasm from our field. We have previously highlighted RAISE in ***Clinical News***. This publication by Kane and colleagues demonstrates that implementation of comprehensive care early in the course of schizophrenia can enhance clinical outcomes as well as, importantly, shorten the duration of untreated psychosis. These findings are important and generalizable since one study sample was drawn from thirty-four community mental health centers.

Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. Am J Psychiatry 2015 Oct 20:appiajp20151515050632. [Epub ahead of print]

Smart Phones for Schizophrenia?

Two recent studies (Firth et al., 2015; Miller et al., 2015) address the growing potential of mHealth and consumer-based technologies to provide enhanced communication between patients with schizophrenia and their providers. In a meta-analysis of twelve studies, Firth and colleagues dispel the myths that psychotic patients will not embrace this novel approach to communication because of paranoia, and they point out that 81% of patients surveyed in the last two years possess a smart phone.

In a complementary U.S.-based study, Miller and colleagues reported that 56% of patients with schizophrenia use text messaging, 48% use email, and 27% of patients access some social media site (most commonly Facebook) on a daily basis. Clearly, there are great opportunities to harness these communication modalities toward better care for people with schizophrenia.

Firth J, Cotter J, Torous J, Bucci S, Firth JA, Yung AR. Mobile phone ownership and endorsement of "mHealth" among people with psychosis: a meta-analysis of cross-sectional studies. Schizophr Bull 2015 Sep 22. pii: sbv132. [Epub ahead of print]

Miller BJ, Stewart A, Schrimsher J, Peeples D, Buckley PF. How connected are people with schizophrenia? Cell phone, computer, email, and social media use. Psychiatry Res 2015;225(3):458-463.

*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.*