Clinical News … Tamminga honored … antipsychotic drug developments … "dirty pot" … neonatal congenital malformation risks with antipsychotics … pharmacogenetics … RAISE program … exercise and schizophrenia …

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Tamminga Receives Prestigious APA Honor

Dr. Carol Tamminga has received the APA Research Award at the APA's recent fall meeting, IPS: The Mental Health Services Conference, in Washington, D.C. The presentation was made during a session on early identification and treatment of psychosis.

Tamminga, who is the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research at the University of Texas Southwestern Medical Center, published a paper in 2016 in the *American Journal of Psychiatry* identifying three neurobiologically distinct psychosis "biotypes" that appear to cross clinical diagnostic boundaries for schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. She and colleagues recruited 800 patients, 1,000 of their family members, and 250 healthy controls to complete a battery of neurocognitive and perceptual tasks. They then characterized the participants according to biomarkers corresponding to cognition, auditory stimulation, brain electrical function as measured by electroencephalogram, and oculomotor movements, among other variables.

Using statistical analyses, Tamminga and colleagues identified three neurobiologically distinct subgroups of psychosis, each including patients representing all *DSM* psychosis categories.

Congratulations, Carol, and thank you for all you do!

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

Update on Putative Antipsychotic Drugs

Rapid absorption loxapine (marketed as Adasuve) is used under a U.S. Food and Drug Administration (FDA) approved Risk Evaluation Mitigation Strategy (REMS). The FDA has recently approved modifications to this REMS; specifically, the removal of the need to have immediate on-site personnel and on-site resources for managing acute bronchospasm. The modification still requires REMS to have a short-acting bronchodilator with a nebulizer and inhalation solution.

Another modification under consideration by the FDA is the extension of the treatment duration/injection interval to a 2-month dosing interval for long-acting aripiprazole lauroxil (Aristada). This supplemental New Drug Application (sNDA) submitted by Alkermes requests extension of aripiprazole lauroxil to a two-month dosing regimen and is based on a recent pharmacodynamics study which showed that aripiprazole lauroxil at a dose of 1,064 mg delivered every 2 months achieved a therapeutic plasma level.

The FDA is also reviewing a sNDA to extend the approval and use of long-acting aripiprazole (Abilify Maintena) for the treatment of bipolar I disorder.

The ENLIGHTEN clinical trials program, launched by Alkermes, seeks to clarify the clinical efficacy and potential metabolic benefits of ALKS 3831—a putative antipsychotic that is a combination of olanzapine and samidorphan. Two key studies are a 4-week, placebo-controlled trial of ALKS 3831 and then a 6-month comparative trial with olanzapine in patients with schizophrenia. A Phase 1, 3-week metabolic study will also assess ALKS 3831, olanzapine, placebo in 50 healthy subjects, evaluating insulin sensitivity and metabolic indices. ALKS 3831 is also being studied in patients with schizophrenia who have comorbid substance abuse.

A recent 6-week study, conducted by Sunovion Pharmaceuticals Inc., showed that lurasidone at doses of either 40 mg/day or 80 mg/day is effective and generally well tolerated in adolescents (aged 13–17 years) with schizophrenia. The efficacy and tolerability profile of lurasidone in adolescents with schizophrenia was similar to that observed in prior studies of lurasidone in adults with schizophrenia. Additionally, another recent study addresses the dosing pro-

file of lurasidone in adult patients with schizophrenia. In a 6-week study—where patients were randomized to lurasidone at doses of 20 mg/day, 80 mg/day or placebo—patients who did not respond by two weeks at the 80 mg/day dose were then randomized to either continue at 80 mg/day or the higher dose of 160 mg/day for the remaining four weeks of the study. The results showed that low-dose lurasidone (20 mg/day) was not effective and so it was determined that 40 mg/day is the lowest effective dose. In patients who did not respond adequately to lurasidone at 80 mg/day for two weeks, increasing the dose of lurasidone to 160 mg/day was superior to continuing for four weeks at the 80 mg/day dose. This is an elegant, dose-finding study.

We previously described the clinical profile of another new antipsychotic, brexpiprazole (Rexulti). Based upon results from an interim analysis of a 36-week, randomized, withdrawal trial of brexpiprazole, the FDA approved a labeling change to include this new clinical data on the use of brexpiprazole as a maintenance treatment for schizophrenia.

Minerva Neurosciences, Inc., a biopharmaceutical company in Massachusetts, has reported the completion of a 12-week, open-labeled extension of a trial of the putative new antipsychotic MIN-101. MIN-101 is an interesting compound devoid of dopaminergic blockade, that has similar affinity for 5-HT2A and sigma 2 neuroreceptors.

Intra-Cellular Therapies has reported results of a 3-week, randomized, double-blind trial of ITI-007—an investigational antipsychotic drug—in patients with schizophrenia. The study showed efficacy, with a favorable tolerability profile for ITI-007.

Acadia Pharmaceuticals Inc., a biopharmaceutical company in San Diego, has begun a Phase 3, 6-week, randomized, double-blind study (ENHANCE 1) of pimavanserin as an augmentation strategy in schizophrenia patients who are unresponsive to antipsychotic medication.

"Dirty Pot" Raises Risk of Psychosis

Murray and colleagues (2016) provide a thoughtful and yet provocative overview of the relationship between cannabis use, purity of content, and risk of psychosis. Longitudinal studies of cannabis use—of variable duration of follow-up—suggest heightened risk with observed/expected ratios for psychosis between 1.1 and 4.5. This is particularly relevant now given the ever increasing legalization of marijuana use in the U.S. The paper highlights the detrimental public health impact of high potency and contaminated versions of cannabis.

Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry 2016;15(3):195-204.

On the Spectrum?

Robinson and colleagues (2016) provide an important analysis from the Psychiatric Genomics Consortium and other databases that relates to normal behavior and autism spectrum disorders. These results are provocative and suggest that there is overlap between genetic abnormalities/variations associated with autism spectrum disorder and social behaviors and communication skills. These data suggest a continuum of expression, genetically influenced of social and communication behaviors.

Robinson EB, St Pourcain B, Anttila V, Kosmicki JA, Bulik-Sullivan B, Grove J, et al. Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. Nat Genet 2016;48(5):552-555. doi: 10.1038/ng.3529.

Founding Father of Schizophrenia Genetics

Irving Gottesman passed away in June 2016. He was a towering figure in psychiatric genetics and helped mentor successive generations of psychiatric geneticists. He was greatly admired for his thoughtful perspectives and acknowledgments of the limitation of current psychiatric nosology.

New Imaging Ligand Holds Broad Promise

Synapses are ubiquitous in our brains … estimated at some 100 trillion synapses! The report by Finnema and colleagues (2016) describes a new radioligand that can visualize and quantify synapses using positron emission tomography. This could be of particular interest to schizophrenia research. There has been substantial research on synaptic pruning and dysfunction in schizophrenia.

Finnema SJ, Nabulsi NB, Eid T, Detyniecki K, Lin SF, Chen MK, et al. Imaging synaptic density in the living human brain. Sci Transl Med 2016;8(348):348-396 doi: 10.1126/scitranslmed.aaf6667.

New Registry Results on Neonatal Congenital Malformations Risk with Antipsychotic Medications

As outlined in a previous issue of ***CS***, Harvard University has set up a specific program evaluating the risk of exposure to psychotropic medications during pregnancy. This is a perplexing and highly emotive issue, and that has also been the case regarding exposure to antipsychotics. The Harvard group has now produced a compelling analysis of

medical data (over 1.356 million females) on exposure to antipsychotic medications during pregnancy. Birth defects—a composite measure—were observed in 3.27% of the comparison cohort, in 3.8% of neonates among mothers exposed to first-generation antipsychotic medications, and in 4.4% of neonates among mothers treated with second-generation antipsychotics. While numerically different, their risks are similar statistically and there were no differences among the various antipsychotic medications—with the exception of risperidone, which was associated with a small but still significant increase in cardiac congenital anomalies. While the authors attempted to control for physical and psychiatric comorbidities in their analyses, this is hard to do in this kind of pharmacovigilance study.

Huybrechts KF, Hernandez-Diaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry 2016;73(9):938-946. doi: 10.1001/jamapsychiatry.2016.1520.

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Antipsychotic Use in Nursing Homes Declined

In 2014, the Centers for Medicare & Medicaid Services (CMS) set a goal of a 25% reduction of antipsychotic drug use in nursing homes. A recent CMS report indicates that there was—as a result of this National Partnership—a notable 27% reduction in the use of antipsychotics, now to a national prevalence of antipsychotic use at 17.4% during the first quarter of fiscal year 2015. This impressive effort was not designed to minimize use in schizophrenia or related conditions but rather to diminish "off label" use given the concerns of potentially heightened mortality with use of antipsychotic medications in the elderly.

https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/SC-Letter-16-28-Partnership-Update-Report.pdf.

Pharmacogenetics: A Cautionary Tale

Jose de Leon (2016) provides a personalized and also broad account of the evolution of pharmacogenetics. Dr. de Leon posits that the clinical translation of pharmacogenetics has been curtailed and variable. He also highlights the "hype" that has been part of these developments. His account, albeit personalized, is a provocative counterpoint to prior articles about the promise of pharmacogenetics for the treatment of mental illness, including schizophrenia.

Jose de Leon. Pharmacogenetic tests in psychiatry: from fear to failure to hype. J Clin Psychopharmacol 2016;36(4):299-304.

Shared Decision-Making and Optimizing Antipsychotic Pharmacotherapy: The RAISE Connection Program

Kreyenbuhl and colleagues (2016) provide an important analysis of medication practices for patients with first-episode psychosis, based upon the RAISE program. The recommendations for dosing and drug selection, as established early on in RAISE, were largely held to during patient involvement. This study concludes that the shared decision-making process that was part of RAISE drove this outcome.

Kreyenbuhl JA, Medoff DR, McEvoy JP, Smith TE, Hackman AL, Nossel IR, et al. The RAISE Connection Program: psychopharmacological treatment of people with a first episode of schizophrenia. Psychiatr Serv 2016;67(12):1300-1306.

Surgeon General's Report on Substance Abuse

Surgeon General Dr. Vivek Murthy has highlighted the remarkable prevalence and profound societal impacts of substance abuse in America (https://addiction.surgeongeneral.gov). One in seven people have addiction problems—21 million people—and this figure is larger than all of cancers. The impact of substance abuse exceeds that of diabetes ($245 billion per year) and is a staggering $442 billion cost. The high prevalence rates are based upon the 2015 National Survey on Drug Abuse and Health. Fatal heroin overdoses have spiraled over the past few years. Heroin overdoses have tripled over the last three years.

WOW … Exercise Helps People with Schizophrenia

Two recent studies (Yoon et al., 2016; Browne et al., 2016) that appeared in *The Journal of Nervous and Mental Disease*—accompanied by a delightful editorial by our good friend, John Talbott, MD—point out, nicely to a granular level, the benefit of exercise and walking ("WOW—Work Out by Walking") for people with schizophrenia. In addition to reported benefits in cardiorespiratory and interpersonal functioning, these studies demonstrate that patients with schizophrenia with appropriate instruction can be motivated and sustain exercise performances over time.

Yoon S, Ryu JK, Kim CH, Chang JG, Lee HB, Kim DH, et al. Preliminary effectiveness and sustainability of group aerobic exercise program in patients with schizophrenia. J Nerv Ment Dis 2016;204(9): 644-650.

Browne J, Penn DL, Battaglini CL, Ludwig K. Work out by walking: a pilot exercise program for individuals with schizophrenia spectrum disorders. J Nerv Ment Dis 2016;204(9):651-657.

Talbott JA. The importance of earnest (exercise). J Nerv Ment Dis 2016;204(9):643.

Integrated Community Mental Health Care

Thornicroft and colleagues (2016) illustrate the considerable progress in community programming (highlighting mostly European health systems) toward better integration of mental health and physical health services. They also present an important conceptual framework for modern day community mental healthcare. They present ten proposals to advance integrated and collaborative care. This is an important, global policy synthesis.

Thornicroft G, Deb T, Henderson C. Community mental health care worldwide: current status and further developments. World Psychiatry 2016;15(3):276-286.

*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.*