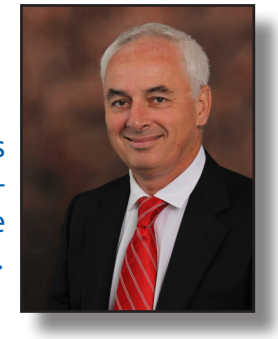
Clinical News … "dopamine-lite" putative antipsychotics … stem cells … cannabis and relapse … nicotine use disorder … long-acting injectable antipsychotics … low fecundity yet persistence of psychosis … antipsychotic use over course of illness … cognitive remediation … fatty acids and psychosis …



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Putative/New Antipsychotics

The U.S. Food and Drug Administration (FDA) has approved lurasidone for use in adolescents (aged 13–17 years) with schizophrenia. The FDA's extension of lurasidone to the adolescent population was based on the positive efficacy results from a six-week, placebo-controlled trial of 40 or 80 mg/day. Both doses of lurasidone were effective.

Sunovion (the company that makes lurasidone) also has another putative antipsychotic, SEP-363856, under development. This is an interesting compound that is devoid of dopamine D2 antagonism. We will keep an eye on this as it unfolds.

MIN-101 is another putative antipsychotic—under development by Minerva Neurosciences Inc.—that is without dopamine D2 antagonism. The agent also has antagonism at sigma 5-HT2A and alpha-1-adrenergic receptors. Recent results from a 12-week study of patients with negative symptoms of schizophrenia demonstrated efficacy for negative symptoms, as well as modest improvement in cognitive function, especially for verbal fluency and in a motor task measurement.

Continuing the focus on negative symptoms and "dopamine-lite" putative antipsychotic drugs, Arcadia Pharmaceuticals has launched a Phase 2, 26-week trial of pimavanserin in patients with schizophrenia who have marked negative symptoms. Pimavanserin is already FDA approved for use in patients with Parkinson's disease who have delusions or hallucinations.

We have previously described the compound ITI-007—a putative antipsychotic of complex pharmacology with partial 5-HT2A antagonism, phosphoprotein modulation at dopamine receptors, glutamatergic modulation, and dopamine D2 presynaptic agonist and post-synaptic antagonism, and serotonin reuptake inhibition. Results of comparative studies with risperidone demonstrate efficacy and tolerability of ITI-007.

Teva Pharmaceuticals Industries Ltd. has a putative agent—SD-809 (deutetrabenazine)—for the treatment of tardive dyskinesia. The FDA has received a new drug application for this agent and will proceed with a priority review.

Otsuka and Lundbeck have presented results of a 52-week trial of long-acting injectable aripiprazole in 133 patients with bipolar disorder. Treatment-emergent adverse effects did not differ between aripiprazole and placebo. The long-acting form of aripiprazole was effective in these patients.

Relationships Between People with Mental Illness: Like Marries Like?

Nordsletten and colleagues (2016) provide a provocative analysis of mating patterns from a population-based Swedish cohort. While one could say "this is just Swedish and not relevant to us in the U.S.," in reality this likely generalizes. Interesting, mating patterns—"like marries like"—were not seen for diabetes and other physical conditions. They were, however, seen in and between eleven major psychiatric categories. The genetic as well as social implications of this are significant.

Peyrot and colleagues (2016), from Amsterdam, the Netherlands, also model the assortative mating patterns among people with various mental illnesses. This analysis confirms the earlier study by Nordsletten and colleagues from a different epidemiological sample that people with mental illness mate among each other. The paper also addresses the conceptual question as to why, from a genetic perspective, mental illness persists even though there is well documented reduced fecundity among patients with mental illness.

Nordsletten AE, Larsson H, Crowley JJ, Almgivst C, Lichtenstein P, Mataix-Cols D. Patterns of nonrandom mating within and across 11 major psychiatric disorders. JAMA Psychiatry 2016;73(4):354-361.

Peyrot WJ, Robinson MR, Phenninx BW, Wray NR. Exploring boundaries for the genetic consequences of assortative mating for psychiatric traits. JAMA Psychiatry 2016;73(11):1189-1195.

Post Mortem Genetic Analysis

Fromer and colleagues (2016) report from the Common Mind Consortium (CMC), a public-private partnership that facilitates genetic analyses of post mortem brain tissue for psychiatric disorders. In a sample from over 250 prefrontal cortex tissue, 26 of 108 previously identified genetic loci were highlighted—with a focus on genes related to neurodevelopment and cell migration. In addition to the complementary value of these findings, this report illustrates the utility of this complex, public-private partnership to elucidate the molecular mechanisms of schizophrenia.

Fromer M, Roussos P, Sieberts SK, Johnson JS, Kavanagh DH, Perumal TM, et al. Gene expression elucidates functional impact of polygenic risk for schizophrenia. Nat Neurosci 2016;19(11):1442-1453.

Stem Cells and Genetic Programming in Schizophrenia

Roussos and colleagues (2016) reprogrammed cultured fibroblasts from four patients with schizophrenia and six normal subjects to create human-induced pluripotent stem cell (hiPSC) neurons and then explored potassium chloride-induced depolarization in these neurons. In an activity-dependent gene expression analysis, there is a different expression among schizophrenia-derived hiPSC. This is also reflected in the different patterns of depolarization. Very interesting read.

Roussos P, Guennewig B, Kaczorowski DC, Barry G, Brennand KJ. Activity-dependent changes in gene expression in schizophrenia human-induced pluripotent stem cell neurons. JAMA Psychiatry 2016;73(11):1180-1188.

Cannabis and Relapse in Schizophrenia

Schoeler and colleagues (2016) evaluated the impact of exposure to cannabis in the first two years of psychosis related to hospitalization among 220 patients with first-episode psychosis. Although the study was based upon a retrospective self-report of cannabis use, the findings suggest a dose-dependent effect of cannabis on a relapse over the early course of schizophrenia. The results are intuitive and actually useful to clinicians to be able to provide supportive evidence for patients and families of the risk of continued cannabis use after a patient's first psychotic episode.

Schoeler T, Petros N, Di Forti M, Pingault JB, Klamerus E, Foglia E, et al. Association between continued cannabis use and risk of relapse in first-episode psychosis: a quasi-experimental investigation within an observational study. JAMA Psychiatry 2016;73(11):1173-1179.

Nicotine Use Disorder: Heightened Comorbidities

The high rates of smoking among people with schizophrenia are well known, with various reasons from self-medication to genetic vulnerability being proposed to explain this robust association. In an analysis of the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Chou and colleagues (2016) noted higher rates (observed to expected ratios between 1.3 and 2.5) for nicotine use disorder and depression, bipolar (I and II) disorder, generalized anxiety disorder, panic disorder, post-traumatic stress disorder and several personality disorders (schizotypal, borderline, and, of course, antisocial personality disorders). Among the entire NESARC sample, lifetime nicotine use disorder was recorded at 27.9%. The high rates give context to the well-known higher rate among patients with schizophrenia.

Chou SP, Goldstein RB, Smith SM, Huang B, Ruan WJ, Zhang H, et al. The epidemiology of DSM-5 nicotine use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. J Clin Psychiatry 2016;77(10):1404-1412.

Long-Acting Injectable Antipsychotics: Scientific Evidence and Pragmatic Experiences

Long-acting injectable (LAI) antipsychotics have been used conspicuously less in the U.S. mental health system than among European counterparts. Correll and colleagues (2016), in a comprehensive and current synthesis of available information, provide a very useful overview, with cogent recommendations of when and how to use LAI antipsychotics. The review covers studies of several design strategies—"standard" randomized controlled clinical trials, mirror image studies, and cohort studies, each of which offers a different and complementary vantage point. Studies that examine healthcare costs, nonadherence and incarceration are also reviewed. The review also alludes to research and educational recommendations, specific recommendation regarding patient eligibility and treatment selection, and overall treatment guidelines.

Correll CU, Citrome L, Haddad PM, Lauriello J, Olfson M, Calloway SM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. J Clin Psychiatry 2016;77(suppl 3):1-24.

Are Antipsychotics Really Needed for All Patients over Long-Term Care?

Robin Murray and colleagues (2016) provide a thoughtful yet quite provocative appraisal of the perceived risk-benefit ratio of long-term use of antipsychotic medications in patients who are early in the course of schizophrenia. The appraisal is erudite and focuses on potentially detrimental effects of long-term antipsychotics on dopamine supersensitivity and physical health, as well as the literature showing some people can do well in their recovery off medica-

tions. The article concludes that every patient's situation should be evaluated on its own merits.

Murray RM, Quattrone D, Natesan S, van Os J, Nordentoft M, Howes O, et al. Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics? Br J Psychiatry 2016;209(5):361-365.

Another Meta-Analysis Shows Clozapine's Superiority over Other Antipsychotics for Treatment-Refractory Schizophrenia

Siskind and colleagues (2016) evaluated clozapine's efficacy over first- and second-generation antipsychotic medications from a variable group of twenty-one published trials on clozapine. Clozapine was superior—especially for positive symptoms—and the efficacy "number-needed-to-treat" was 9. On the other hand, the authors highlight the adverse effects profile and they conclude that if there is inadequate response to clozapine after six months, then a trial of a different medication with a more favorable adverse effect profile is warranted. Noteworthy, the "number-needed-to-harm" for clozapine's side effects includes 7 for tachycardia, 7 for sedation, 12 for constipation, and 17 for seizures.

Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2016;209(5):385-392.

High Doses of Olanzapine or Risperidone for Inadequate Treatment Response

Sakurai and colleagues (2016) report on a 4-week study of over 100 patients with schizophrenia who had inadequate prior response to either olanzapine (at 10 mg) or risperidone (at 3 mg) in which patients were randomized to either continue on their present medication dosage or double the dosage. The outcomes were similar with both strategies, although the duration of study is too short to be conclusive. Interestingly, lower olanzapine blood levels were associated with better outcome. Not clear what the implications are of this study.

Sakurai H, Suzuki T, Bies RR, Pollock BG, Mimura M, Kapur S, et al. Increasing versus maintaining the dose of olanzapine or risperidone in schizophrenia patients who did not respond to a modest dosage: a double-blind randomized controlled trial. J Clin Psychiatry 2016;77(10):1381-1390.

Cognitive Remediation: Staying the Course

Dillon and colleagues (2016) provide an important and informative contribution to the role and feasibility of cognitive remediation (CR) for the treatment of schizophrenia. This 8-week study examined how patients "stay the course" and adhered to a computerized CR program. Just 46% of patients completed the CR program. Cognitive impairment and/or negative symptoms did not drive the adherence rate. These findings speak to the generalizability of CR in clinical practice.

Dillon R, Hargreaves A, Anderson-Schmidt H, Castorina M, Corvin A, Fitzmaurice B, et al. Adherence to a low-support cognitive remediation training program for psychosis. J Nerv Ment Dis 2016;204(10):741-745.

Can Fatty Acids Head Off Psychosis?

A formative, earlier study by Amminger and colleagues (2010) produced exciting results that omega-3-fatty acids could obviate the later occurrence of psychosis among an Australian group of patients that were high risk for developing psychosis. In keeping with the rigor of science ("replication is compelling"), the same group conducted a replication study called NEURAPRO—a double-blind, placebo-controlled study of long chain ω-3 polyunsaturated fatty acids (PUFAs) in combination with cognitive behavioral therapy (CBT) case management over 6 months. Among 304 adults at high risk for psychosis, transition (to psychosis) rates at 6 months were 6.7% (versus 5.1% in the control group), and at 12 months were 4.5% (versus 11.2% among controls). While ostensibly a failure-to-replicate study, the study (while very large for this population) might still have been underpowered and also the CBT likely also influenced the results, especially since the conversion seems a little lower than historical trends.

Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010;67(2):146-154.

McGorry PD, Nelson B, Markulev C, Yuen HP, Schäfer MR, Mossaheb N, et al. Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. JAMA Psychiatry 2016;74(1):19-27.

*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.*