Highlights from the Biennial International Congress on Schizophrenia Research (ICOSR), March 24–March 28, 2017

Hakon Heimer [1]

Abstract

The 2017 International Congress on Schizophrenia Research, held in San Diego, California (March 24–28, 2017), attracted over 900 attendees from 34 countries. With the gracious assistance of Congress president James Meador-Woodruff, we bring you the following reports on the prospects for new drugs to treat schizophrenia.

The Prospects for New Drugs to Treat Schizophrenia

The ICOSR meeting had its usual mix of basic and clinical science, and among the clinical researchers there was a sense of taking stock of the disappointing results of the past few decades and trying to find more modest advances in what is available today. The topic came up in the opening plenary lecture on Saturday (March 25) by Josh Gordon, director of the U.S. National Institute of Mental Health. Gordon acknowledged that neither genetic research nor the study of complex circuits was likely to produce new treatments any time soon, and he said he was willing to entertain any novel ideas for new drug development. But he also said, "The path forward to better treatments, in the short term, is to use the treatments we have in a more efficacious way and make them available to more people."

Audience members pushed back on this limitation, suggesting, for example, that evidence of immune system involvement in psychotic disorders, and the psychiatric symptoms found in immune system disorders, warranted drug development efforts in this area. However, Gordon said he was not interested in just trying out various immune system drugs in mental illness without some knowledge of what targets were being engaged.

An attendee from a pharmaceutical company opined that we can't just wait on genetics, but that we need to have an iterative process in drug development, going back and forth between basic science and drug development, especially focusing on biomarkers and human studies.

How Far Have We Come?

On Monday, March 27, John Kane took on the topic "The Pharmacologic Treatment of Schizophrenia: How Far Have We Come?" in his plenary talk. He began with a mention of the Recovery After an Initial Schizophrenia Episode (RAISE) study that he led. While the study demonstrated that early, coordinated specialty care for psychosis can in theory be effected in the United States, Kane noted that it was disappointing that there was no effect of such care on hospitalizations, despite the expert advice on optimal medication that the RAISE study provided to participating clinics. This is not entirely unexpected, as people in the early stages of psychosis generally don't like the medications and are likely to stop using them.

[1]Schizophrenia Research Forum, Providence, RI

Address for correspondence: Hakon Heimer, Executive Editor, Schizophrenia Research Forum, 470 Lloyd Avenue, Providence, RI 02906 Fax: 401-273-6035; E-mail: hakon@schizophreniaforum.org

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A message from the ICOSR president …

We are delighted that Hakon Heimer has provided readers of *Clinical Schizophrenia & Related Psychoses* this detailed synthesis on the prospects for new drugs to treat schizophrenia sessions from the Seventeenth Biennial International Congress on Schizophrenia Research recently held in San Diego, California, March 24–March 28, 2017. Scientists representing the broad range of disciplines involved with discovery in schizophrenia gathered at the Congress to exchange data, techniques and ideas. Their cutting-edge experimental work stimulated lively discussion and open exchange of ideas toward a better understanding of the neurobiology and treatment of schizophrenia. We were particularly pleased that the Congress also provided a special opportunity for introducing young investigators to the colleagueship of the schizophrenia scientific community.

Understanding schizophrenia is a leading challenge for medical research today. We are delighted that the Congress plays a formative role in advancing new knowledge concerning this disabling condition. As you read this excellent report, we hope that you share the same excitement that we have concerning our field's development.

James Meador-Woodruff
President
International Congress on Schizophrenia Research

While there is a subset of patients who can discontinue their medications and fare well, Kane said that we still can't predict who will have success with this approach and who will relapse. He discussed a number of studies that show long-acting injectables being better at preventing relapse than their oral equivalents, and suggested that they should be offered in the early phase of the illness. Another approach that could help people in the early stages of psychosis is finding biomarkers that predict who will do better on which medication.

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Nonetheless, Kane asked the field to reflect on the fact that for most antipsychotic drugs on the market, the number needed to treat (NNT, a measure of drug effectiveness) was about three, signifying at least a satisfactory drug response in most people.

Kane also extolled the advantages of clozapine. Although some studies have failed to find it superior to other drugs, Kane said that many more studies have put it ahead of the competition, enough to suggest that clozapine should also be an option for people in the early stages of psychosis.

Kane touched on tardive dyskinesia (TD), the sometimes permanent movement disorder caused by older antipsychotic drugs. Even some of the newer drugs, particularly the partial dopamine agonists, can cause this side effect. However, two new drugs—deutetrabenazine and valbenazine—may soon be available to treat TD, giving psychiatrists more options in choosing an antipsychotic medication.

Nonetheless, Kane admitted that the field did not have an easy path to new medications. The failure to capitalize on the decades-old discovery that clozapine can be more effective than other drugs, albeit with a different suite of side effects, demonstrates the difficulty of developing new drugs. Unfortunately, major pharmaceutical companies have largely chosen to abandon mental illness research—indeed, most central nervous system disorders. The biological complexity is partly to blame, but Kane also pointed to other factors that have plagued clinical trials, including the difficulty of recruiting study subjects, leading to non-ideal patient populations; high placebo response rates, leading to failed studies; and, the lack of biomarkers or other ways to detect subpopulations who might do better than others on a given drug.

Clinical Trials Update

An afternoon symposium on Saturday, March 25—an update on some of the recent clinical trials of medication or supplements in psychotic disorders—provided many cases to buttress Kane's points.

Several studies were derived from the hypothesis that metabolic abnormalities contribute to psychosis, and that supplementation with omega-3 fatty acids (O-3FAs) might have beneficial effects. Paul Amminger of the University of Melbourne in Australia presented secondary analyses from

the high-profile NEURAPRO study of O-3FAs to prevent conversion to psychosis. However, these data were on antidepressant use in that study, which had failed to replicate an earlier report of O-3FAs' protective effects, but the authors noticed that 60% of study participants used antidepressant medications at some point during the trial. There were dose increases in many cases, which might have helped counteract an effect of the O-3FAs; however, in further analyzing the data, Amminger and colleagues did not find that those patients who took antidepressants had a lower risk of conversion to a psychotic disorder. In Amminger's view, this clearly refutes the hypothesis that antidepressants can reduce or slow the transition to psychosis in this population, whether or not they have beneficial effects on other symptoms or functionality.

Kristin Cadenhead of the University of California, San Diego, presented the results of a similar study of O-3FAs in a subset of subjects from the North American Prodrome Longitudinal Studies (NAPLS). In their six-month trial of 127 clinical high-risk patients, the researchers found no significant decrease in conversion to psychosis for patients who took O-3FA supplements. However, they noted cardiometabolic abnormalities already at baseline in their young study participants, and found significant evidence that those with low O-3FAs in their diet were statistically more likely to have converted by the end of the study. They are now looking into adherence to taking the supplements, since the nonadherent group also had increases in serum cholesterol and serum triglyceride.

Another report from the NAPLS O-3FA trial, presented by Skylar Kelsven of San Diego State University, focused on the baseline metabolic characteristics of the cohort, specifically, comparing Latino and non-Latino patients. The Latino patients were found to have significantly higher rates of metabolic syndrome, elevated serum glucose, greater obesity, and dyslipidemia. They also had higher levels of omega-6 to omega-3 fatty acids, considered to be a less healthy ratio. Higher serum glucose and body mass index were significantly related to poorer clinical symptoms.

Mixed Medication Bag

For session chair Philip Harvey of the University of Miami, the results presented were a mixed bag, but he singled out one that he thought stood out: "The results for the (Newron Pharmaceuticals) sodium channel blocker were very interesting and innovative," he said.

Ravi Anand of Newron, headquartered near Milan, Italy, presented the animal and human clinical trial data on evenamide, which blocks voltage-gated sodium channels, but only of hyper-excited neurons. The drug inhibits glutamate release, and does not cause the severe side effects of earlier, less specific sodium channel antagonists. Because of animal data, the company feels that the best use of the drug is to combine it with current antipsychotic drugs. In a four-week Phase 2 study, evenamide, added onto risperidone in low-symptom patients, was well tolerated and did not increase side effects. Although the study was not structured to evaluate efficacy, evenamide reduced PANSS positive scores significantly or near significantly on each clinic visit. The next step is a real efficacy study, especially in early stages of the illness, said Anand.

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David Daniel of Bracket Global LLC in Wayne, Pennsylvania, presented data from a post-hoc analysis of cariprazine. The drug, sold as Vraylar in the United States and Canada and being studied in Europe, was licensed to Allergan by Gedeon Richter and approved for bipolar disorder and schizophrenia in the U.S. in 2015. As described in a recent article in *The Lancet* (Németh et al., 2017), the partial agonist at dopamine D3 and D2 receptors showed an advantage over risperidone in the treatment of negative symptoms. The effect was seen at the last assessment of the six-week study, and Daniel suggested that the trial may have been too short for a proper evaluation. He also acknowledged that the study population had been selected for experiencing an acute schizophrenia exacerbation, and that the negative symptom improvement could have been due to a supportive environment and/or the reduction of positive symptoms. And, as an audience member pointed out, risperidone also had a significant effect on negative symptoms relative to placebo.

Christine Marx of Duke University, Durham, North Carolina, reported on a Phase 2 trial of the neurosteroid pregnenolone. The compound has various pro-neuronal effects in animals, and because clozapine upregulates pregnenolone in the hippocampus in an animal model, it has been hypothesized that some of the beneficial effects of clozapine may come via pregnenolone. In an add-on study parallel to one in 2014 (Marx et al., 2014), which had shown some benefits in functional capacity, Marx and colleagues again found no overall effects on cognition as assessed by the MATRICS Consensus Cognitive Battery (MCCB), though there were

improvements in verbal learning. But Marx and colleagues did find significant improvements on the communication subscale of the UCSD Performance-based Skills Assessment (UPSA). There were no effects on positive or negative symptoms. Marx said that pregnenolone was well tolerated and suggested that higher doses might be more effective.

In another attempt to improve cognition in people with schizophrenia, Jose Apud of the U.S. National Institute of Mental Health in Bethesda, Maryland, presented a study of tolcapone, an inhibitor of the enzyme catechol-O-methyltransferase (COMT), which regulates dopamine release in prefrontal cortex. The NIMH group had previously shown that tolcapone could both improve executive function and alter the fMRI BOLD signal in prefrontal cortex, suggesting more efficient information processing in that region. In a study of volunteers with schizophrenia, Apud and colleagues found that tolcapone increased performance on the N-back task, a test of working memory, and produced changes on fMRI similar to those seen in the earlier experiments. The trouble with tolcapone is that it is not well tolerated and does not cross the blood-brain barrier well, so while experiments like these provide support for the hypothesized intervention via COMT, other compounds would have to be found.

Harvey noted that some promising hopes had been dashed recently. "I was very disappointed about the failure of the Boehringer Ingelheim drug, despite their excellent research design," he said.

As reported by Michael Sand of Boehringer Ingelheim Pharmaceuticals, their phosphodiesterase 9 inhibitor, BI 409306, failed to show a benefit over placebo on the primary endpoint, which was improvement on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) at Week 12. The drug is targeted at cognitive deficits via glutamate neurotransmission.

Similarly, a drug that we have reported on extensively in previous meetings—Intra-Cellular Therapies' ITI-007—failed to separate from placebo in a Phase 3 trial, while the active comparator, risperidone, did outperform placebo. This novel, potent 5-HT2A serotonin receptor antagonist with some dopamine receptor modulation at higher doses, now called lumateperone, had been promising in Phase 2 studies. Cedric O'Gorman of Intra-Cellular Therapies indicated that the company is not willing to call it quits yet. O'Gorman blamed the failure of the third trial on placebo response. He said that combining the three trials produced a separation from placebo.

In the end, Harvey declined to endorse the notion that the field is still in a famine period for new drug development. "I think that there are some things still working. Minerva's new drug looks like it reduces negative symptoms and maybe enhances cognition," he said.

Harvey was referring to MIN-101, a drug from Minerva Pharmaceuticals in Waltham, Massachusetts, that targets sigma 2 and 5-HT2A receptors. As described by Michael Davidson of Minerva in a therapeutics session on Sunday, March 26, two different doses of the drug reduced negative symptoms, with medium effects sizes. The study was conducted in patients with stable schizophrenia who had been taken off their antipsychotic medications in order to take MIN-101 as a monotherapy. There were no major side effects, and it was promising that positive symptoms and extrapyramidal symptoms did change for the study patients, which also argues that the improvements in negative symptoms were not secondary to improvements in positive or extrapyramidal symptoms. In reply to an audience member, Davidson conceded that it was possible that patients who had been on long-acting injectable antipsychotics before entering the trials still had enough in their systems to interfere with the interpretation of the results.—Hakon Heimer.

Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Németh G, Laszlovszky I, Czobor P, Szalai E, Szatmári B, Harsányi J, et al. Lancet 2017;389(10074):1103-1113.

Proof-of-concept randomized controlled trial of pregnenolone in schizophrenia. Marx CE, Lee J, Subramaniam M, Rapisarda A, Bautista DCT, Chan E, et al. Psychopharmacology (Berl) 2014;231(17):3647-3662.