Highlights from the 2014 Schizophrenia International Research Society Conference April 5–9, 2014

Allison A. Curley [1]

Abstract

The 2014 Schizophrenia International Research Society (SIRS) Conference, held in Florence, Italy, attracted more than 1,700 attendees from over 55 countries to the stately Firenze Fiera Conference Center from April 5–9, 2014. Providing plenary sessions, special sessions, symposia, workshops, oral presentations and poster presentations, this 4th Biennial SIRS Conference was jointly sponsored by Vanderbilt University School of Medicine, Department of Psychiatry and SIRS. In conjunction with the Schizophrenia Research Forum, a Web project of the Brain and Behavior Research Foundation, and with our thanks to the SIRS organizers and staff, we bring you the following report on the meeting's discussions concerning drug therapy developments for schizophrenia.

Refining Schizophrenia Clinical Drug Trials

In the Tuesday, April 8 SIRS plenary session entitled "Update on Therapeutics: Improving the Clinical Yield," speakers from academia and industry discussed lessons learned from past failed clinical trials and ways to improve those of the future. One common theme was the need to think beyond a single definition of "schizophrenia" and to select subgroups of patients that are relevant for the specific compound being tested.

In support of this argument, Bruce Kinon, Eli Lilly, Indianapolis, Indiana, provided several possible reasons why Lilly's mGluR2/3 agonist pomaglumetad methionil failed to meet its endpoints. The antipsychotic-responsive patients (who presumably have a dopamine-mediated illness) who were used in trials may not have responded to a glutamate-based treatment, he suggested. The glutamate drug could also require a patient who is hyperglutamatergic, which studies have suggested is a state associated with early-stage patients, not the more chronically ill tested in Lilly's trials. A third reason for the drug's failure, said Kinon, could be mGluR2 downregulation resulting from prior exposure to atypical antipsychotics that block 5HT2A receptors. In fact, a post hoc analysis found that patients treated only with D2-predominant drugs did respond to pomaglumetad (in contrast to those exposed to serotonin-blocking agents).

Richard Keefe, Duke University, Durham, North Carolina, also emphasized a careful consideration of the characteristics of trial participants. Although it may be easier to recruit stable, chronic patients with schizophrenia, he said, this population may not be the mostly likely to show cognitive improvement. Instead, he suggested that younger subjects earlier in their course of illness may be a better choice, citing data showing that younger subjects benefit more from cognitive remediation than older ones.

[1]*Schizophrenia Research Forum*

Address for correspondence: Allison A. Curley, Schizophrenia Research Forum, c/o Brain and Behavior Research Foundation, 90 Park Avenue, 16th Floor, New York, NY 10016
E-mail: allison@schizophreniaforum.org

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Keefe also emphasized the need to pay attention to study parameters such as the time of day that cognitive tests are performed. He described two clinical trials (encenicline and GABA agonist/dopamine antagonist BL-1020) in which larger effect sizes of cognitive improvement were achieved in patients who received baseline and endpoint cognitive batteries at the same time of day compared to subjects with inconsistent timing of testing. Ensuring consistency across raters is also important, he added.

The challenges of assessing negative symptoms in schizophrenia were addressed by Daniel Umbricht, F. Hoffman-La Roche, Basel, Switzerland. He discussed whether caregiver information should be incorporated into ratings of negative symptoms, which often deal with inner mental states that can be difficult to observe, and presented data from Roche's Phase 2 trial of now-abandoned glycine transporter inhibitor bitopertin demonstrating that placebo response was significantly smaller in patients for whom caregiver information was incorporated into clinical assessments.

Umbricht also discussed whether negative symptoms should be lumped together or split into two factors (avolition/asociality and expressive deficits), arguing for separate evaluations of key dimensions. In order to minimize the expectation bias that can contribute to placebo response, he underscored the need for fully blinded raters. Finally, he also emphasized the importance of detailed characterizations of patients in order to identify subgroups of responsive patients.

Chris Schmidt, Pfizer, Groton, Connecticut, discussed lessons learned from the PDE10 inhibitor drug development program. He suggested that in addition to looking for efficacy, researchers need to pay attention to the value of clinical trials for furthering the understanding of the underlying neurobiology of schizophrenia. "We need to walk away from these programs actually knowing that we tested the mechanism," he said.

Jonathan Rabinowitz, Bar-Ilan University, Israel, reviewed the advantages of data sharing across clinical trials and showed how real-time data sharing can improve patient selection by identifying and eliminating duplicate enrollments. He also presented data suggesting that studies can be made shorter and smaller, with the benefits of reducing placebo exposure and conserving resources.

Finally, session chair John Kane, Zucker Hillside Hospital, Glen Oaks, New York, touched on the struggle of the ever increasing placebo response across time. He also called for better assessments of inter-rater reliability, which he reminded the audience can greatly affect statistical power. Like many of the other speakers, Kane emphasized the importance of selecting the specific population of patients that is most likely to benefit from a particular treatment. "We need to think a lot about subgroups," he said.—Allison A. Curley.

Reports from Schizophrenia Clinical Drug Trials

Several SIRS sessions discussed data from clinical trials testing novel antipsychotics and a variety of other drugs. Reading a description of every study presented could take as long as the wait to climb to the top of the city's iconic Basilica di Santa Maria del Fiore dome (Il Duomo); what follows is a subset of the clinical studies presented.

Drip, Drip, Drip

The April 6 afternoon session covering the latest from the schizophrenia pharmaceutical pipeline was, unfortunately, dominated largely by negative data. Speakers reported that several drugs failed to meet their primary endpoints, including a glycine transport inhibitor, a combination GABA agonist/dopamine antagonist, an alpha 7 nicotinic receptor agonist, a dopamine D1 agonist, and a D2/D3 partial agonist. However, the pipeline was not completely dry, and a few speakers presented promising efficacy data from Phase 2 studies.

Kimberly Vanover, Intra-Cellular Therapies, New York, discussed results from a trial of IT-007, a pharmacological jack-of-all-trades that acts as a serotonin 5HT2A antagonist, a dopamine and glutamate phosphoprotein modulator, and a serotonin reuptake inhibitor. Compared to those given placebo, patients receiving the 60 mg (but not 120 mg) dose of IT-007 for one month had improved scores on the total Positive and Negative Syndrome Scale (PANSS) and on its positive symptom subscale. IT-007 improved symptoms across a variety of domains, consistent with a lessening of social impairment, said Vanover. It decreased negative symptoms in a subgroup of patients who had exhibited prominent negative symptoms at the start of the trial. In addition, in contrast to the active control risperidone, IT-007 improved some negative symptoms such as stereotyped thinking. Importantly, also unlike risperidone, it did not worsen other negative symptoms such as blunted affect. The drug was well tolerated, noted Vanover, and lacked many of the side effects such as metabolic syndrome and extrapyramidal symptoms that plague other antipsychotics.

Another compound with complex action was presented by Marc Cantillon of Reviva Pharmaceuticals, San Jose, California. He described his company's four-week Phase 2 REFRESH trial of the dopamine-serotonin system stabilizer RP5063 that balances partial agonism of D1, D2, D4, 5HT1A, and 5HT2A receptors with antagonism of 5HT6 and 5HT7 receptors. Cantillon reported clinically meaningful remission rates based on PANSS scores with all three doses tested (ranging from 34 to 46%), compared to 22% with placebo. Significant remission was also achieved using a second definition that combined PANSS and Clinical Global Impres-

sion (CGI) scale scores. Depression, anxiety, and cognitive symptoms also showed trends toward improvement, and the drug was safe and well tolerated at all three doses, he added.

Ilise Lombardo, FORUM Pharmaceuticals (formerly EnVivo Pharmaceuticals), Watertown, Massachusetts, reviewed the Phase 2b results of the nicotinic alpha 7 agonist encenicline for cognitive deficits in schizophrenia. She reported that treatment with the drug for four weeks improved global cognitive function, as measured by the CogState Battery and the PANSS cognitive scale. Encenicline also improved performance on a functional measure, the Schizophrenia Cognition Rating Scale (though only at the higher dose), and on the PANSS negative scale. A Phase 3 trial is currently underway.

Off Label, but on Target?

A drug repurposing session held on the final afternoon of the conference, a beautiful, sunny day in Florence, was attended by a few dedicated souls. Discussant Peter Buckley, Georgia Regents University, praised the session's speakers for their methodological rigor, and for the fact that their studies were rooted in biology.

Mark Weiser, Sheba Medical Center, Israel, presented a post hoc analysis of a prior 16-week trial of aspirin, minocycline, and pramipexole as add-ons to antipsychotics in schizophrenia. A small but significant improvement on the total PANSS was observed with aspirin but not the other two drugs. When Weiser and colleagues divided subjects into thirds in a post hoc analysis according to baseline levels of C-reactive protein (CRP)—an acute marker of inflammation—those in the high CRP group showed a more substantial improvement on the PANSS positive subscale with aspirin. Harking back to the theme of the plenary session, these data suggest that only patients with high levels of inflammation should be included in further trials of aspirin.

The antibiotic minocycline has been proposed as an adjunctive treatment in chronic schizophrenia patients who are partially resistant to clozapine. Deanna Kelly, University of Maryland, Baltimore, discussed a pilot study showing that after 10 weeks of treatment, patients had significantly improved avolition, working memory performance, and anxiety/depressive symptoms, and trended toward a significant improvement in positive symptoms. She noted that nearly all patients wanted to continue minocycline after the trial ended and that the drug was well tolerated.

Jamie Hallak, University of São Paulo, Brazil, examined the role of nitric oxide (NO) in schizophrenia. In a preliminary acute study, patients on antipsychotics administered a single dose of the NO donor (and current treatment for high blood pressure) sodium nitroprusside displayed symptom improvement in as few as four hours (Hallak et al., 2013). This improvement on the Brief Psychiatric Rating Scale and the negative subscale of the PANSS was still present after four weeks. Hallak also described unpublished data from the same trial indicating that acute sodium nitroprusside also improved some domains of cognitive function.

In the final presentation of the session, Joshua Roffman, Massachusetts General Hospital, Boston, reviewed his earlier data demonstrating that—compared to those on placebo—patients taking folate and B12 (a cofactor in the folate metabolism pathway) supplements for 16 weeks showed an improvement in negative symptoms, but only when genetic variants in folate absorption were accounted for. In the second part of his talk, Roffman described unpublished MRI data from a subset of the original sample. After folate plus B12 treatment, patients displayed increased cortical thickness; in the mid-cingulate region this was correlated with an improvement of negative symptoms. The supplements also increased activity in the frontoparietal control network. Roffman is currently conducting a clinical trial of the related compound L-methylfolate, with results expected later this year.—Allison A. Curley.

Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: a randomized, double-blind, placebo-controlled trial. Hallak JE, Maia-de-Oliveira JP, Abrao J, Evora PR, Zuardi AW, Crippa JA, et al. JAMA Psychiatry 2013;70(7):668-676.