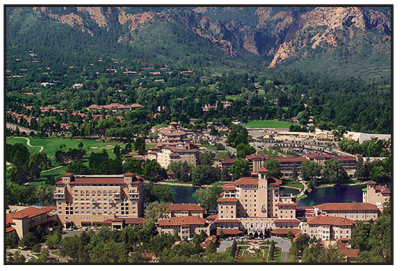

Highlights from the New Drug Session at the Biennial International Congress on Schizophrenia Research, April 2–6, 2011

Hakon Heimer [1]

Abstract

The 2011 International Congress on Schizophrenia Research, held in Colorado Springs, Colorado, attracted nearly 1,200 attendees to the Broadmoor Hotel from 2–6 April 2011, not to mention the satellite meetings on cognition and the schizophrenia prodrome. With the gracious assistance of Congress directors Carol Tamminga and Chuck Schulz, as well as meeting staff Dorothy Denton and Cristan Tamminga, we bring you the following report on the Congress' "New Drug Session: Advances in Medication Development and Assessment."

Introduction

The standing International Congress on Schizophrenia Research (ICOSR) session on pharmacotherapeutic advances has not offered much to write about in recent times, with the exception of the 2007 report of a successful trial of Eli Lilly and Company's metabotropic glutamate receptor agonist. Even that story has grown complicated with the increasing placebo response that plagues psychiatric clinical trials.

Some hopeful signs appeared at the new drug session of this year's meeting on 4 April 2011, however. "A couple of compounds that were developed for cognitive impairment in schizophrenia have shown effects on negative symptoms," said session co-chair Steve Marder of UCLA, referring to two α7 nicotinic cholinergic drugs and the glycine transporter inhibitor RG1678. Here, we briefly summarize these and other possibilities in the pipeline.

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The Atypicals

Peter Weiden of the University of Illinois, Chicago, kicked off the "New Drug Session: Advances in Medication Development and Assessment" with an update on the atypical antipsychotic iloperidone, which has been approved for use in the United States since the last ICOSR meeting was held. It has a hypothesized dopamine D2/5HT mechanism of action, and many studies show antipsychotic efficacy with only relatively modest weight gain (perhaps in the same range as risperidone) and favorable metabolic markers. There is also little evidence that it causes extrapyramidal symptoms, Weiden reported.

Antony Loebel of Sunovion, Inc., Fort Lee, New Jersey, then gave an update on lurasidone, highlighting its approval in the U.S. last fall, and the fact that it first became available in February of this year. It is also a D2/5HT antagonist, but Loebel cited evidence that it has some unique qualities in terms of affinity for several of the serotonin receptors, especially 5HT7. He described the side effect profile as being good on both weight gain and metabolic markers, but there is evidence for some extrapyramidal symptoms and akathisia.

He was followed by Ronald Landbloom of Merck and Co., Rahway, New Jersey, who reported on asenapine. Land-

A message from the ICOSR co-founders …

We are delighted that Hakon Heimer, Executive Editor of Schizophrenia Research Forum, has provided for readers of ***Clinical Schizophrenia & Related Psychoses*** this detailed synthesis of the New Drug Session from the Thirteenth Biennial International Congress on Schizophrenia Research recently held in Colorado Springs, April 2–6, 2011. 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.

Carol Tamminga, MD and Charles Schulz, MD
Co-Founders and Co-Organizers
International Congress on Schizophrenia Research

bloom highlighted a receptor profile that also shows high affinity for DRD2 and some 5HT subtypes, but low affinity for muscarinic cholinergic receptors. As have others, Landbloom and colleagues are seeing high placebo response rates in their trials. He described asenapine's effect on weight gain and metabolic markers as limited, though there is evidence of greater rates of akathisia relative to placebo in the trials reported.

Anyone Excited by Glutamate?

There is always an interest in updates on development of mGluR2/3 agonists, and Bruce Kinon from Lilly's labs in Indianapolis, Indiana, reviewed some of the data Lilly has generated over the past several years in animal models (see, e.g., Rorick-Kehn et al., 2007; Fell et al., 2009). In particular, Kinon said, the preclinical data suggest the possibility of synergism between mGluR2/3 agonists and D2 blockers, pointing to the obvious question of whether the mGluR2/3 drugs could enhance responses to current antipsychotic drugs.

Moving to the ongoing patient trials, Kinon said that Lilly does not have the final story in hand on the efficacy of mGluR2/3 agonists as monotherapy. Acute efficacy testing is underway on the mGluR2/3 agonist LY2140023 monohydrate, an oral pro-drug of LY404039. Kinon mentioned a recent open-label safety study on patients with pronounced negative symptoms. Efficacy data from this study suggest some significant improvement, indicated by increases in PANSS scores in the LY2140023-treated group. He also tantalized the audience with hints that Lilly's pharmacogenetic data suggest that variation in the genes for the 5HT2A receptor and the protein neuregulin can help predict who will respond well to mGluR2/3 agonists.

The other major direction of research that follows from the glutamate hypothesis of schizophrenia attempts to boost activation of the NMDA receptor via a glycine-centered approach. The NMDA receptor requires that both the amino acid glycine and the neurotransmitter glutamate (or aspartate) bind to it, at separate sites, in order for ions to flow through.

Daniel Umbricht of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, reported on continuing work that aims to provide more glycine to the NMDA receptor by interfering with the glycine transporter molecule as it goes around mopping up spare glycine. The inhibitor RG1678 has shown in some trials that it might be effective as an add-on therapy, and Umbricht presented data indicating that this drug improves negative symptoms better than placebo. Because the effect seemed to increase toward the end of the eight-week trial, they are continuing the study to determine if the improvement persists. He also mentioned that the data indicate that the drug's efficacy depends on low doses.

Agonizing Nicotinic Receptors

The α7 nicotinic cholinergic receptor is a popular target for boosting cognition in schizophrenia, and also in Alzheimer's and other diseases. The early news on manipulating the α7 receptor in schizophrenia was not compelling; however, Robert Freedman, University of Colorado, Denver, presented additional analyses of data from an earlier study on the partial nicotinic agonist DMXB-A, which point to pro-cognitive effects in nonsmokers. Interestingly, Freedman reported that the drug appeared to improve negative symptoms as well.

The effects on negative symptoms were echoed in a presentation by David Hosford of Targacept, Inc., Winston-

Salem, North Carolina. Targacept's drug, TC-5619, is a full, selective agonist at the α7 receptor, Hosford said. A newly completed Phase 2 trial found statistically significant improvements over placebo in both the cognitive and negative symptom domains. In contrast to the data that Freedman reported, smokers seemed to drive the improvement for this drug, in this trial.

And Now for Some Things Completely Different …

Jeff Anderson, from Cypress Bioscience of San Diego, California, was one of three speakers who described different tracks to schizophrenia treatment. Originally developed by the Israeli company BioLineRx, the Cypress compound Cyp-1020 features the typical antipsychotic perphenazine with the neurotransmitter γ-aminobutyric acid (GABA) attached to it. The logic is that enhancing GABA transmission might be effective against cognitive symptoms of schizophrenia, although there has been no clinical success with this approach yet. Anderson said that this hypothesis was supported by animal studies that found pro-cognitive effects of Cyp-1020, but not perphenazine alone.

In its six-week Phase 2 study of Cyp-1020, Cypress found significant improvement in cognitive tests over both risperidone and placebo, Anderson said. He noted that the occurrence of extrapyramidal side effects was comparable between the two drugs. This study was limited to acutely ill patients, and the researchers are now studying longer-term effects.

The next talk featured the drug ITI-007, from Intra-Cellular Therapies. Originally developed by Bristol-Myers Squibb Company, it is an antagonist at both dopamine D2 receptors and 5HT2A receptors, though it has a much higher affinity for the serotonergic receptors. Because it also acts as an intracellular inhibitor of pathways downstream of the D2 receptor, the notion is that, if the doses are kept low enough, the drug would block the 5HT2A receptor, but also function as an antipsychotic. Since it barely blocks D2, it may avoid extrapyramidal symptoms.

Kimberly Vanover of Intra-Cellular Therapies, New York, said that with this drug they are going after sleep deficits, depression, and cognitive deficits linked to sleep, as well as psychosis. In studies to date, both in insomnia patients without schizophrenia and patients with schizophrenia, the drug is well tolerated and promotes sleep. The next step will be to assess its efficacy in schizophrenia.

Both of these compounds represent novel approaches, but fit within the usual synaptic transmission framework. The last study of the session, presented by Dan Javitt, Nathan Kline Institute, Orangeburg, New York, was something completely different. He spoke about davunetide, the more friendly name of the peptide NAPVSIPQ (or NAP). This fragment of activity-dependent neuroprotective protein (ADNP) helps stabilize microtubules, restoring neuronal structure and function.

Although the evidence for neuronal lesions in schizophrenia remains vague, the drug is in development for disorders such as Alzheimer's disease because of evidence that it improves cognitive function in animal models of neurodegenerative disease. Thus, the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) program selected it for a clinical trial as adjunctive therapy in schizophrenia. Javitt reported that, in a very small sample, davunetide produced non-significant improvements on primary cognition measures that warrant more study. This assessment was reinforced, he said, by positive results from secondary outcome assessments.

Open, Public Discourse

"I like the breadth of the presenters and ideas," said co-chair of the session, ICOSR co-director Chuck Schulz of the University of Minnesota. "Different modes of action of medicines, different levels, ranging from pilot data through Phase 3. And I like that people from different sectors come together." Indeed, said Schulz, this was one of the purposes of the New Drugs session when it was instituted many Congresses ago: to prevent the traditional Balkanization of researchers at conferences—sessions geared only toward academic or industry scientists, or even toward a single company.

Though he wasn't surprised by any of the compounds, Schulz said, "I thought the idea of the perphenazine-GABA conjugate was great. That was new stuff." His co-chair, Marder, was hopeful that the session both reflected and could spur a renewed interest in developing drugs for negative symptoms of schizophrenia.

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