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Novel Atypical Antipsychotic Seeks Balanced Control of Symptom Complexes

Stockholm - Improved control of both positive and negative symptoms in schizophrenia was one of the defining advances of atypical vs. typical antipsychotic agents. In bipolar disease, the most effective atypicals are those that control both mania and depression without exacerbating either symptom set. However, given relative differences in the affinity or activity along specific neurotransmitter pathways, each atypical antipsychotic has the potential to offer different effects against symptom sets in each of these 2 psychiatric disorders. They are also likely to have different profiles for tolerability and risk of adverse events, such as weight gain. Here at the CINP, a series of presentations focused on the relative role of asenapine, a novel atypical antipsychotic recently approved in Canada for schizophrenia and manic or mixed bipolar I disorder episodes.

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One of the challenges in the management of psychiatric diseases has been effective control of different, often opposing symptoms. In schizophrenia, for example, traditional neuroleptics such as haloperidol were notoriously ineffective for treating negative symptoms, such as lack of affect. Bipolar disease, which is characterized by both manic and depressive symptoms, may be an even greater challenge because of the risk that an agent effective against one symptom set will exacerbate the other. The co-existence of different symptoms sets is a common problem, emphasizing the importance of selecting a balanced therapy.

"If we consider subsyndromal symptoms, some 70% of [bipolar] patients have mixed symptoms," noted Prof. Ana Gonzalez-Pinto, University of the Basque Country, Vitoria, Spain. The risks of exacerbating one symptom complex by treating the other have been best demonstrated by bipolar patients misdiagnosed with unipolar depression and inappropriately treated with antidepressants, but a greater balance of effect in bipolar treatment generated the initial interest in atypical agents.

Several atypical antipsychotics now have an indication for bipolar disease, but these agents differ markedly by mechanisms which may be relevant to specific symptom complexes and to risk of adverse events. As in schizophrenia, where early control of symptoms and a reduction in the number of psychotic breaks has been linked to better long-term outcomes, such as ability to live independently, frequent cycles of mania and depression in bipolar disease appears to diminish full recovery of function, such as cognitive capacity.

"The solution is to treat patients early to best preserve insight," commented Prof. Gonzalez-Pinto, "because once patients experience further manic episodes, insight is never completely recovered."

Mechanism of Action

Asenapine was recently introduced in both Canada (where it is approved for schizophrenia and the acute treatment of manic or mixed bipolar I disorder) and Europe. It was a focus of interest here at the CINP because of its potential to offer a more balanced activity against the mix of symptoms, such as negative symptoms in schizophrenia and mania in bipolar disease, which remain suboptimally treated with current options. The relative activity of this agent on specific neurotransmitter receptors increases the potential for the range of effects needed to provide control of a broad array of symptoms. For example, it acts as an antagonist at the 5-HT_{2a} receptor, a common activity of most classical antipsychotics and as a partial agonist at the 5-HT_{1a} receptor, which triggers the dopamine release thought beneficial against both schizophrenia and depression.

"The agonist action at the 5-HT_{1a} receptor combined with the antagonist action at the 5-HT_{2a} receptor act synergistically to increase levels of dopamine in the cortex to a greater extent than compounds that target each receptor independently," explained Dr. Frank Tarazi, Harvard Medical School, Boston, Massachusetts. It is also a full D_2 receptor antagonist and blockade of this receptor remains a cornerstone of antipsychotic drug action. In addition, the same agent has a strong affinity for the adrenergic alpha-$_2$ receptor, which enhances the release of dopamine and norepinephrine in the frontal cortex and subsequently may contribute to the improvement of cognitive deficits and negative symptoms of schizophrenia.

Unlike other atypicals, asenapine upregulates the D_1 receptor in the striatum and this action may counteract upregulation of the D_2 receptor in the same brain region, which is implicated in the development of undesirable extrapyramidal side effects. The same compound has a higher affinity for both the 5-HT_{2c} as well as the 5-HT_7 receptors than any of the other atypicals. Both 5-HT_{2c} and 5-HT_7 constitute novel targets that may mediate the beneficial actions of antidepressant agents.

Manic or Mixed Episodes

Placebo-controlled trials established the efficacy of asenapine in schizophrenia and bipolar disease, but the most recent

comparisons of asenapine to active comparators are exploring efficacy in the context of other therapeutic options. This includes a series of studies in which patients were randomized to a flexible dose of asenapine, placebo or olanzapine. New analyses of these data are generating insight into potential differences, according to Prof. Heinz Grunze, Newcastle University, UK, who presented data from one of these studies. In these studies, both active agents could be titrated down if not well tolerated. After 3 weeks of treatment, the placebo arm was discontinued and patients were randomized to either active treatment for an additional 9 weeks.

At the end of the initial 3 weeks, reductions in the Young Mania Rating Scale (YMRS) were identical for the 2 active arms and were clearly superior to placebo controls. About twice as many patients on an active therapy also achieved remission during those 3 weeks—"quite remarkable that some 40% of patients achieved clinical remission in such a short time period," Prof. Grunze noted. In the subsequent 9-week, head-to-head study, asenapine maintained efficacy and was comparable to olanzapine in terms of improving the YMRS score, with a mean reduction of approximately 25 points in each arm.

While the similarity in response on the mania rating was reassuring for the newer agents, a post-hoc analysis of data from a 40-week extension of this study did show differences in depressive symptoms on the Montgomery-Asberg Depression Rating Scale (MADRS). While almost 100% of patients remained in remission over the course of a one-year extension, the post-hoc analysis was conducted in patients who entered the studies with significant depressive symptoms (MADRS total score ≥20). In this group, "there was a clear-cut reduction in the MADRS score of almost 60% at day 7 and 70% at day 21, which was statistically significant from placebo and in this case, also significant from olanzapine, where we did not see the same marked reduction in depressive symptoms as we saw with asenapine," Prof. Grunze reported.

In a post-hoc analysis that pooled data from several similarly designed placebo-controlled trials that included both asenapine and olanzapine, differences in efficacy were also apparent, according to Prof. Jean-Michel Azorin, University of Aix-Marseille II, France. The pooled analysis included 977 patients randomized to a flexible dose of asenapine (5 to 10 mg), placebo, or 5 to 20 mg of olanzapine and then followed for 3 weeks. Of these, 102 entered a 9-week extension study. Dr. Azorin reported efficacy differences between the 2 active agents at 3 weeks relative to placebo and at 12 weeks relative to each other.

At week 3, decreases in YMRS and MADRS scores were significant for asenapine (-15 and -8.2, respectively) but not for olanzapine (-13.3 and -6.5, respectively) relative to placebo (-11.5 and -4.5, respectively), according to Dr. Azorin. Over the subsequent 9 weeks, the effect of asenapine on manic and depressive symptoms was maintained and was not statistically different from olanzapine. At week 12, asenapine was significantly superior to olanzapine in improving "disruptive/aggressive behaviour," "appearance" and "inability to feel."

Antipsychotics in Schizophrenia

Regarding the use of asenapine in schizophrenia, Dr. Steven Potkin, University of California, Irvine, presented pooled results of 2 sets of 26-week core and 26-week extension studies carried out in patients chosen for their preponderance of persistent negative symptoms. At week 26, there was no difference in mean reductions in the Negative Symptom Assessment-16 (NSA-16) score between asenapine and olanzapine at -11.1 vs. -11.2, respectively. However, statistical superiority of asenapine was reached by week 30 and maintained through week 52 (-16.5 vs. 13.6 for olanzapine).

As has been widely reported, weight gain and metabolic changes associated with antipsychotic use are important issues from the perspective of quality of life and risk of adverse events, including the exacerbation of cardiovascular risk. In both schizophrenia studies, mean weight change was less at week 26 with asenapine (-0.6 kg vs. a gain of 2.7 kg with olanzapine; $P<0.0001$) and at week 52. Metabolic measures, such as changes in serum lipids or blood sugar, have also been reassuring. Based on these safety data, "I think physicians will find this drug is helpful when treating patients with schizophrenia," Dr. Potkin remarked.

Summary

The difficulty of treating different symptom sets in schizophrenia and bipolar disease has been the basis of great interest in novel atypical antipsychotic agents with the potential to achieve a more balanced effect on neurotransmitter pathways. The clinical trials with asenapine, including those reported at the CINP, are encouraging. In addition to broad effects with favourable activity relative to active comparators, the novel agent has a relatively low risk of weight gain. The overall clinical experience suggests it will be an important addition to current options. □

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