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Research report

Effect of asenapine on manic and depressive symptoms in bipolar I patients with mixed episodes: Results from *post hoc* analyses

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ABSTRACT

Background: The efficacy of agents useful for mania is largely unproven in patients with mixed episodes.
Methods: The efficacy of asenapine in the treatment of mixed episodes was assessed using *post hoc* analyses on pooled data from two identically designed 3-week, randomized, double-blind, flexible dose, placebo- and olanzapine-controlled trials and their 9-week, double-blind olanzapine-controlled extension study. Efficacy was measured by changes on Young Mania Rating Scale (YMRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) total scores, and was analysed through analysis of covariance on observed cases of the intent-to-treat dataset.
Results: In the intent-to-treat population, 295 patients had a DSM-IV-TR mixed episode (placebo: 66; olanzapine: 122; asenapine: 107) in the 3-week trials. Of these, 102 patients (olanzapine: 56; asenapine: 46) entered the 9-week extension study.

At week 3, decreases in YMRS and MADRS total scores, were significantly ($p < 0.01$) greater with asenapine (YMRS: −15.0; MADRS: −8.2) versus placebo (YMRS: −11.5; MADRS: −4.5); olanzapine did not separate from placebo (YMRS: −13.3; MADRS: −6.5). At week 12, further decreases in YMRS and MADRS total scores were observed with asenapine (YMRS: −22.4; MADRS: −11.9); non-statistically different from olanzapine (YMRS: −20.2; MADRS: −7.9).
Limitations: Results are from *post hoc* analyses of trials that were not designed to specifically evaluate mixed episodes.
Conclusions: These exploratory analyses provide supportive evidence for the efficacy of asenapine in treating the associated symptoms of mania and depression in bipolar I patients with mixed episodes.

1. Introduction

The concept of mixed states is old, predating that of bipolar disorder itself (Swann, 2011). Various definitions have been and are still being proposed, but the concept always refers to a combination of depressive and manic features in the same episode. The DSM-IV-TR criteria require that patients have both full syndromal mania and depression. Depending on the definition, there is a wide range of reported rates of mixed states in the literature; from 5% to 75% (Hantouche et al., 2006). Mixed episodes represent a severe presentation of bipolar disorder. Mixed patients are characterized by an earlier appearance of bipolar symptoms, a higher risk of suicide, a higher occurrence of manic and depressive episodes, higher rates of rapid cycling, and more co-morbidities related to substance abuse and dependence, as well as anxiety disorders (Azorin et al., 2009; Swann, 2011).

The treatment of mixed states is made difficult by the fact that the efficacy of drugs shown useful for pure manias is largely unproven in the subset of patients with mixed episodes (Stahl et al., 2010).

Usually the magnitude of response to manic symptoms' treatment exceeds that of depression symptoms. Valproate and carbamazepine have shown some effectiveness, but the efficacy of lithium appears questionable. A small number of atypical antipsychotics were found to improve both manic and depressive symptoms, used as monotherapy or in combination to mood stabilizers (Fountoulakis et al., 2012).

Asenapine has been shown to be effective in the treatment of patients with manic or mixed episodes associated with bipolar I disorder, in two companion randomized, double-blind, placebo - and olanzapine-controlled 3-week trials (McIntyre et al., 2009a; McIntyre et al., 2010). Across trials, reductions in Young Mania Rating Scale (YMRS) total score were significantly greater with asenapine and olanzapine compared with placebo. In a 9-week extension of these trials (McIntyre et al., 2009b), asenapine met the criteria for non-inferiority to olanzapine. The effect of asenapine on depressive symptoms in subgroups of patients who

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participated in the same 3-week lead-in trials, but experienced clinically relevant depressive symptoms, was assessed by Szegedi et al. (2011). Three populations were selected: (1) Montgomery-Åsberg Depression Rating scale (MADRS) total score ≥ 20; (2) Clinical Global Impression for Bipolar Disorder-Depression (CGI-BP-D) scale severity score ≥ 4; (3) diagnosis of mixed episode according to DSM-IV-TR. The decreases in MADRS total scores were found to be statistically greater with asenapine versus placebo at days 7 and 21 in all populations, whereas differences between olanzapine and placebo were not significant. In conclusion, the authors state the need for randomized controlled studies of asenapine in patients with bipolar depression to confirm the generalizability of their findings.

Nonetheless, there is still a lack of data on the efficacy of asenapine in mixed patients in the studies that have been conducted so far. For example, changes in YMRS scores in the specific population of DSM-IV-TR mixed patients were analyzed in only one of the two short-term trials (McIntyre et al., 2009a), response and remission rates were defined as percentage improvement on the YMRS only and threshold scores on YMRS were missing in both trials for the subpopulation of mixed patients. Data for this subpopulation were also completely absent in the 9-week extension study. In the analyses carried out by Szegedi et al. (2011), the efficacy of asenapine on manic symptoms and response rates based on percent improvement on the MADRS in the population of mixed patients were not assessed, neither was the tolerability of asenapine assessed. The latter may be worth considering as side effects such as extrapyramidal (Goodwin, 2009) or metabolic symptoms (Fagiolini et al., 2005) may worsen depressive features in bipolar patients.

Moreover, before implementing randomized controlled studies of asenapine in bipolar depression, it may be of interest to get some signal as to whether the efficacy of asenapine on depressive symptomatology is driven by its impact on the core features of depression.

The objective of these *post hoc* analyses is to try to yield further information on those missing data in order to better evaluate the efficacy and tolerability of asenapine in the treatment of manic and depressive symptoms in a cohort of patients with mixed episode defined according to DSM-IV-TR criteria.

2. Methods

These *post hoc* analyses include data from two identically designed 3-week, randomized, double-blind, flexible dose, placebo- and olanzapine-controlled trials (NCT00159744; NCT00159796) and their 9-week, double-blind olanzapine-controlled extension study (NCT00143182).

Each study was conducted in compliance with the Declaration of Helsinki, the principles of Good Clinical Practice and was approved by the appropriate institutional review boards. All enrolled patients provided written informed consent at the start of both the 3-week trials and the extension study.

2.1. Study designs and patient populations

The study designs and patient populations have been previously described (McIntyre et al., 2009a; McIntyre et al., 2009b; McIntyre et al., 2010). Briefly, the trials were conducted in 10 countries (Bulgaria, India, Malaysia, the Philippines, Romania, Russia, South Korea, Turkey, Ukraine, and the United States). The 3-week trials included adult patients with a current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) diagnosis of manic or mixed episodes associated with bipolar I disorder, assessed using the Mini International Neuropsychiatric Interview (Sheehan et al.,1998), and a YMRS (Young et al., 1978) total score of at least 20 at screening and baseline, a current episode that began less than 3 months before screening, and a documented history of at least 1 moderate to severe manic or mixed episode, with or without psychotic features. Patients who completed one of the 3-week trials, regardless of clinical status, were eligible for the 9-week extension study, if they had no major protocol violations, and if the investigator judged that continued treatment could be of clinical benefit. Principal exclusion criteria in both the lead-in and extension studies were a primary diagnosis other than bipolar I disorder, a rapid-cycling mood course, substance abuse or dependence, or being at imminent risk of harm to self or others.

To allow for washout of medications whose use was not permitted during the trial, a single-blind placebo run-in period of up to 7 day preceded randomization. Limited doses of specific benzodiazepines and non-benzodiazepine sedative-hypnotics were allowed during treatment week 1 of the 3-week trials. All other psychotropic medications were prohibited in the lead-in and extension studies (McIntyre et al., 2009a; McIntyre et al., 2009b; McIntyre et al., 2010).

2.2. Treatment

After single-blind placebo run-in periods of up to 7 day in the lead-in studies, patients were randomized to 3 weeks of asenapine (20 mg on day 1, dose divided morning and evening; flexible-dose 20 or 10 mg daily thereafter), placebo, or olanzapine (15 mg on day 1, flexible-dose 5–20 mg daily thereafter) in a 2:1:2 ratio (McIntyre et al., 2009a; McIntyre et al., 2010). In the extension study, patients who had received active treatment with asenapine or olanzapine in the 3-week trials continued the same double-blind regimen (McIntyre et al., 2009b). Patients who had received placebo in the 3-week trials were blindly randomised to asenapine (20 mg or 10 mg daily, dose divided morning and evening), and, as with the original studies, they are not included in the present analyses to avoid bias due to differences in exposure.

These *post hoc* analyses were conducted on the pooled 3-week data of the subset of patients diagnosed with a mixed episode according to DSM-IV-TR, and complemented by the data collected during the 9-week extension trial.

2.3. Assessments

The effect of treatment on manic symptoms was evaluated by the change from baseline to week 3 (day 21) and to week 12 (day 84) in the YMRS total score and for each individual item score.

The effect of treatment on depressive symptoms was evaluated by the change from baseline to week 3 (day 21) and to week 12 (day 84) in the MADRS (Montgomery, 1979) total score and for each individual single item score. Composite response, defined as $\geq 50\%$ reduction from baseline in YMRS and MADRS scores, and composite remission, defined as YMRS ≤ 12 and MADRS ≤ 10, were also analysed.

Safety was evaluated on the basis of treatment emergent adverse events, potentially clinically significant weight changes ($\geq 7\%$ gain or loss) and changes in metabolic parameters.

Treatment-emergent adverse events (hereafter referred to as adverse events) included any adverse events observed by the investigator or reported spontaneously by the patient during the treatment period. These were classified according to Medical Dictionary for Regulatory Activities (MedDRA) version 8.1. As with the original studies (McIntyre et al., 2009a; McIntyre et al., 2009b; McIntyre et al., 2010), we report AEs that occurred in $\geq 5\%$ of patients treated and that occurred at twice the frequency of placebo. Weight and metabolic parameters (fasting triglycerides, fasting glucose, total cholesterol, high-density lipoproteins (HDL), and low-density lipoproteins (LDL)) were assessed at baseline and study endpoint (day 21).