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Research report

DSM-5 mixed specifier for manic episodes: Evaluating the effect of depressive features on severity and treatment outcome using asenapine clinical trial data

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ABSTRACT

Background: To describe the frequency of mixed specifier as proposed in DSM-5 in bipolar I patients with manic episodes, and to evaluate the effect of mixed specifier on symptom severity and treatment outcome.
Methods: This post-hoc analysis used proxies for DSM-5 mixed features specifier by using MADRS or PANSS items.
Results: Of the 960 patients analysed, 34%, 18% and 4.3% of patients, respectively, had ≥3 depressive features with mild (score ≥1 for MADRS items and ≥2 for PANSS item), moderate (score ≥2 MADRS, ≥3 PANSS) and severe (score ≥3 MADRS, ≥4 PANSS) symptoms. In patients with ≥3 depressive features and independent of treatment: MADRS remission (score ≤12) rate decreased with increasing severity (61–43%) and YMRS remission (score ≤12) was similar for mild and moderate patients (36–37%), but higher for severe (54%). In asenapine-treated patients, the MADRS remission rate was stable regardless of baseline depressive symptom severity (range 64–67%), whereas remission decreased with increasing severity with olanzapine (63–38%) and placebo (49–25%). Reduction in YMRS was significantly greater for asenapine compared with placebo at day 2 across the 3 severity cut-offs and continued to decrease throughout the treatment period. The difference between olanzapine and placebo was statistically significant in mild and moderate patients.
Limitations: Results are from post-hoc analyses.
Conclusions: These analyses support the validity of proposed DSM-5 criteria. They confirm that depressive features are frequent in bipolar patients with manic episodes. With increasing baseline severity of depressive features, treatment outcome was poorer with olanzapine and placebo, but remained stable with asenapine.

1. Introduction

The symptom structure of bipolar disorder encountered during both acute and long-term maintenance phases is typically an admixture of depressive and manic symptoms. Mixed states, as codified in DSM-IV-TR, are defined as the contemporaneous presence of a threshold major depressive and manic episode. The acceptability of this definition is belied by the observation that the modal presentation of "mixed states" is the presence of subsyndromal "opposite-pole" symptoms during an affective episode which is a condition not described in DSM-IV-TR. It has therefore been proposed that the requirement for contemporaneous syndromal severity leads to under-detection, misdiagnosis, insufficient appraisal of suicide risk, and in many cases, the initiation of inappropriate treatment (e.g., conventional monotherapy with antidepressants (Kupfer et al., 2011; McElroy, 2008; Swann et al., 2013).

The DSM-5 has proposed supplanting the DSM-IV-TR definition of mixed episodes with the "mixed" specifier. The "with mixed features" specifier applies in episodes where syndromal or

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subthreshold symptoms from the opposing pole are present during a full mood episode (i.e., depressive symptoms during hypo/manic episodes and vice versa).

The DSM-5 has identified specific features of a major depressive or manic episode that would be considered as part of the mixed specifier definition (see www.DSM5.org). For manic episodes, mixed features are present if at least three of the following depressive symptoms are present nearly every day during the episode: dysphoria or depressed mood; diminished interest or pleasure; psychomotor retardation; fatigue or loss of energy; feelings of worthlessness or guilt; suicidal thoughts.

The DSM-5 proposes a minimum of three depressive symptoms for the mixed specifier, but some studies have suggested that a threshold of two associated depressive symptoms would be enough to confirm the mixed specifier (Tohen et al. 1990; McElroy et al., 1992).

There is a pressing need to further validate the mixed specifier criteria that appears in DSM-5, and as well evaluate and compare the efficacy of anti-manic treatments in these individuals. The objective of the present post-hoc analyses was to describe the frequency of mixed features in bipolar I patients with manic episodes in two pivotal randomised placebo-controlled asenapine studies. Mixed features were defined either according to DSM-5 by the presence of at least three depressive symptoms, or by the presence of only two depressive symptoms. Treatment outcome was correlated with clinical variables (e.g., number and severity of depressive symptoms). Using patient-level data from these studies, this paper aimed to evaluate the effect of asenapine, olanzapine or placebo treatment on manic and depressive symptoms in bipolar I patients with manic episodes with depressive features as defined in DSM-5.

2. Methods

These *post-hoc* analyses include patient-level data from two identically designed 3-week, randomised, double-blind, flexible dose, placebo- and olanzapine-referenced clinical trials in patients with bipolar I disorder (NCT00159744; NCT00159796). 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 before enrollment to either of the trials.

2.1. Study designs and patient populations

The study designs and patient populations have been previously described (McIntyre et al., 2009, 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 trials included adult patients with a current DSM-IV-TR diagnosis of bipolar I disorder associated with manic/mixed episodes with a Young Mania Rating Scale (YMRS) (Young et al., 1978) total score ≥20 at screening and baseline, a current episode that began <3 months before screening, and a documented history of ≥1 moderate to severe manic or mixed episode, with or without psychotic features. Principal exclusion criteria 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.

Limited doses of specific benzodiazepines and non-benzodiazepine sedative-hypnotics were only allowed during the first week of treatment. All other psychotropic medications were prohibited (McIntyre et al., 2009, 2010).

2.2. Treatments

After single-blind placebo run-in periods of up to 7 days, patients were randomised to 3 weeks of asenapine (20 mg on day 1, flexible-dose 10 or 20 mg daily thereafter, dose divided morning and evening), placebo, or olanzapine (15 mg on day 1, flexible-dose 5–20 mg once daily thereafter) in a 2:1:2 ratio (McIntyre et al., 2009).

2.3. Assessments

YMRS and Clinical Global Impression for Bipolar Disorder (CGI-BP) scale (Guy, 1976) assessments were conducted at baseline and treatment days 2, 4, 7, 14, and 21 (or at endpoint). Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery, 1979) and Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) assessments were conducted at baseline and treatment days 7 and 21 (or at endpoint). All the raters underwent formal training in the YMRS, PANSS and MADRS in order to maximize inter-rater reliability.

To ascertain approximate specifiers for DSM-5 mixed features, each mixed feature was linked to the corresponding MADRS/PANSS item:

- depressed mood (MADRS item 1 or 2),
- fatigue, loss of energy (MADRS item 7),
- diminished interest/pleasure (MADRS item 8),
- psychomotor retardation (PANSS item G7),
- worthlessness, guilt feelings (MADRS item 9),
- suicidal thoughts (MADRS item 10).

Different cut-offs on MADRS/PANSS item scores were used to define depressive symptom severity: items with a score of (A) ≥1 on the MADRS items and ≥2 on the PANSS item (mild symptoms), (B) ≥2 on the MADRS items and ≥3 on the PANSS item (moderate symptoms), (C) ≥3 on the MADRS items and ≥4 on the PANSS item (severe symptoms). Severity was also determined according to the number of depressive symptoms (i.e. at least 2 and at least 3).

2.4. Statistical analyses

These *post-hoc* analyses were based on the modified intent-to-treat (ITT) dataset, which comprised all randomised patients who took at least one dose of study medication and had at least one valid post-baseline YMRS assessment. Analyses were conducted for observed cases data on selected visits, as well as study endpoint (using last observation carried forward [LOCF]), for each dataset. Statistical analyses were conducted on change scores using an analysis of covariance (ANCOVA) model, with baseline values used as covariates; neither study nor the interaction of study × treatment effect were included as factors because no significant differences were found between studies. For continuous measures, comparisons were made for asenapine versus placebo, olanzapine versus placebo, and asenapine versus olanzapine at each visit using the difference in least squares (LS) mean change from baseline. Within-subject mean changes from baseline were assessed using *t*-tests. For categorical measures, the *p*-values are based on a Cochran–Mantel–Haenszel test for the association between treatment groups and response/remission status. All statistical tests were 2-tailed, with statistical significance set at $p<0.05$. No adjustments were made for multiple comparisons.