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Major depressive disorder with subthreshold hypomania (mixed features): Clinical characteristics of patients entered in a multiregional, placebo-controlled study☆

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ABSTRACT

Major depressive disorder (MDD) associated with subthreshold hypomanic symptoms (mixed features), has been identified as a distinct nosological entity in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). We identified the predominant manic symptoms present at baseline in a multiregional, placebo-controlled trial involving 211 patients with MDD with mixed features (Clinicaltrials.gov NCT01421134). Patients with 2 or 3 DSM-5 criteria defined manic symptoms were eligible for the study. At study baseline, increased talkativeness (pressure to keep talking) and flight of ideas (racing thoughts) were endorsed by approximately 65% of patients and a decreased need for sleep was endorsed by 40% of patients. Approximately 60% of patients also endorsed irritability and distractibility at baseline although these symptoms are not generally counted as part of the "mixed" depression diagnosis as they may overlap with criteria for MDD. Thus, five clinical symptoms characterized the manic presentation in the majority of patients diagnosed as having MDD with "mixed" features in this first placebo-controlled trial examining the use of a psychotropic medication (lurasidone) in this population. Our findings support the designation of MDD with mixed features specifier and suggest that this subpopulation of depressed patients may warrant additional medication beyond antidepressants.

1. Introduction

Twenty-five to forty percent of patients with major depressive disorder (MDD) present with concurrent manic symptoms during acute mood episodes that fall short of meeting the criteria for hypomania (bipolar II disorder) or mania (bipolar I disorder) (Judd and Akiskal, 2003; Sato et al., 2003; Benazzi, 2003, 2008; Suppes et al., 2005; Gazalle et al., 2005; McElroy, 2008; Goldberg et al., 2007, 2009; Gonzalez-Pinto et al., 2011; Nusslock and Frank, 2011; Angst et al., 2010, 2011; Merikangas et al., 2011; APA, 2013; Mcintyre et al., 2013, 2015; Targum and Nierenberg, 2011; Koukopoulos et al., 2013; Sani et al., 2014; Zaninotto et al., 2014). The DSM-5 classification added a specifier for depressive disorders to account for subthreshold manic symptoms that occur in acutely depressed patients and designated this new diagnostic category major depressive disorder with mixed features (APA, 2013; Hu et al., 2014). Using these criteria in a multi-site survey of 506 acutely depressed MDD patients, McIntyre et al. (2015) reported that 26% of these patients met the "mixed" features specifier. Conventional antidepressants may be ineffective in treating the manic and/or depressive components of "mixed" depression and may even precipitate or exacerbate manic symptoms (Sato et al., 2003; Goldberg et al., 2007; Benazzi, 2008; Zimmermann et al., 2009; Angst et al., 2011; APA, 2013). Consequently, some clinical studies have evaluated the use of atypical antipsychotic medications for patients with "mixed" depression (Patkar et al., 2012; Mcintyre et al., 2013; Suppes et al., 2015).

Some researchers believe that this new diagnostic designation is simply a precursor of bipolar disorder and that patients meeting these criteria should be treated as such (Benazzi, 2005; APA, 2013; Zaninotto et al., 2014). Koukopoulos et al. (2013) believe that the DSM-5 designation of MDD with mixed features is inadequate because it does not include psychomotor agitation or irritability as symptoms and may fail to identify many depressed patients who have mixed states. Recently, Sani et al. (2014) reported that psychic agitation, marked irritability, and mood reactivity were common symptoms in a study of 406 MDD patients presenting with mixed depression.

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Ultimately, the value of any change in a diagnostic classification system is to provide a more consistent and clinically meaningful representation of the disorders it attempts to classify and to facilitate earlier diagnostic differentiation to abet more effective treatment strategies (Targum et al., 2008; Stahl, 2013; Hu et al., 2014). One approach to examine the utility of a "new" diagnostic designation is to examine the clinical presentation of patients that clinicians believe meet criteria for the disorder. In the present study, we examined the presence and severity of depressive and manic symptoms in 211 patients with depression with mixed features who participated in a multiregional, placebo-controlled clinical trial. These findings reflect the thorough clinical assessments of investigators in 5 different countries regarding the clinical characteristics of patients meeting the diagnostic criteria for "mixed" depression.

2. Materials and methods

This study was done as part of the subject selection approval process for a clinical trial called RESOLVE 1: a randomized, 6-week, double-blind, placebo-controlled, flexible-dose, parallel group study of lurasidone for the treatment of major depressive disorder with mixed features (Clinicaltrials.gov NCT01421134). Forty-four clinical trial sites located in Russia, Serbia, Ukraine, United Kingdom, and the United States participated in the study between April 2011 and October 2014. A full description of the study design and treatment results has been reported elsewhere (Suppes et al., 2015).

In this study, "mixed" depression was defined as a patient who currently met the diagnostic criteria for MDD, was currently experiencing a major depressive episode (diagnosed by DSM IV TR with the current major depressive episode duration of at least 2 weeks but less than 12 months) and who had *two or three* manic symptoms that occurred on most days over at least the last 2 weeks prior to screening. These criteria differ from the DSM-5 criteria that specified that 3 manic symptoms were required for this diagnosis (APA, 2013).

The eligible manic symptoms included the following seven symptoms (per DSM-5):

- Elevated, expansive mood
- Inflated self-esteem or grandiosity
- More talkative than usual or pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Increase in energy or goal-directed activity (either socially, at work or school, or sexually)
- Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted from insomnia).

The diagnosis was confirmed by the Structured Clinical interview for DSM-IV, clinical trial version (SCID-CT) that was modified to include "mixed" features for this study (First et al., 2007). Patients were excluded from the study if they had a lifetime history of any bipolar I manic, mixed manic episode, or psychotic disorder, had treatment resistant depression, or any Axis I or Axis II diagnosis (other than MDD) that was the primary focus of treatment within 3 months of the screen visit (including all anxiety disorders, PTSD, eating disorders, or alcohol or substance abuse or dependence).

In addition, eligible patients had a minimum score of 26 on the Montgomery Asberg Depression Rating Scale (MADRS) at screening and baseline utilizing the Structured Interview Guide for the MADRS (Montgomery and Asberg, 1979; Williams and Kobak, 2008). The Young Mania Rating Scale (YMRS) was used to assess manic symptoms; no minimum YMRS entry criterion was used (Young et al., 1978). A "dual" review process was used for diagnostic verification, identification of excluded psychiatric diagnoses, and confirmatory scoring of the MADRS and YMRS that included audio-digital recording of the key screening instruments and a site-independent review (Targum and Pendergrass, 2014).

The study was conducted in compliance with the informed consent regulations of an Institutional Review Board (IRB) and International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) Guidelines at the 44 clinical trial sites. All potential subjects consented to participate in the study and to the use of audio-digital recording instruments for independent clinical review. Raters at all trial sites participated in a standardized, formal rater training and certification program and met minimum qualification standards for inter-rater reliability between raters and demonstration of interviewing competence. The training program included didactic training for all efficacy measures at the investigator meeting or on-line, observation and scoring of expert demonstration MADRS and YMRS interviews with subsequent inter-rater reliability assessment of their scoring performance, and interviewing skills assessment via mock recorded MADRS and YMRS interviews. Audio-digital recording and site-independent scoring of the MADRS and YMRS interviews during the study provided additional opportunities to identify poor ratings performance. Rater remediation was provided when necessary although some raters were ultimately exempted from rating in this study.

Statistical analysis included Student's t test and Chi-square analyses to evaluate group differences and examine the frequency of each presenting manic or depressive symptom.

3. Results

211 patients met the study eligibility criteria and were enrolled in the study across 44 clinical trial sites. The study enrolled 62 patients from the United States, 4 from the United Kingdom, 52 from Serbia, 62 from Ukraine, and 31 from the Russian clinical trial sites. The study was conducted between April 2011 and October 2014.

3.1. Characteristics of the enrolled subjects

Table 1 lists the demographic and symptom severity scores for the 211 patients who met the entry criteria for "mixed" depression and were randomized in the study. The mean MADRS score was 33.2 ± 4.2 (SD), the mean YMRS score was 10.7 ± 4.5, and the mean Ham-A score was 16.9 ± 6.4 for the study population at the baseline visit.

Table 2 presents the individual mean item scores of the MADRS and YMRS as scored by site-based raters at baseline. The MADRS items of

Table 1
Patients with "mixed" depression: demographic and clinical characteristics.

All subjects	211
Male n (%)	64 (30.3%)
Age, years n (SD)	44.8 (12.2)
Age ≤ 30 n (%)	31 (14.7%)
Age 31–50	109 (51.7%)
Age ≥ 51	71 (33.6%)
Race n (%)	
Black	27 (12.8%)
Caucasian	181 (85.8%)
Other	3 (1.4%)
	Mean (SD)
Number of lifetime major depressive episodes	
Total number	4.4 (4.0)
Number with mixed features	2.4 (3.3)
Duration of current episode, days	
Major depressive features	104.1 (83.8)
Concurrent mixed features	77.2 (80.5)
MADRS score	33.2 (4.2)
CGI-S score	4.5 (0.6)
Young Mania Rating Scale (YMRS) score	10.7 (4.5)
HAM-A total score	16.9 (6.4)
Sheehan Disability Scale total score	20.2 (5.0)