Journal of Affective Disorders 197 (2016) 1–7

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Evaluating response to mood stabilizers in patients with mixed depression: A study of agreement between three different mania rating scales and a depression rating scale

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ARTICLE INFO

Article history:
Received 13 November 2015
Received in revised form
18 February 2016
Accepted 26 February 2016
Available online 3 March 2016

Keywords:
Agreement study
Bipolar disorder
Depression rating scale
Mania rating scales
Mixed symptoms
Mood stabilizers

ABSTRACT

Background: The aim of the present study was to evaluate agreement between three pairs formed by one of three mania scales (Young Mania Rating Scale [YMRS], Bech-Rafaelsen Mania Scale [BRMS], or the Clinician-Administered Rating Scale for Mania [CARS-M]) and a single depression scale (21-item Hamilton Depression Rating Scale [21-HAM-D]) for evaluation of response to mood stabilizers in patients with mixed bipolar disorder.

Methods: Between 2010 and 2014, 68 consecutive bipolar type I and II outpatients with mixed depression as per DSM-IV-TR and Cincinnati criteria were included in this 8-week open-label trial to randomly receive carbamazepine, lithium carbonate, or valproic acid as monotherapy.

Results: Patterns of response (defined as a reduction of at least 50% in one of the mania scales and on the 21-HAM-D) were strikingly similar: 21-HAM-D+YMRS=22.1%, 21-HAM-D+BRMS=20.6%, and 21-HAM-D+CARS-M=23.5% ($p<0.368$). Assessment of agreement revealed very high kappa coefficients: 21-HAM-D+YMRS vs. 21-HAM-D+CARS-M, kappa=0.87; 21-HAM-D+YMRS vs. 21-HAM-D+BRMS, kappa=0.78; 21-HAM-D+CARS-M vs. 21-HAM-D+BRMS, kappa=0.91 ($p<0.001$).

Limitations: The decision to combine a depression rating scale with any one mania rating scale to assess treatment response in patients with mixed depression is questionable.

Conclusions: The present study suggests that any one of the three tested mania rating scales (YMRS, BRMS, and CARS-M) can be combined with the 21-HAM-D to assess treatment response in patients with mixed bipolar disorder. This should give clinicians an added measure of confidence in using this strategy until valid, and specific instruments are developed for assessment of mixed states.

1. Introduction

Mixed states were first described by Emil Kraepelin and Wilhelm Weygandt in 1899 (Kraepelin, 1899; Weygandt, 1899). In the decades immediately after Kraepelinian delineation of manic-depressive illness, the crucial role of mixed states was almost completely neglected (Perugi et al., 2014). The renaissance of mixed states began in the 1970s, in the U.S. and Europe (Akiskal, 1992; Angst et al., 2010; Benazzi and Akiskal, 2001; Bourgeois et al., 1995; Kotin, 1972; Koukopoulos et al., 2007; Koukopoulos and Koukopoulos, 1999; Perugi et al., 1997, 2014; Swann et al., 2007; Winokur, 1969). Following the publication of an important review article on bipolar mixed states by McElroy in 1992 (McElroy et al., 1992), there has been increased clinical and research interest in this issue, with more than 2000 articles on bipolar mixed states published since (Faedda et al., 2015).

The nosological definition of these states has undergone several changes since the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Pacchiarotti et al., 2011). In the DSM I, published in 1952, the term “manic depressive reaction, mixed type” was used. The second edition, in 1968, required that “manic and depressive symptoms appear[ed] almost simultaneously” in order to diagnose “mixed” manic-depressive disorder. In 1980 and 1987, in the DSM-III and DSM-III-R, respectively, the diagnosis of “bipolar disorder, mixed” required a “full symptomatic

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http://dx.doi.org/10.1016/j.jad.2016.02.064
0165-0327/

picture of both manic and major depressive episodes, intermixed or rapidly alternating every few days." In the DSM-IV and DSM-IV-TR, in 1994 and 2000, the term "mixed episode" was introduced and required that criteria were met for both manic and depressive episodes each day for at least one week. Both the DSM-IV-TR and the World Health Organization International Classification of Diseases, 10th edition (ICD-10) definitions of a mixed state were too restrictive and were rarely satisfied in clinical settings, resulting in the exclusion of many patients who may be clinically considered to be experiencing such a state (Shim et al., 2014, 2015). Finally, in DSM-5, the mixed episode as defined in DSM-IV-TR has been removed, and sub-threshold non-overlapping symptoms of the opposite pole are identified using a "mixed features" specifier to be applied to mania, hypomania, and major depressive episode (Perugi et al., 2014). DSM-5 introduced a less stringent specifier to supplement categorical diagnoses with dimensional approaches, with a "mixed categorical-dimensional" approach, in which three symptoms of the opposite pole suffice, thereby creating depression and mania with mixed features, respectively (Malhi et al., 2014; Vieta and Valenti, 2013). The effects and clinical implications associated with use of the DSM-5 specifier "with mixed features", including the presence of specific clinical characteristics, have yet to be fully assessed (Shim et al., 2015). The mixed-features specifier of DSM-5 remains a matter of discussion and a target of criticism, particularly when applied to the subgroup of patients with mixed depression (Koukopoulos and Sani, 2014; Perugi et al., 2015). In the DSM-5, both Bipolar Disorder and Major Depressive Disorder can be diagnosed with mixed features, and the mixed specifier definition requires "non-overlapping" symptoms. As a consequence, for a diagnosis of Major Depression Disorder with mixed features, depression is present but the allowed manic symptoms exclude irritability, agitation, and distractibility, which are clinically relevant and common in mixed episodes (Sani et al., 2014a). Some authors believe that the diagnosis of mixed symptoms should receive special attention in the revision process of the future edition of ICD from WHO, ICD-11 (Ostergaard et al., 2012).

Compared with patients with bipolar disorder who exhibit pure manic/hypomanic or depressive episodes, the presence of mixed mood states is associated with a more severe course of illness, younger age of onset, more frequent occurrence of psychotic symptoms, major risk of suicide, higher rates of comorbidities, and longer time to achieve remission (Baldessarini et al., 2010; Shim et al., 2014, 2015; Undurraga et al., 2012).

Hence, the search for objective measures that can be used to assess mixed symptoms in bipolar patients is particularly important. Despite the need for specific instruments to measure mixed symptoms in patients with bipolar disorder (Cassidy et al. 1998a,b; Gonzalez-Pinto et al., 2003; Pacchiarotti et al., 2013; Zimmerman et al., 2014), to date, the concomitant use of a mania scale and a depression scale has been the most common strategy used for this purpose, however controversial. Whether differences in the frequency of response to mood stabilizer therapy exist when distinct manic rating scales are combined with a single depression rating scale for assessment of patients with mixed bipolar disorder remains unclear.

The present study sought to evaluate agreement between three pairs of instruments, each of which was composed of a distinct mania rating scale and the same depression rating scale, for assessment of response to mood stabilizers in bipolar patients with mixed symptoms.

2. Methods

2.1. Patients

Volunteers for the present study were recruited through the Teaching and Research Program in Mood Disorders (PROPESTH) of Hospital Psiquiátrico São Pedro, in the city of Porto Alegre, Brazil. The provenance of volunteers varied widely, including public basic health units and private practices; some had responded to advertisements placed on the local media and through PROPESTH profiles on social media. Subjects aged 18–65 years, who were not on psychopharmacological therapy or any other psychoactive drug specifically for mood disorders in the preceding 30 days, were eligible for inclusion. Those with substance abuse disorder were required to be substance-free for at least 30 days. Patients with organic brain syndrome, pregnant women, nursing mothers, individuals at current risk of suicide, and those meeting any criteria for inpatient psychiatric treatment were not included in the study. This study was approved by the Ethics Committee of Hospital Psiquiátrico São Pedro, Porto Alegre, Brazil, with protocol #09013.

After a full explanation of the purpose of the study, written informed consent was obtained from each participant. First, participants were asked to complete two self-report instruments for mood disorders screening: the Patient Health Questionnaire (PHQ9) for unipolar mood disorder (de Lima Osorio et al., 2009) and the Hypomanic Symptoms Checklist, Brazilian Version (HCL-BV-32) for bipolar mood disorder (Soares et al., 2010). Volunteers who scored above the cutoff point for at least one of the two screening instruments subsequently underwent a structured diagnostic interview with administration of the MINI (Sheehan et al., 1998) and Mini Mental (Folstein et al., 1975). Subjects who received a DSM-IV-TR diagnosis of mood disorder through the MINI (depressive, hypomanic, or mixed episode) underwent a diagnostic clinical interview to confirm or rule out the screening diagnosis. Due to the outpatient nature of the program, volunteers with manic symptomatology were referred for psychiatric admission and were considered ineligible to participate further in the present study. The clinical interview was conducted by a clinical psychiatrist with ample experience in mood disorders. In the clinical interview, the diagnosis of mixed bipolar symptoms was not restricted to the DSM-IV-TR mixed episode criteria; it was also based on the Cincinnati criteria (McElroy et al., 1992; Swann et al., 2013a) for mixed symptoms, which better approximate the criteria for the current DSM-5 mixed specifier (Table 1). Patients who received a diagnosis of bipolar mood disorder with mixed symptoms at clinical interview were referred for treatment under a specific protocol. In an open trial design, patients were randomized to receive one of the three protocol mood stabilizers (carbamazepine, lithium carbonate, or valproic acid) as monotherapy. After 8 weeks, response to medication was assessed (defined as a reduction of at least 50% in both the depression rating scale score and a mania rating scale score from baseline).

Regarding dosage, carbamazepine doses could range from 800 to 1200 mg/day (corresponding to plasma levels of 8–12 mcg/mL), lithium carbonate doses from 900 to 1200 mg/day (serum levels of 0.8–1.2 mEq/L) and valproic acid doses from 1000 to 1500 mg/day (plasma levels of 50–125 mcg/mL).

Assessments included the 21-item Hamilton Depression Rating Scale (21-HAM-D) (Hamilton, 1960) and the Mania Rating Guide (MRG) (Shansis et al., 2003). The MRG is a semi-structured interview designed by Shansis et al. (2003) to aid in simultaneous completion of three mania rating scales: the Young Mania Rating

Table 1
Cincinnati criteria for mixed mania according to McElroy et al. (1992).

A	A full manic syndrome by DSM–III-R criteria
B	Simultaneous presence of at least three associated depressive symptoms
C	Simultaneous presence IS defined as manic and depressive symptoms occurring at the same time OR alternating extremely rapidly, within minutes
D	Manic and depressive symptoms are simultaneously present for at least 24 h