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Symptoms of depression as possible markers of bipolar II disorder

Franco Benazzi *

Hecker Psychiatry Research Center, Forli, Italy
University of California at San Diego (USA) Collaborating Center, United States
Department of Psychiatry, University of Szeged, Szeged, Hungary
Department of Psychiatry, National Health Service, Forli, Italy

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Abstract

Underdiagnosis and misdiagnosis of bipolar-II disorder (BP-II) as a major depressive disorder (MDD) are frequently reported. The study aim was to find which symptoms of depression could be possible cross-sectional markers of BP-II, in order to reduce underdiagnosing BP-II.
Methods: Consecutive 379 BP-II and 271 MDD major depressive episode (MDE) outpatients were interviewed with the Structured Clinical Interview for DSM-IV, the Hypomania Interview Guide, and the Family History Screen, by a senior psychiatrist in a private practice. Inside-MDE hypomanic symptoms (elevated mood and increased self-esteem always absent by definition) were systematically assessed. Mixed depression was defined as an MDE plus 3 or more inside-MDE hypomanic symptoms, a definition validated by Akiskal and Benazzi.
Results: The MDE symptoms significantly more common in BP-II versus MDD were weight gain, increased eating, hypersomnia, psychomotor agitation, worthlessness, and diminished ability to concentrate. The inside-MDE hypomanic symptoms significantly more common in BP-II were distractibility, racing/crowded thoughts, irritability, psychomotor agitation, more talkativeness, increased risky and goal-directed activities. Multiple logistic regression showed that hypersomnia, racing/crowded thoughts, irritability, and psychomotor agitation were independent predictors of BP-II. Irritability had the most balanced combination of sensitivity and specificity predicting BP-II. Psychomotor agitation had the highest specificity but the lowest sensitivity. Racing/crowded thoughts had the highest sensitivity but the lowest specificity. These symptoms had a similar positive predictive value (PPV) for BP-II, which was around 70% (PPV is more clinically useful than sensitivity and specificity), which in turn was similar to the PPV of mixed depression and atypical depression (two diagnostic clinical markers of BP-II). All possible combinations of these symptoms had a PPV similar to that of the individual symptoms. The validity as BP-II markers of these symptoms was supported by a significant association with bipolar family history.
Conclusions: Hypersomnia, racing/crowded thoughts, irritability, and psychomotor agitation may be useful, cross-sectional markers of BP-II. Finding these symptoms in depression should lead the clinician to careful probing for history of hypomania, which should reduce the BP-II misdiagnosed as MDD. Results may also have treatment impacts, as antidepressants used alone (i.e., no concurrent mood stabilising agent) in BP-II depression misdiagnosed as MDD may increase cycling.

Keywords: Bipolar II disorder; Depressive mixed state; Mixed depression; Hypersomnia; Irritability; Psychomotor agitation

1. Introduction

Bipolar-II disorder (BP-II) is frequently misdiagnosed as major depressive disorder (MDD) (Dunner, 2003; Howard et al., 2003; Hirschfeld et al., 2003). Instead, in recent community and clinical samples studies, the BP-II to MDD ratio was found to be near one by improving the probing for history of hypomania (Hantouche et al., 1998; Akiskal and Pinto, 1999; Manning et al., 1999; Benazzi, 2003a,b; Angst et al., 2003; Benazzi, 2004; Rybakowski et al., 2005; Smith et al., 2005).

Abbreviations: BP-II, bipolar II disorder; CI, confidence interval; *df*, degrees of freedom; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; DSM-IV-TR, diagnostic and statistical manual of mental disorders, fourth edition, text revised; GAF, global assessment of functioning scale; MDD, major depressive disorder; MDE, major depressive episode; NPV, negative predictive value; OR, odds ratio; SCID-CV, structured clinical interview for DSM-IV axis I disorders, clinician version; SE, sensitivity; SP, specificity; PPV, positive predictive value.

* Via Pozzetto 17, 48010 Castiglione di Cervia RA, Italy. Tel.: +39 335 6191 852; fax: +39 054 330 069.
E-mail address: FrancoBenazzi@FBenazzi.it.

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In clinical practice, cross-sectional clinical markers (i.e., current features directly observed by the clinician, and not retrospective features) suggesting that what seems to be MDD may actually be BP-II would be very useful. Clinical markers of BP-II should then induce a careful probing for history of hypomania.

Two cross-sectional features of the major depressive episode (MDE) were found to be useful clinical markers of BP-II: atypical depression and atypical depression symptoms (Angst et al., 2002, 2003; Akiskal, 1996; Perugi et al., 2003; Agosti and Stewart, 2001; Benazzi, 2002a), and mixed depression (depressive mixed state, defined as an MDE mixed with hypomanic symptoms) (Akiskal and Pinto, 1999; Benazzi, 2002b; Koukopoulos, 2003; Akiskal and Benazzi, 2003; Sato et al., 2003; Ducrey et al., 2004; Mantere et al., 2004; Benazzi, 2005).

The present report focuses on the search for symptoms of depression (MDE symptoms and inside-MDE hypomanic symptoms) which could be useful cross-sectional markers of BP-II.

A clinical marker has similarities with a screening test and it could share similar statistics. The most common statistics in diagnostic testing are sensitivity, specificity, positive predictive value, and negative predictive value (Altman et al., 2000; Dawson and Trapp, 2001; Armitage et al., 2002; Zimmerman et al., 2004). Among these, the positive predictive value is more important in clinical practice because it is the probability that a person who is identified as ill by the marker actually has the illness.

Study aim was to test the positive predictive value for BP-II of MDE symptoms and of inside-MDE hypomanic symptoms.

2. Methods

More details on study methods can be found in previous reports (Akiskal and Benazzi, 2003; Benazzi and Akiskal, 2003; Benazzi, 2003c).

2.1. Study setting

An outpatient psychiatry private practice in Emilia-Romagna region, northern Italy. This setting is more representative of the mood disorders usually seen in psychiatric clinical practice in this area (apart from the psychotic ones) because (1) it is the first or second (after general practitioners) line of treatment of mood disorders, (2) the most severe and socially disadvantaged individuals are usually seen in tertiary-care centers (i.e., national health services and academic centers), (3) mood disorder patients do not like to be treated in the national health services for fear of stigma, and 4) most individuals can afford a private psychiatrist (fee-for-service) in this area, reducing a possible income bias.

2.2. Interviewer

A senior clinical and mood disorder research psychiatrist.

2.3. Patient Population

Consecutive 379 BP-II and 271 MDD outpatients, presenting voluntarily (i.e., self-referred) for the treatment of a major depressive episode (MDE), were included in the last 6 years. Substance-related and borderline personality disorders were excluded because may confound the diagnosis of BP-II, due to the high background mood instability present in these disorders (Akiskal and Pinto, 1999). Anyway, these disorders are rare in the study setting (Benazzi, 2000). Clinically significant general medical illnesses and cognitive disorders were also excluded. Patients had to present off psychoactive drugs for at least 2 weeks (apart from a few individuals on small doses of benzodiazepines) in order not to include patients with drug-induced or drug-suppressed hypomanic symptoms.

2.4. Assessment instruments

During the first visit, the following instruments were used: (1) the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (First et al., 1997) (SCID-CV, reported inter-rater reliability $k=0.70-1.0$), as modified by Benazzi and Akiskal (2003) to improve the detection of BP-II; the question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' (1999) definition of crowded thoughts (i.e., mind continuously full of non-stop thoughts), following Kraepelin's description of the grading of the thought disorders of hypomania (1921); (2) the Global Assessment of Functioning scale (GAF, in the SCID-CV) for assessing MDE severity; (3) the Hypomania Interview Guide (Williams et al., 1994) (reported inter-rater reliability $k=0.88$) to assess inside-MDE hypomanic symptoms; (4) the structured Family History Screen (Weissman et al., 2000) (reported inter-rater reliability $k=0.85$) for assessing bipolar disorders (type I and II) family history in probands' first-degree relatives. Often, family members or close friends supplemented clinical information during the interview, increasing the validity of the diagnosis of BP-II and of the family history (Akiskal et al., 2000; American Psychiatric Association, 2000). The interviewer's inter-rater reliability k for the diagnosis of BP-II was 0.73 (Benazzi, 2003c). Ratings were cross-sectional: for the MDE, the time frame was the last 2 weeks before the interview, for the inside-MDE hypomanic symptoms, it was the last week before the interview.

2.5. Interview methods

Systematic interviews about history of hypomanic and manic episodes were always conducted soon after the diagnosis of MDE and before the assessment of study variables, in order to avoid a possible bias related to knowledge of bipolar signs (Ghaemi et al., 2002). The SCID-CV is partly semi-structured and based on clinical evaluation (not on simple yes/no answers to structured questions). Wording of the sentences can be changed to improve and to check the understanding by the interviewee. This is an important advantage versus fully structured interviews because this interview method has been