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Research report

Self-assessment and characteristics of mixed depression in the French national EPIDEP study

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ABSTRACT

Background: Studies on mixed depression have been conducted so far on the basis of DSM-IV manic symptoms, i.e., a list of 7 symptoms which may provide limited information on the subsyndromal features associated with a full depressive episode.
Methods: As part of the EPIDEP National Multisite French Study of 493 consecutive DSM-IV major depressive patients evaluated in at least two semi-structured interviews 1 month apart, 102 (23.8%) were classified as mixed depressives (≥ 3 hypomanic symptoms), and 146 (34%) as pure depressives (0 hypomanic symptom), after exclusion of bipolar I patients; hypomanic symptoms were assessed with the Multiple Visual Analog Scales of Bipolarity (MVAS-BP, 26 items) of Ahearn–Carroll in a self assessment format. A narrower definition of mixed depression, resting on those MVAS-BP items referring to DSM-IV hypomanic symptoms was also tested, as a sensitivity analysis.
Results: Compared to pure depressives, mixed depressive patients had more psychotic symptoms, atypical features and suicide attempts during their index episode; their illness course was characterized by early age at onset, frequent episodes, rapid cycling, and comorbidities. Mixed depressive patients were more frequently bipolar with a family history of bipolar disorder, alcohol abuse, and suicide. A dose–response relationship was found between intradepression hypomania and several clinical features, including temperament measures. The following independent variables were associated with mixed depression: hyperthymic temperament, cyclothymic temperament, irritable temperament, and alcohol abuse. Using the narrower definition of mixed depression missed risk factors such as suicidality and comorbidities.
Limitations: The following are the limitations of this study: retrospective design, recall bias, lack of sample homogeneity, no cross-validation of findings by hetero-evaluation of hypomanic symptoms.
Conclusions: EPIDEP data showed the feasibility and face validity of self-assessment of intradepressive hypomania. They replicated previous findings on the severity and high suicidal risk of mixed depression profile. They confirmed, for mixed depression, that mixed states occur when mood episodes are superimposed upon temperaments of opposite polarity. They finally suggested that a definition of mixed depression only based on DSM-IV-TR hypomanic symptoms may not allow to identify the most unstable subforms of the entity.

1. Introduction

Mixed states combine manic and depressive symptoms within the same episode of illness (Swann, 2011). They are narrowly defined in DSM-IV on the basis of the simultaneous presence of a full manic and a full depressive syndrome for at least 1 week, excluding therefore mixed states with hypomania, or within the rest of the bipolar spectrum (American Psychiatric Association, 1994). Nevertheless, predominately manic and predominately depressive mixed states have been recognized at least since Kraepelin (1921). The former, better known as 'dysphoric' or 'depressive' mania, have been the focus of numerous studies, in recent years (McElroy et al., 2000; Swann, 2011). Although they may be even more common than depressive mania, predominately depressive mixed states ('mixed depression') have been far less studied (Swann, 2011). Most of the time, the recognition of manic or hypomanic features during depressive episodes was based on the list of symptoms provided in DSM-IV (Goldberg et al., 2009). As this is a limited list of symptoms,

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we hypothesized than a more complete and fine-grained instrument based on self-assessment would be capable to capture more accurately the subthreshold hypomanic symptomatology of mixed depression (Hantouche et al., 2001a).

The current study was designed to (1) assess, by means of self-rating, the prevalence of mixed depression and intradepressive hypomanic features in a large sample of major depressive patients, (2) examine the main characteristics of mixed (vs. pure) depressives in this population, (3) determine the risk factors associated with mixed depression in the latter.

2. Methods

2.1. EPIDEP design and general findings

EPIDEP involved 48 specially trained psychiatrists working in 15 different centers in France. It was scheduled in two phases. In phase 1537 patients with major depressive episode (MDE) were recruited by using a semi-structured interview based on DSM-IV criteria (American Psychiatric Association, 1994) and assigned to DSM-IV subtypes on clinical grounds. Based on this interview, patients meeting DSM-IV criteria for mania or hypomania were excluded from the study. Intensity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and mood disturbances were self-reported by assessing the Multiple Visual Analog Scales of Bipolarity (MVAS-BP) (Ahearn and Carroll, 1996; Hantouche et al., 2001a). In phase 2, scheduled an average of four weeks after the first visit, a systematic search for DSM-IV hypomanic episodes was made by using a semi-structured interview and the checklist of hypomania (Angst, 1992). Sociodemographic characteristics, illness course, family history, psychiatric comorbidity and information on affective temperaments were also recorded during the second visit. Family history for mental disorders was assessed according to the Research Diagnostic Criteria family history version (Andreasen et al., 1977). Lifetime comorbidity for anxious, substance use and eating disorders was recorded by using a semi-structured interview based on DSM-IV criteria. Self-reporting of affective temperaments (hyperthymic, depressive, cyclothymic and irritable) with 4 questionnaires was filled out by the patient. Categorical definitions of temperament were used for the current analyses, excepted when correlations were computed: in this case, we used dimensional measures (Hantouche et al., 2001b).

From the 537 patients included at visit 1493 returned at visit 2. Among the latter, 256 were classified as unipolar (UP), 41 as bipolar (BP) I and 196 as BP spectrum (including 144 patients with spontaneous hypomanias and 52 whose hypomanias were associated with antidepressant treatment).

For further details on the methodology and previous findings of EPIDEP, the reader is referred to Hantouche et al. (1998, 2003), Akiskal et al. (2003a, 2003b).

2.2. Patient selection for the present study

Mania/hypomania during depression was evaluated by self-assessment with the MVAS-BP. This scale permits the simultaneous evaluation of each dimension of bipolarity on the basis of its manic or depressive poles. MVAS-BP has 26 dimensions. In the French version, the evaluation of each dimension varied from 0 to 100, i.e., extreme depressive *pole*=0, extreme manic *pole*=100 (Hantouche et al., 2001a). For each dimension ≥ 65, the corresponding manic/hypomanic symptom was judged to be present. Patients were considered as suffering from "mixed depression" when at least 3 manic/hypomanic symptoms were associated to their depression (Benazzi, 2007a); patients without any associated manic/hypomanic symptom were considered as having "pure depression". As the MVAS symptoms reflect a broad definition of manic/hypomanic symptoms, which may be questionable to those who are skeptical about the mixed depression concept, especially those wedded to DSM-like manic symptoms, we also tested a narrower definition, restricting the mixed depression criteria to those who had 3 or more of DSM-like manic symptoms. With respect to this, the following were selected among the MVAS list: Thoughts are racing, Nothing can go wrong in my future, Making decisions in a snap, Always looking for new and exciting, Life extremely exciting, Feel totally capable, Feel like constantly on the go, Feel to have lots of energy, Have no faults, Feel charged with intensity, Moving in fast lane, Too busy to sleep, Feel best ever felt, Will be big success, Sex drive unbelievable, Enjoy everything, I am the greatest.

2.3. Statistical analyses

To compare the likelihood of having been exposed to a risk factor among mixed depressive patients to the likelihood of exposure among pure depressives, raw odds ratios were computed in univariate analyses. A stepwise logistic regression model was then used to identify risk factors associated with mixed depression. Based on the results of univariate analyses and literature data, the following variables were entered into the model as independent variables: age, gender, first episode polarity, diagnosis, number of hypomanic episodes in past year, hypomanic switches with antidepressants, number of suicide attempts in past year, family history of suicide attempt, family history of suicide, family history of alcohol abuse, family history of bipolar disorder, panic disorder, bulimia, anorexia, alcohol abuse, other substance abuse, valproate treatment during the year prior to study entry, hyperthymic temperament, cyclothymic temperament, depressive temperament, and irritable temperament. Adjusted odds ratios were subsequently computed in multivariate analyses. Odds ratios with 95% confidence intervals were used for observed associations.

For analysis of correlations, Pearson's test was used; where assumptions of normality were not adequately met, correlations were computed with Spearman's test.

3. Results

3.1. Patients

From the 493 patients re-examined at visit 2 in EPIDEP, only 429 were included in the current study. The forty-one BP I patients were excluded from the present analyses and for 23 patients, MVAS-BP scores were not documented. The mean age of the current study population was 46.15 ± 13.58 years. Seventy-three percent were female. The mean number of prior episodes was 6.35 ± 7.89. Multiple hospitalizations were recorded in 32%.

3.2. Epidemiology of intradepressive hypomanic symptoms

Fig. 1 presents the distribution of associated MVAS-BP hypomanic symptoms for the 429 depressed patients. Only 34% of the subjects had no hypomanic symptoms during their depressive episode (pure depression), while 23.8% had at least three associated hypomanic symptoms (mixed depression). Using the narrow definition of mixed depression, these rates were of 88.8% for the former and 11.2% for the latter. The frequency of the 26 MVAS-BP hypomanic symptoms during an index episode of mixed depression is shown in Table 1. The highest frequencies ($>40\%$) were for "People don't annoy me", "Feel angry", "Thoughts are racing" and "Fell special connection to people".