Overview of Mixed Depression in Italy

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According to a large international study, BD-II mixed depression can easily be misdiagnosed as major depressive disorder. Proper assessment and treatment of mixed depression in BD-II could have a positive impact on outcomes in bipolar disorder.

According to DSM-IV-TR, a mixed episode can occur only in bipolar I disorder (BD-I). A mixed episode requires a concurrent full-criteria major depressive episode (MDE) and a manic episode. Mixed mania has also been defined in the research as a manic episode plus three or more depressive symptoms (McElroy et al., 1992).

Until recently, mixed depression (i.e., MDE plus manic-hypomanic symptoms during the episode) was understudied. Most of the research comes from Perugi et al. (2001, 1997) in BD-I and Akiskal and Benazzi in bipolar II disorder (BD-II) and major depressive disorder (MDD) (Akiskal and Benazzi, 2003; Benazzi, 2000; Benazzi and Akiskal, 2001). Many of the main findings were replicated by Sato et al. (2003), Maj et al. (2003) and Judd et al. (2003).

This review will focus on BD-II and MDD outpatient mixed depression. The study setting is a large outpatient solo private practice in Italy that is more representative of mood disorders (apart from BD-I) usually seen in clinical practice in Italy. The most severe and socially disadvantaged (less representative) cases are usually seen through the national health service or university centers.

Community and clinical outpatient depression studies found that the BD-II to MDD ratio is near 1 (Angst et al., 2003; Benazzi, 2003a, 1997). Two long-term follow-up studies of MDD have also shown that around 50% of patients with MDD develop BD-I or BD-II (Angst et al., 2003; Goldberg et al., 2001). The high frequency of BD-II found in clinical outpatient depression samples is mainly related to interview methods. These include focusing more on overactivity than on mood change; use of semi-structured interviews; interviews by clinicians; and interviews of family members or close friends (Benazzi, 2003b; Benazzi and Akiskal, 2003b). The diagnosis of BD-II has higher inter-rater reliability and more correct diagnoses of BD-II and other mood disorders by these methods (Benazzi and Akiskal, 2003a; Brugha et al., 2001; Dunner and Tay, 1993; Simpson et al., 2002).

By strictly following the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV), hypomanic symptoms cannot be assessed during an MDE (Dunner and Tay, 1993). Instead, our studies in Italy always require the assessment of hypomanic symptoms using the Hypomania Interview Guide. In mixed depression, hypomanic symptoms of high mood and increased self-esteem were absent. The core hypomanic symptoms of mixed depression were irritability, racing thoughts, psycmohotor agitation and talkativeness (Akiskal and Benazzi, 2003). Systematic probing, and not spontaneous reporting, showed the presence of hypomanic symptoms during depression (which are less severe than manic symptoms and therefore less easily observable) (Benazzi and Akiskal, 2003a).

In our studies, hypomanic symptoms of mixed depression had to last at least one week and be present at the time of the interview. Patients were off psychoactive drugs for at least two weeks in order to avoid including antidepressant-induced mixed states (Akiskal and Pinto, 1999). Cross-sectional interviews were performed when individuals presented voluntarily for treatment of depression. Probing for BD-II followed soon after the diagnosis of depression was given, in order to avoid a possible bias related to the knowledge of bipolar signs (Ghaemi et al., 2002). The Table shows a picture of our current sample.

Mixed depression was more common in BD-II than in MDD. However, an interesting finding was that mixed depression was not uncommon in MDD. The best definition (i.e., the most clinically useful definition as a cross-sectional marker of BD-II) of mixed depression was found to be one based on a minimum of three hypomanic symptoms during major depression (Benazzi, 2001), compared to definitions based on combinations of specific hypomanic symptoms. This definition of mixed depression was similar to that used in mixed mania. Mixed depression had the best combination of sensitivity and specificity for BD-II diagnosis, as compared to several markers of BD-II, such as...
atypical depression, young age at onset, many MDE recurrences or family history (Benazzi, 2003c, 2002a, 2000; Ghaemi et al., 2002). An important finding was that a family history of BD in patients with MDD mixed depression was similar to that of patients with BD-II and that it was significantly higher than for MDD non-mixed depression. This finding was replicated by Sato et al. (2003).

The presence of hypomanic symptoms in MDD supports the continuity between MDD and BD-II (Benazzi, 2003d). The distribution of the number of hypomanic symptoms between BD-II and MDD was near normal, not supporting the two depressive syndromes as distinct disorders (i.e., categories). Following Kendell and Jablensky's (2003) approach to diagnostic validity, points of rarity between the two syndromes would support a categorical definition. By applying this method to a sample of patients with mixed depression, a near normal curve of hypomanic symptoms was found, supporting our dimensional definition of mixed depression.

The bipolar nature of mixed depression, studied in mixed BD-II and MDD samples, was strongly supported by a high family history of BD. Family history was assessed by interview of probands (and often of a family member) by the Family History Screen. This structured interview has the important advantage of assessing both BD-I and BD-II in first-degree relatives. There was a high frequency of BD-II in the probands of patients with mixed depression and a similarly high frequency to that of probands of patients with BD-II. Currently, family history is probably the most important diagnostic validator (Akiskal and Benazzi, 2003; Ghaemi et al., 2002).

The diagnostic validity of mixed depression was supported by its association with classic bipolar disorder and diagnostic validators (Akiskal, 2003; Akiskal et al., 1995; Angst et al., 2003; Ghaemi et al., 2002; McMahon et al., 1994). The diagnostic validity and bipolar nature of mixed depression was also supported by finding a dose-response relationship between the number of hypomanic symptoms present during the depression and positive family history of bipolar loading.

The bipolar nature of a subtype of mixed depression, i.e., psychomotor agitated depression, was supported by its links with bipolar validators. Mixed depression was found to be very common in BD-II samples (around 60%) and in MDD samples (around 30%), supporting its diagnostic utility (Benazzi and Akiskal, 2003c). The most common hypomanic symptoms during mixed depression were irritable mood, racing thoughts, psychomotor agitation, talkativeness and distractibility. An important finding was the positive association between racing thoughts and suicide ideation. Our studies on the increased mental activity of mixed depression were not limited to racing thoughts (increased speed of thoughts). We also included "crowded thoughts" (mind full of non-stop thoughts). This link between racing or crowded thoughts and suicide ideation could explain why treatment of mixed depression with antidepressants sometimes led to suicidal behavior, probably by increased mental and behavioral agitation (Benazzi, 2003e; Koukopoulos and Koukopoulos, 1999).

Temperamental mood lability was found to be more common in mixed depression than in non-mixed depression, suggesting that frequent baseline mood swings may facilitate the onset of mixed depression by pushing hypomanic symptoms into depression. Akiskal et al. (1995) already showed that mood lability predicted the shift of MDD to BD-II. Mixed depression, as compared to non-mixed depression, was more likely to occur in females and at a younger age (Benazzi, 2002b). Mixed depression was found to be no more common in BD-II with hypomania-depression cycles versus BD-II without these cycles.

The impact of treatment on our mixed depression study suggests that the current underdiagnosis of BD-II could be overcome by systematic probing for a history of hypomania and improving clinicians' interviewing skills. The interview should focus on assessing any history of overactivity rather than on mood change (behavior is easier to remember and is observable and verifiable by others). Negative outcomes of antidepressant treatment (without mood stabilizers) of BD-II misdiagnosed as MDD could thus be avoided. Some of these unwanted effects include switching to hypomania, increased cycling, induction of hypomanic symptoms during depression and increased severity of mixed depression (Altshuler et al., 1995; Ghaemi et al., 2003; Koukopoulos and Koukopoulos, 1999). By diagnosing mixed depression, the possible negative outcomes of antidepressants used alone, such as increased agitation, racing thoughts, and irritability, anger and aggressivity, could potentially be avoided.

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