Ph.D. Thesis

Clinical Features of Bipolar-II Disorder:

Focus on Mixed Depression

Dr. Franco Benazzi

E. Hecker Outpatient Psychiatry Center, Ravenna, Italy
Department of Psychiatry, National Health Service, Forli, Italy
Department of Psychiatry, University of Szeged, Hungary

2004

List of selected papers on which the Thesis is based:

(IF, impact factor)

I. Benazzi F, Koukopoulos A, Akiskal HS. Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). *European Psychiatry* 2004, 19, 85-90.
IF (2002): 1.327

II. Benazzi F. Clinical and family history markers of bipolar II disorder. *Canadian Journal of Psychiatry* 2003, 48, 208-209.
IF (2002): 1.808

III. Benazzi F. Bipolar II disorder family history using the family history screen: findings and clinical implications. *Comprehensive Psychiatry* 2004, 45, 77-82.
IF (2002): 1.562

IV. Benazzi F. Is depressive mixed state a transition between depression and hypomania? *European Archives of Psychiatry and Clinical Neuroscience* 2004, 254, 69-75.
IF (2002): 2.076

V. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. *Journal of Affective Disorders* 2003, 73, 113-122.
IF (2002): 2.176

VI. Benazzi F, Akiskal HS. The dual factor structure of self-rated MDQ hypomania: energized-activity versus irritable-thought racing. *Journal of Affective Disorders* 2003, 73, 59-64.
IF (2002): 2.176

VII. Benazzi F. Depression with racing thoughts. *Psychiatry Research* 2003, 120, 273-282.
IF (2002): 1.808

VIII. Benazzi F. Bipolar II depressive mixed state: finding a useful definition. *Comprehensive Psychiatry* 2003, 44, 21-27.
IF (2002): 1.562

IX. Benazzi F. Depressive mixed state: dimensional versus categorical definitions. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2003, 27, 129-134.
IF (2002): 1.433

X. Benazzi F. Major depressive disorder with anger: a bipolar spectrum disorder? *Psychotherapy and Psychosomatics* 2003, 72, 300-306.
IF (2002): 3.188

XI. Benazzi F. Which could be a clinically useful definition of depressive mixed state? *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2002, 26, 1105-1111.
IF (2002): 1.433

XII. Benazzi F. Age at onset of bipolar II depressive mixed state. *Psychiatry Research* 2001, 103, 229-235.
IF (2001): 1.775

XIII. Benazzi F. Atypical depression with hypomanic symptoms. *Journal of Affective Disorders* 2001, 65, 179-183.
IF (2001): 1.868

Cumulative impact factor (IF) = 24.192

Summary

The results of the present studies showed that mixed depression was common in bipolar-II disorder (BP-II) and not uncommon in major depressive disorder (MDD) depression outpatients. Mixed depression was found to be closely linked to many bipolar validators, especially bipolar family history, supporting its bipolar nature. The best definition of mixed depression was found to be a dimensional one, based on 3 or more intra-MDE (major depressive episode) hypomanic symptoms, because it had the strongest associations with bipolar validators, especially family history (a dose-response relationship was found). Mixed depression may have an important impact on the treatment of BP-II and MDD depressions, because antidepressants used alone (i.e., no concurrent mood stabilising agents) in mixed depression may increase the intra-MDE hypomanic symptoms and worsen depression. Mood stabilising agents could be required to treat the excitement symptoms of mixed depression, before tackling the core symptoms of depression by the antidepressants (mood stabilising agents-antidepressants combination therapy). Controlled treatment trials are needed to test these clinical observations.

Introduction

Bipolar-II disorder. Prevalence. Bipolar-II disorder (BP-II), defined by DSM-IV as recurrent major depressive episodes (MDE) and hypomanic episodes, has recently been found much more common than the 0.5% lifetime prevalence reported by DSM-IV. Previous community studies had underdiagnosed BP-II, according to the American Psychiatric Association review on bipolar disorder (2002). Recent community and clinical samples studies found that BP-II was much more common (5 to 11% in the community, 30 to 55% compared to MDD in clinical samples). The higher prevalence of BP-II is probably mainly related to improved probing for history of hypomania and to interviews done by trained clinicians. **The probing for history of hypomania.** Probing for history of hypomania was improved by focusing more on episodes of overactivity (increased goal-directed activity) than on past mood

changes. Instead, the Structured Clinical Interview for DSM-IV (SCID) has a single stem question about periods of past mood changes; if the answer is negative the interviewer has to assess a nonbipolar disorder. Overactivity is an observable behavior easier to remember than mood changes. Many false negative BP-II may result by following the SCID skip out instruction on past mood changes. Recent studies have shown that, for the diagnosis of hypomania, overactivity may have at least the same priority that mood changes have in DSM-IV. In the assessment of history of hypomania, use of semi-structured interviews reduces the false negative BP-II compared to structured interviews which require interview by trained clinicians and not simple yes/no answers to structured questions asked by lay interviewers. **Functioning in hypomania of bipolar-II disorder.** DSM-IV requires an observable change in functioning during hypomania. Recent studies have shown that functioning in hypomania may be increased or decreased according to the setting (non-tertiary-care versus tertiary-care settings). BP-II was called “sunny” when functioning was increased, and “dark” when functioning was decreased. It was shown that the “dark” BP-II often had a background of highly unstable temperament (cyclothymic temperament), while the “sunny” BP-II were more likely to be relatively stable between the episodes. **Duration of hypomania of bipolar-II disorder.** A duration of 2-3 days was found in 30%, a duration of more than 3 days and less than 4 weeks in 40%, and a duration of more than 4 weeks in 30% of BP-II. Previous studies had found that the most common duration of hypomania was some weeks. A minimum duration of 2 days was validated (versus DSM-IV 4 days, which is not data-based). **Bipolar-II depression.** The cross-sectional picture of BP-II depression (MDE) was shown to be that of an atypical depression in 40 to 50%, and to have concurrent intra-MDE hypomanic symptoms in 50-60%. An MDE plus concurrent hypomanic symptoms was named mixed depression (or depressive mixed state).

Mixed depression (depressive mixed state). Overview. Mixed depression, i.e., a depression mixed with hypomanic symptoms, was described by the classics (Heinroth, 1818; Falret, 1854; Griesinger, 1845; Kahlbaum, 1882; Hecker, 1898; Weigandt, 1899; Kraepelin, 1913), reporting that it was common in clinical practice. Kraepelin and Hecker systematically described mixed depressions. Kraepelin observed that between pure hypomania and pure depression there were mixed states, i.e., a mixture of excitement (manic) and inhibition (depressive) symptoms. Kraepelin described two mixed depressions: “excited depression” and “depression

with flight of ideas". Hecker described mixed depression in "cyclothymia" (corresponding to DSM-IV BP-II) in private practice outpatients, while Kraepelin described mixed depression in inpatients with "manic-depressive insanity" (mainly corresponding to DSM-IV bipolar I disorder (BP-I) and MDD). Kraepelin's unitary view of mood disorders was then followed by the unipolar-bipolar distinction, which led to the disappearance of mixed states from classification systems. This approach became the basis of DSM-IV and ICD-10. DSM-IV classifies only a mixed episode in BP-I, requiring full criteria MDE and mania concurrently present. In research, mixed mania was defined as a manic episode plus at least 2-3 concurrent depressive symptoms. A rebirth of studies on mixed depression started in the late 90s. Perugi et al (1997, 2001) studied mixed depression in BP-I tertiary-care inpatients, Benazzi (2000-2004), and Benazzi and Akiskal (2001-2004) studied mixed depression in BP-II and MDD non-tertiary-care outpatients (as Hecker did). Then, independent groups studies replicated most of the findings in mainly BP-I and MDD samples. Perugi et al (1997, 2001) found that BP-I mixed depression had mainly irritability, more talkativeness, flight of ideas, distractibility, and psychomotor agitation. Maj et al (2003) found that BP-I agitated depression was often mixed, showing a clinical picture similar to Perugi et al's mixed depression. Pure (i.e., not including BP-I) large samples of BP-II were systematically studied only by Benazzi and Akiskal in a non-tertiary care setting (an outpatient private practice). The study of BP-II depression is important, as recent studies, using better probing methods for assessing the history of hypomania, have found that BP-II may be as common as MDD in non-tertiary-care depression outpatients. By strictly following DSM-IV SCID, assessment of hypomanic symptoms in depression cannot be done. Instead, Benazzi, and Benazzi and Akiskal systematically assessed all hypomanic symptoms in depression. It was the systematic probing, and not the spontaneous reporting, which showed that hypomanic symptoms were frequent in BP-II depression. Hecker (1898) had made the same clinical observation. An important study method was that patients had to present for treatment of depression off psychoactive drugs, in order to avoid inclusion of antidepressant-induced mixed states.

Study aims were to assess the frequency and to study the clinical features of mixed depression, to validate the diagnosis of mixed depression, to investigate the factor structure of mixed depression, and to discuss the treatment impact of mixed depression.

Subjects and Methods

More details on study methods can be found in the list of selected studies the Thesis is based on. **Study setting**. An outpatient psychiatry private practice. This setting is more representative of mood disorders usually seen in clinical practice in Italy (apart from BP-I). **Interviewer.** A senior clinical and mood disorder research psychiatrist. **Patients.** Consecutive BP-II and MDD outpatients, presenting for MDE treatment off psychoactive drugs, were included in the last 5 years. Substance-related and borderline personality disorders were excluded because confounding the diagnosis of BP-II, and rare in the study setting. Clinically significant general medical illnesses and cognitive disorders were also excluded. **Interview methods.** During the assessment visit (conducted off psychoactive drugs for at least 2 weeks, in order not to have drug-induced or drug-suppressed hypomanic symptoms) the following instruments were used: 1) Structured Clinical Interview for DSM-IV (SCID-CV) as modified by Benazzi and Akiskal (2003) to improve the probing for history of hypomania; the question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' definition of crowded thoughts (i.e., mind continuously full of non-stop thoughts) (1999); 2) Global Assessment of Functioning scale (GAF) for grading MDE severity; 3) Hypomania Interview Guide (HIG) to assess intra-MDE hypomanic symptoms; 4) Family History Screen for assessing bipolar disorders (BP-I, BP-II) family history in probands' first-degree relatives. Often, family members/close friends supplemented clinical information. Systematic interviews about history of hypomanic episodes were always conducted soon after the diagnosis of MDE, before the assessment of study variables, in order to avoid a possible bias related to knowledge of bipolar signs. 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 check the understanding by the interviewed. This is an important advantage versus fully structured interviews because semi-structured interviews can reduce the false negatives BP-II and mood disorders. The skip out instruction of the stem question on history of mood changes (periods of elevated and/or irritable mood) was not followed, in order to assess all past hypomanic symptoms, especially overactivity. This behavioral change is easier to remember than mood changes (always required for the diagnosis of BP-II according to DSM-IV). Mixed depression (depressive mixed state) was defined as an MDE plus concurrent *intra-MDE* hypomanic symptoms. Hypomanic symptoms

had to last at least one week, and to have appeared during the MDE (a hypomanic symptom-free interval of at least four weeks was required). As diagnostic and bipolar validators were used young age at onset, many recurrences, atypical depression, and bipolar family history.

Results

1. Mixed depression (defined as MDE plus 3 or more *intra-MDE* hypomanic symptoms) was found in around 60% of BP-II, and in around 30% of MDD. Mixed depression, versus non-mixed depression, had significantly more BP-II, more females, younger index age and age at onset of the first MDE, more MDE recurrences, more atypical depressions, and more bipolar family history. The most common intra-MDE hypomanic symptoms were racing/crowded thoughts, distractibility, irritable mood, psychomotor agitation, and more talkativeness. Mixed depression was significantly associated with most atypical and hypomanic symptoms.
2. Mixed depression and non-mixed depression were compared in a BP-II sample only. Mixed depression, versus non-mixed depression, had significantly younger age at onset, more atypical depressions, and more bipolar family history.
3. Kraepelin (1913) viewed mixed states mainly as transition states between depression and mania. This view was tested by comparing the frequency of cycling course (cycles of depression-hypomania and vice versa, no free intervals) in a BP-II sample, between mixed depression and non-mixed depression. If mixed depression were a transition state, BP-II with mixed depression should have had more history of cycles. In BP-II without mixed depression, history of cycles was present in 86%, while in BP-II with mixed depression history of cycles was present in 77%, a non-significant difference.
4. Temperamental mood lability (defined as frequent ups and downs of mood since young age, distinct from major mood episodes, according to Kraepelin, 1913) was significantly more common in mixed versus non-mixed BP-II depression (69% versus 41%). Mixed depression was significantly more common in atypical depression versus non-atypical depression, a relationship significant even after controlling for BP-II.

5. *Depression with racing thoughts* (one of Kraepelin's depressive mixed states) was studied. Depression with racing thoughts, versus depression without racing thoughts, had significantly more BP-II (73% of depression with racing thoughts had BP-II), younger age at onset, more atypical depressions, and more bipolar family history. Depression with racing thoughts was not uncommon in MDD. Depression with racing thoughts was significantly associated with psychomotor agitation and suicidal ideation.
6. *Depression with psychomotor agitation* (excited-agitated depression, the second depressive mixed state described by Kraepelin) was studied. Agitated depression, versus non-agitated depression, had significantly more BP-II, a younger age at onset, more atypical depressions, and more bipolar family history. Agitated depression had significantly more mixed depressions (70% of agitated depressions were mixed). Racing thoughts and psychomotor agitation were found to be independent predictors of suicidal ideation.
7. The definition of mixed depression suggested by Koukopoulos and Koukopoulos (1999), i.e., an MDE plus psychomotor agitation, racing/crowded thoughts, and inner tension (at least two), was tested, finding that it was strongly associated with many bipolar validators, supporting its bipolar nature.
8. *Factor analysis of MDE and intra-MDE hypomanic symptoms* found an "excitement" factor (including irritability, racing/crowded thoughts, psychomotor agitation, and more talkativeness), supporting psychometrically the concept of mixed depression.
9. Sensitivity and specificity of mixed depression for predicting BP-II was studied compared to other bipolar validators. Compared to bipolar family history, mixed depression had a similar balanced combination of sensitivity and specificity for predicting BP-II (sensitivity = 59%, specificity = 73%), better than that of other bipolar validators. Discriminant analysis, including bipolar family history and mixed depression (and other bipolar validators) showed that mixed depression was an independent predictor of BP-II. MDD mixed depression, versus MDD non-mixed depression, was significantly associated with most bipolar validators, especially bipolar family history.
10. In order to validate the bipolar nature of the definition of mixed depression used in the present studies, the *dose-response relationship* between number of *intra-MDE* hypomanic symptoms and bipolar family history loading in probands' first

degree relatives was studied. It was found a significant dose-response relationship (i.e., the higher was the number of intra-MDE hypomanic symptoms, the higher was the bipolar family loading) (Table 1). Different definitions of mixed depression were tested, in order to find if the best definition was a dimensional one or a categorical one. Univariate and multivariate logistic regression, and factor analysis were used. The testing of the different definitions was based on the power to predict a BP-II diagnosis. It resulted that a dimensional definition (i.e., *3 or more intra-MDE* hypomanic symptoms) was a stronger predictor of BP-II versus categorical definitions requiring an MDE plus one or more specific hypomanic symptoms (such as irritability, racing thoughts, psychomotor agitation). This definition of mixed depression also had a more balanced combination of sensitivity and specificity for predicting BP-II. The same finding was shown by using bipolar family history as the dependent variable versus which to regress the different definitions of mixed depression. This approach may be a more powerful way to support the diagnostic validity of a definition of mixed depression, as family history is seen as the current most important diagnostic validator. Multiple logistic regression showed also that a definition of mixed depression requiring 3 or more intra-MDE hypomanic symptoms was the only independent predictor of a bipolar family history among several other definitions.

11. Following DSM-IV criteria for mixed state in BP-I, requiring full criteria mania and MDE concurrently present, it was tested if the definition of mixed depression in BP-II required full hypomania (i.e., irritability plus 4 symptoms, as elevated mood was always absent by definition), versus definitions requiring a lower number of hypomanic symptoms (2 or more, 3 or more, but not 5 or more). It resulted that no significant differences were found on most bipolar validators among the different definitions. It was also found that the distribution of intra-MDE hypomanic symptoms scores was near-normal (by histogram and by Kernel density estimate), supporting a dimensional definition. The *distribution of hypomanic symptoms between BP-II and MDD* depressions was tested. It was expected a clustering of hypomanic symptoms on one side, as mixed depression was more common in BP-II. Instead, the distribution of hypomanic symptoms (by histogram and by Kernel density estimate) showed a near normal shape, and no zone of rarity (Figure 1).

12. Using sensitivity and specificity for predicting BP-II as a test of validity of mixed depression is only one approach. A better approach to test different definitions of mixed depression could be one based on bipolar family history as the dependent variable versus which to study the associations. Several definitions of mixed depression were studied. Mixed depression, defined by 3 or more intra-MDE hypomanic symptoms, had the best predictive power for bipolar family history. Multivariate logistic regression found that the only independent predictor of bipolar family history was this definition of mixed depression.
13. *Factor analysis of intra-MDE hypomanic symptoms* found two factors: a motor activation factor (including psychomotor agitation, more talkativeness) and a mental activation factor (including racing/crowded thoughts, distractibility, irritability).

Discussion

1. Results showed that mixed depression (defined as *an MDE plus 3 or more intra-MDE hypomanic symptoms*) was present in around 60% of BP-II, and in around 30% of MDD, clinically significant figures. Mixed depression, versus non-mixed depression, had significantly more BP-II, more females, a younger age at onset, more recurrences, more atypical depressions, and more bipolar family history. These findings support the bipolar nature of mixed depression, as it was associated with many bipolar validators. The most common *intra-MDE* hypomanic symptoms were irritability, distractibility, racing/crowded thoughts, psychomotor agitation, and more talkativeness. In a BP-II sample, mixed depression versus non-mixed depression had significantly younger onset, more atypical depressions, and more bipolar family history, which may be the core features of mixed depression. More bipolar family history in BP-II and MDD mixed depression suggests that mixed depression may require more bipolar vulnerability to appear.
2. The impact of young *age at onset* on the clinical features of BP-II mixed depression was studied, showing that mixed depression was more likely to have a young age onset. This finding runs against Kraepelin's observation (1913) that his six mixed states (which included only two depressive mixed states) were more likely to have a late onset. Kraepelin's observation on the age at onset of mixed

states might be more likely to be true for mixed mania, and for the more severe inpatients he studied.

3. Kraepelin viewed mixed states mainly as *transition states* between depression and mania. This view was tested by comparing the frequency of cycling course (cycles of depression-hypomania), between mixed depression and non-mixed depression, finding that BP-II with and without mixed depression had a similar history of cycles frequency. If mixed depression had been a transition state, it should have had more history of cycles. Interestingly, antidepressant-associated hypomania was much more common in BP-II with history of cycles. *Temperamental mood lability* (trait “ups and downs”, “mood swings”) seemed to be a background facilitating the onset of mixed depression, in line with Akiskal et al (1995) finding that trait mood lability was a strong predictor of the shift of MDD to BP-II. Mixed depression was significantly more common in *atypical depression* versus non-atypical depression. The relationship was significant even after controlling for BP-II, suggesting that the relationship is strong and independent of BP-II. The finding may have a treatment impact, as atypical depression was shown to respond better to MAOI than to TCA (i.e., to be pharmacologically distinct, and, by inference, biologically different), and makes the clinical picture of BP-II depression more complex and more difficult to treat.
4. *Depression with racing thoughts* (one of Kraepelin’s depressive mixed states) was common. Depression with racing thoughts, versus depression without racing thoughts, had significantly more BP-II, younger age at onset, more atypical depressions, and more bipolar family history, supporting its bipolar nature. However, it was not uncommon in MDD. Depression with racing thoughts was significantly associated with psychomotor agitation and suicidal ideation.
5. *Depression with psychomotor agitation* (agitated depression, the second depressive mixed state described by Kraepelin), versus non-agitated depression, had significantly more BP-II, a younger age at onset, more atypical depressions, and more bipolar family history, supporting its bipolar nature. The definition of mixed depression suggested by Koukopoulos and Koukopoulos (1999), i.e., an MDE plus psychomotor agitation, racing/crowded thoughts, and inner tension (at least two), was strongly associated with many bipolar validators, supporting its bipolar nature. These findings support the bipolar nature of agitated depression. Agitated depression had also significantly more mixed depressions (70% of

agitated depressions were mixed), suggesting that psychomotor agitation may not be the main distinguishing feature of this suggested subtype of depression, but instead that the clustering of hypomanic symptoms around agitation may be more important. Agitated depression had also significantly more racing/crowded thoughts and suicidal ideation. Racing thoughts and psychomotor agitation were found to be independent predictors of suicidal ideation. It was reported that mixed states predicted suicidal behavior during long follow-ups (Maser et al 2002; Allen et al 2004), that psychomotor agitation was present one week before 50% of suicides (Busch et al 2003), that antidepressant-induced mania was associated with suicidal behavior (Slama et al 2004), and that antidepressants induced more switching in mixed depression versus non-mixed depression (Bottlender et al 2004). These reports suggest the direction of a possible causal association (which cross-sectional studies like the present ones cannot show) found in the present studies between racing thoughts/psychomotor agitation and suicidal ideation (i.e., these excitement symptoms might increase or induce suicidal behavior) (Rihmer et al 2002). However, at present, these findings are very preliminary, need replication, and any possible causal association needs to be shown by controlled clinical trials. Recently, the USA Food and Drug Administration warned about the possible suicidal behavior-inducing effects of the newer antidepressants. Clinical observations (Akiskal and Pinto 1999; Koukopoulos and Koukopoulos 1999) suggest that mixed depression may become more severe by using antidepressants alone. It has been suggested that first treating the intra-MDE hypomanic symptoms by mood stabilising agents, before starting the antidepressants, may be the best treatment approach for mixed depression.

6. The *diagnostic validity and utility* of mixed depression were studied by several methods. The association of mixed depression with BP-II and bipolar family history (and other bipolar validators) supported the bipolar nature of mixed depression. Psychometrically, the diagnostic validity of mixed depression was supported by factor analysis, showing an “excitement” factor among several depression factors. Compared to bipolar family history, mixed depression (defined as an MDE plus 3 or more intra-MDE hypomanic symptoms) had a similar balanced combination of sensitivity and specificity for predicting BP-II. Discriminant analysis including bipolar family history and mixed depression (and

other bipolar validators) showed that mixed depression was an independent predictor of BP-II. This similar predictive power of BP-II compared to a strong diagnostic and bipolar validator such as bipolar family history supports the clinical utility of mixed depression. The bipolar nature of mixed depression was also supported by studying mixed depression in an MDD sample. MDD mixed depression, versus MDD non-mixed depression was significantly associated with most bipolar validators, especially bipolar family history. In order to further support the bipolar nature of mixed depression and the validation of its definition used in the present studies, a *dose-response relationship* between number of intra-MDE hypomanic symptoms and bipolar family history loading in first degree relatives was studied, finding that the higher was the number of intra-MDE hypomanic symptoms, the higher was the bipolar family loading. Different definitions of mixed depression were tested, in order to find if the best definition was a dimensional one or a categorical one. Univariate and multivariate logistic regression, and factor analysis were used. The testing of the different definitions was based on the power to predict the BP-II diagnosis. It resulted that a dimensional definition (i.e., 3 or more intra-MDE hypomanic symptoms) was a stronger predictor of BP-II versus categorical definitions, requiring an MDE plus one or more specific hypomanic symptoms (such as irritability, racing thoughts, psychomotor agitation), and that it had a more balanced combination of sensitivity and specificity for predicting BP-II. The same finding was shown by using bipolar family history as the dependent variable versus which to regress different definitions of mixed depression. This last approach may be a more powerful way to support the diagnostic validity of a definition of mixed depression, as family history is seen as the current most important diagnostic validator. Multiple logistic regression showed that a definition of mixed depression requiring 3 or more intra-MDE hypomanic symptoms was the only independent predictor of a bipolar family history among several other definitions.

7. Following DSM-IV criteria for mixed state in BP-I, it was tested if the definition of mixed depression in BP-II required full hypomania (without elevated mood), versus definitions requiring a lower number of hypomanic symptoms. It resulted that no significant differences were found on most bipolar validators among the different definitions, and that the distribution of intra-MDE hypomanic symptoms scores was near-normal. These findings support a dimensional definition of mixed

depression. The distribution of hypomanic symptoms between BP-II and MDD depressions was also tested. A clustering of hypomanic symptoms on one side was expected, as mixed depression was more common in BP-II. Instead, the distribution of hypomanic symptoms showed a near normal shape, and no zone of rarity. This finding supports a continuity between BP-II and MDD, in line with Kraepelin's unitary view of mood disorders, and against DSM-IV categorical classification.

8. Using sensitivity and specificity for predicting BP-II as a test of validity of mixed depression is only one approach. A better approach to test different definitions of mixed depression could be one based on bipolar family history as the dependent variable versus which to study the associations. Several definitions of mixed depression were tested versus bipolar family history. Mixed depression, defined by *3 or more intra-MDE* hypomanic symptoms, had the best predictive power for bipolar family history, and multivariate logistic regression found that the only independent predictor of bipolar family history was this definition of mixed depression.
9. The specificity of the hypomanic symptoms most commonly found in mixed depression should be discussed. While overactivity and elevated mood (the first one uncommon, the second one always absent in mixed depression) are seen as core features of hypomania, several of the DSM-IV hypomanic symptoms which define mixed depression in the present studies (such as irritability, distractibility, psychomotor agitation, and crowded thoughts which are similar to the MDE ruminations) can be found not only in BP-II diagnostic criteria for hypomania, but also in the MDE criteria or text description, apparently questioning the bipolar nature of these symptoms. Even if these symptoms, apart from elevated mood and overactivity, can be found in BP-I, BP-II, and MDD depressions, they are more common in BP depressions. These symptoms were strongly associated with classic bipolar validators. The bipolar nature of these symptoms was strongly supported by the association between mixed depression and bipolar family history. An even stronger point supporting the bipolar nature of mixed depression was the finding of a dose-response relationship between number of hypomanic symptoms intra-depression and bipolar family history loading in relatives. Furthermore, mixed depression in MDD had a significantly higher bipolar family history loading versus MDD non-mixed depression.

10. *Factor analysis of intra-MDE hypomanic symptoms* found a motor activation factor and a mental activation factor. These findings are in line with factor analysis studies of hypomania and mania, showing activation factor/s in hypomania and mania. Interestingly, the hypomanic factors found in mixed depression were very similar to the factors found in hypomania. Factor analysis results further support the bipolar nature of mixed depression by showing that “parts” of hypomania can appear inside a depression. Kraepelin’s subtyping of depressive mixed states into “excited depression” and “depression with flight of ideas” seems also supported. These factors were tested versus a dimensional definition of mixed depression, resulting in the dimensional definition (3 or more intra-MDE hypomanic symptoms) showing the highest specificity for predicting BP-II diagnosis and a similar predictive power.
11. **Treatment impact of mixed depression.** The treatment impact of the diagnosis of mixed depression may be important. As mixed depression is more common in BP-II, it could increase the detection of BP-II. By finding more BP-II, several possible negative outcomes of antidepressant treatment of BP-II misdiagnosed as MDD could be avoided or reduced, such as switching to hypomania and increased cycling. By diagnosing mixed depression, the possible negative outcomes of antidepressants used alone (i.e., no concurrent mood stabilising agents) may be avoided or reduced, such as increasing agitation, racing thoughts, and irritability-anger-aggressivity. Controlled trials, ideally in usual clinical practice, should be designed to compare the effects of antidepressants in mixed versus non-mixed depression, and test if mood stabilising agents may be needed to treat the hypomanic symptoms of mixed depression.

Table 1.

Dose-response relationship between number of intra-depression (MDE) hypomanic symptoms and bipolar disorders family history loading.

	%(N)	BP-FH, %
Variables		
MDE + 0 hypomanic symptoms	5.5(24)	20.8
MDE + 1 hypomanic symptom	14.8(64)	14.0
MDE + 2 hypomanic symptoms	22.4(97)	22.6
MDE + 3 hypomanic symptoms	25.6(110)	42.7
MDE + 4 hypomanic symptoms	18.5(80)	43.7
MDE + 5 hypomanic symptoms	10.8(47)	48.9
MDE + 6 hypomanic symptoms	(7)	
MDE + 7 hypomanic symptoms	(2)	
MDE + 8 hypomanic symptoms	(1)	
Chi-squared test for trend	X2=7.5	P=0.0061

(MDE=major depressive episode; BP-FH=bipolar disorders family history loading)
(MDE + 6, 7, and 8 hypomanic symptoms not included in the analysis because samples were too small)

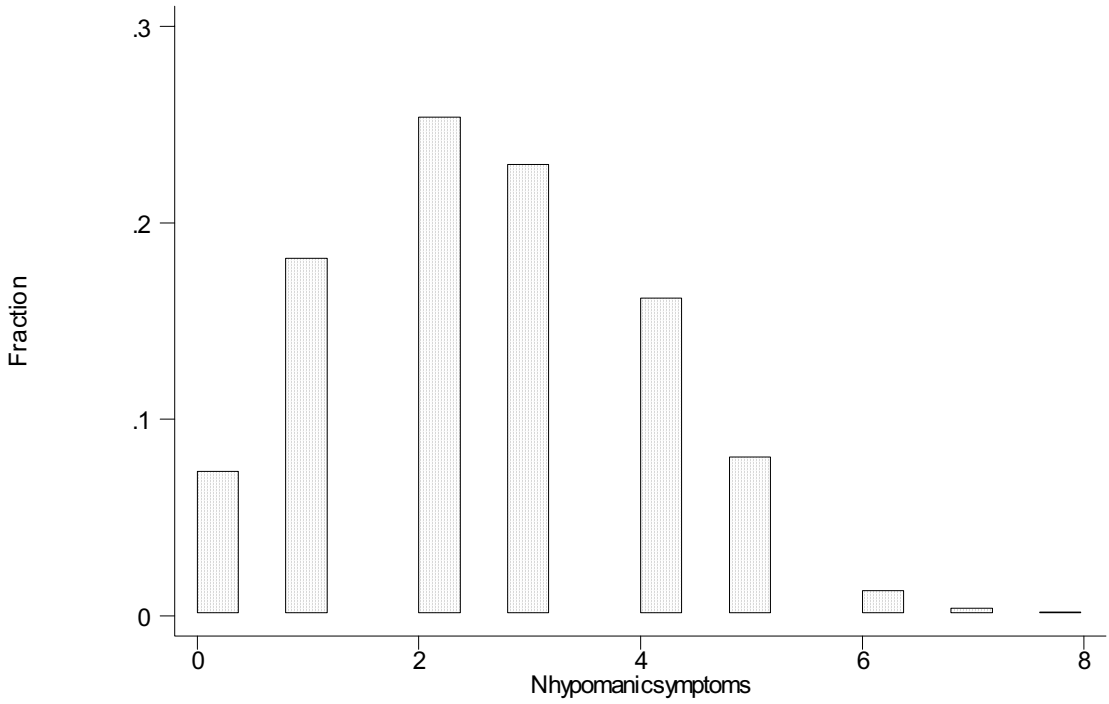

Figure 1. Histogram of the distribution of the number of hypomanic symptoms (Nhypomanicsymptoms) between bipolar-II and major depressive disorder depressive syndromes.

Original Observations

1. Mixed depression (defined as a depression plus *3 or more intra-depression* hypomanic symptoms) was present in around 60% of bipolar-II depressions, and in around 30% of unipolar major depressive disorder depressions.

2. Mixed depressions did not seem to be mainly transition states between depression and mania (Kraeplin's view of mixed states in general), but independent episodes.

3. *Depression with racing thoughts* (one of Kraepelin's depressive mixed states), versus depression without racing thoughts, had significantly more bipolar-II disorders, bipolar family history, psychomotor agitation and suicidal ideation.

4. *Depression with psychomotor agitation* (agitated depression, the second depressive mixed state described by Kraepelin), versus non-agitated depression, had significantly more bipolar-II disorders, bipolar family history, concurrent hypomanic symptoms, racing/crowded thoughts and suicidal ideation. Racing thoughts and psychomotor agitation were independent predictors of suicidal ideation.

5. Psychometrically, the diagnostic validity of mixed depression was supported by factor analysis, showing an "excitement" factor among several depression factors.

6. Discriminant analysis including bipolar family history and mixed depression (and other bipolar validators) showed that mixed depression was an independent predictor of bipolar-II disorder.

7. Unipolar mixed depression versus unipolar non-mixed depression had significantly more bipolar family history, supporting its bipolar nature, and a link between bipolar-II and unipolar depression.

8. A *dose-response relationship* between number of *intra-depression hypomanic* symptoms and *bipolar family history* loading in relatives was found, i.e., the higher was the number of intra-depression hypomanic symptoms, the higher was the bipolar family loading, supporting the bipolar nature of mixed depression and its dimensional definition.

9. Multivariate analyses showed that, among different dimensional and categorical (i.e., requiring specific hypomanic symptoms) definitions of mixed depression, the strongest predictor of bipolar-II disorder and bipolar family history was a dimensional definition (i.e., *3 or more intra-depression* hypomanic symptoms).

10. The *distribution of hypomanic symptoms between bipolar-II depression and unipolar depression* showed a near normal shape, *no zone of rarity* (a clustering on one side was expected, as mixed depression was more common in bipolar-II), supporting a *continuity* between bipolar-II disorder and unipolar major depressive disorder, in line with Kraepelin's unitary view of mood disorders (and against DSM-IV categorical classification)

11. Factor analysis of *intra-depression* hypomanic symptoms found a motor activation factor and a mental activation factor, which were the same factors found in *inter-depression* hypomania, supporting the bipolar nature of mixed depression, and Kraepelin's subtyping of depressive mixed states into "excited depression" and "depression with flight of ideas".