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Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes

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Abstract

Background—There is increasing evidence that subsyndromal manic symptoms occur frequently during bipolar major depressive episodes (MDEs) and may be a subtle form of 'depressive mixed state.' This paper examines the prevalence and clinical characteristics of MDEs with subsyndromal manic symptoms. The specific effects of overt irritability and psychomotor agitation are examined.

Methods—Bipolar (type I or II) patients with an MDE at intake (N=142) were compared based on the presence or absence of concurrent subsyndromal manic symptoms. The groups were further subdivided by the presence of symptoms of overt irritability and/or psychomotor agitation.

Results—Subsyndromal manic symptoms during bipolar MDEs were highly prevalent (76.1%), and were associated with significantly increased severity of depression/dysphoria in the intake episode, longer episode duration, and more suicidal ideation and behavior (past, current, and during long-term follow-up). Overt irritability and psychomotor agitation were the most prevalent

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Conflict of interest

Drs. Judd, Akiskal, Coryell, and Fawcett declare that they have no conflicts of interest or potential conflicts of interest. During the past three years Dr. Schettler has provided statistical consulting services to Brain Cell, Inc., Methylation Sciences, Novartis BioVentures, and Clintara LLC. Dr. Fiedorowicz currently serves in an unpaid capacity on a colleague's study that is supported by Neurosearch. Dr. Solomon is an employee of UpToDate, Inc. During the past three years Dr. Keller has served as a consultant to CENEREX, Forest Laboratories, Medtronic, Organon, Pfizer, Sierra Neuropharmaceuticals, Shire, and Wyeth; has served on the advisory boards for CENEREX, Forest Laboratories, and Organon; and has conducted research using Pfizer and Wyeth products.

subsyndromal manic symptoms (co-occurring in 57% and 39% of MDEs, respectively), and accounted for most of the negative effects associated with subsyndromal manic symptoms.

Limitations—The findings need to be confirmed in larger samples, which also examine the relationship to adequate antidepressant and/or mood stabilizing treatment.

Conclusions—The presence of one or more subsyndromal manic symptoms appears to be the modal presentation of bipolar MDEs and a marker for a subtle form of bipolar mixed depressive state. In particular, patients with symptoms of overt irritability and/or psychomotor agitation should be monitored closely to avoid serious clinical outcomes such as longer affective episodes, exacerbation of manic symptoms syndromal mania, and heightened suicidality.

Keywords

Bipolar; Major depressive episodes; Subsyndromal manic symptoms; Irritability; Psychomotor agitation

1. Introduction

Kraepelin (1907) first described mixed polarity subtypes of ‘excited depression’ and ‘depression with flight of ideas’ as important and common aspects of the course of bipolar disorders. Since that time, the ‘mixed depressive state’ has been the focus of much attention. The concept of ‘mixed state,’ according to the DSM-IV-TR definition (American Psychiatric Association, 2000), is limited to a full syndromal major depressive episode (MDE) plus mania co-occurring for at least one week. Since first being systematically examined in patient samples by Benazzi and Akiskal (2001), other recent studies have suggested that the presence of *subsyndromal* manic symptoms (i.e., those below the threshold for mania) during bipolar MDEs constitutes a prevalent and important form of mixed state.

In a large study of 1380 patients with either bipolar I or bipolar II disorder entering the STEP-BD study in an MDE, 54.0% of the patients had concurrent subsyndromal manic symptoms at a subsyndromal level, and an additional 14.8% met criteria for a full DSM-IV-TR mixed episode, and 31.2% had no manic symptoms concurrent with their index MDE (“pure” MDE) (Goldberg et al., 2009). These authors reported that the most common manic symptom during bipolar MDEs was irritability (present in 73.1% of the sample), followed by distractibility (37.2%), psychomotor agitation (31.2%), flight of ideas or racing thoughts (20.6%), and increased speech (11.0%).

It appears not only that the majority of bipolar MDEs are accompanied by co-occurring manic symptoms, but also that this combination may have important clinical implications. In a review, Hawton et al. (2005) found that mixed affective state was a primary risk factor for suicidal behavior. Other investigators have specifically found that even modest manic symptoms during bipolar MDEs are associated with a greater history of suicide attempts (Akiskal and Benazzi, 2005; Balázs et al., 2006; Goldberg et al., 2009; Swann et al., 2007). The importance of assessing manic symptoms during bipolar MDEs is also underscored by the finding, from several studies, that manic symptoms worsen during treatment with antidepressants (Frye et al., 2009; Goldberg et al., 2007; Koukopoulos et al., 1992).

Of particular interest are reports of the high prevalence of irritability and psychomotor agitation, which are symptoms of mania as well as specific qualifiers of MDEs. Irritable and agitated qualities of MDEs, defined in various ways, are prominent in the clinical and research literature on ‘mixed depressive states.’ Because these two characteristics have a high degree of overlap with each other and with other manic symptoms (Benazzi, 2004;

Benazzi and Akiskal, 2005, 2006; Goldberg et al., 2009; Maj et al., 2003), their specific relationship to each other and to important clinical outcomes is unclear.

This investigation is designed to examine the prevalence and clinical significance of subsyndromal manic symptoms that occur during bipolar MDEs, and to disentangle clinical outcomes associated with irritability and psychomotor agitation from those associated with other manic symptoms. The National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS) is an observational, naturalistic, long-term study of a clinical cohort of patients with bipolar and unipolar depression. It is useful for studying the prevalence and importance of manic symptoms co-occurring with bipolar MDEs at intake. Patients in the CDS are comprehensively evaluated at intake and during long-term follow-up (up to 27 years) for their affective illness state, psychosocial function, emergent comorbid mental disorders, substance abuse, and suicidal ideation and behaviors. The CDS database provides a rich resource for analyzing the wide range of clinical correlates of mixed bipolar MDEs mentioned in the literature.

2. Methods

2.1. Subjects

Subjects entered the NIMH CDS (Katz and Klerman, 1979; Katz et al., 1979) at five academic medical centers (Boston, MA; Chicago, IL; Iowa City, IA; New York, NY; and St. Louis, MO), from 1978 to 1981, while seeking treatment for a major affective episode. Intake research diagnoses were made using Research Diagnostic Criteria (RDC) (Spitzer et al., 1977) based on the Schedule for Affective Disorders and Schizophrenia (SADS) interviews (Spitzer and Endicott, 1979), as well as available medical and research records. Patients with bipolar disorder (type I or II) entering the CDS in a major depressive episode (MDE) were selected for these analyses. We excluded from the analysis all patients who were manic at intake (N=60), along with a small group of patients (N=5) who met DSM-IV-TR criteria for a mixed episode at intake (i.e., had full concurrent MDE plus mania) in order to focus on MDEs with vs. without concurrent *subsyndromal* yet clinically significant manic symptoms (i.e., below the threshold for a diagnosis of concurrent mania). Subjects with any evidence of schizophrenia or schizo-affective disorder by the end of follow-up were also excluded from the analyses, as were subjects with no follow-up data (N=4). This left 142 bipolar patients entering the CDS during an MDE, of whom 52 were bipolar I (bipolar I subtype, or BP-I), and 90 were bipolar II (bipolar II subtype, or BP-II).

Demographic and clinical characteristics of the analysis sample are shown in Table 1. The mean age was 36.7 years and the majority of the sample were female (58.5%). Bipolar illness tended to begin early in life (60.6% of the sample experienced their first affective episode before age 21) and be chronic (76.1% had four or more lifetime episodes).

All patients in the CDS were required to be Caucasian (in order to test genetic hypotheses), speak English, have an IQ score of at least 70, and have no evidence of organic brain syndrome or terminal medical illness. Written informed consent was obtained at each of the 5 sites for participation in the research.

2.2. Assessments for defining analysis groups

The SADS interview can be used to identify all DSM-IV-TR symptom criteria for mania/hypomania. Most symptoms are covered in the section on manic/hypomanic symptoms. Two symptoms (flight of ideas and distractibility) are observable and are rated for all subjects based on behavior during the interview. Irritability and psychomotor agitation are included in the SADS interview not only as manic/hypomanic symptoms, but also in the depression section of the interview, as qualifiers for the MDE (i.e., specifically for periods of the intake

MDE when the subject did not have evidence of a manic syndrome). Irritable mood is one of two A-criterion (gateway) symptoms, one of which must be present for a DSM-IV-TR diagnosis of mania (American Psychiatric Association, 2000). It is also included in the SADS as a descriptor of MDEs, where it is more narrowly rated in terms of *overt expressions* (not mere subjective feelings) of irritability, annoyance, and/or anger. Psychomotor agitation, along with increased goal-directed activity, is one of the two DSM-IV-TR criterion B-6 symptoms for mania. Also included in the SADS as a descriptor of MDEs, it is rated based on behaviors such as the inability to sit still, pacing, fidgeting, movement of lips or fingers, wringing of hands, or pulling at clothes; it specifically excludes mere subjective feelings of tension or restlessness. We have included these two characteristics of intake MDEs as subsyndromal manic symptoms because we believe they are clinically indistinguishable from criteria A-2 and B-6 for mania and may, therefore, represent a subtle and little recognized form of mixed bipolar MDE.

In the SADS interview, the severity of each manic symptom is rated on a 6-point scale, with specific descriptors for each value, where 1=absent; 2=slight but of doubtful clinical significance; 3=mild (definitely present and having some impact on functioning); 4=moderate; 5=severe; and 6=extreme. For these analyses, a manic spectrum symptom was counted as “clinically significant” and subsyndromal only if it was rated 3 or higher in severity.

Using the SADS symptom ratings described above, the 142 patients entering the CDS for treatment of a bipolar MDE were classified into two groups: (1) patients with one or more clinically significant manic spectrum symptoms including irritability or psychomotor agitation (but not full mania) concurrent with their intake MDE, and (2) patients with no clinically significant concurrent symptoms of mania (“pure” MDE). We further analyzed groups based on having the MDE qualities of overt irritability and/or psychomotor agitation, compared to purely depressive MDEs.

2.3. Assessments for comparing analysis groups

The intake SADS interview provided information to compare the analysis groups on various measures of episode severity, as well as current and past suicidality. Other comparisons of the analysis groups were based on longitudinal outcome data. As described in detail elsewhere (Judd et al., 2002), trained professional raters interviewed patients every 6 months for the first 5 years and yearly thereafter, using variations of the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987). Weekly Psychiatric Status Ratings (PSRs) in the LIFE forms, which are keyed to diagnostic thresholds, provide the basis for describing the long-term course of affective and other psychiatric disorders (Judd et al., 2003a, 2003b, 2003c), during up to 27 years of follow-up. Weekly PSRs were used as the basis for identifying the point when patients met RDC criteria for recovery from their index MDE, as well as identifying the onset and recovery from subsequent affective episodes and characterizing overall levels of affective symptom severity during all of follow-up (Judd et al., 2008a). Information on suicide attempts during each follow-up interval was also obtained from the LIFE interviews, as were monthly ratings of psychosocial impairment (Judd et al., 2005, 2008b).

2.4. Statistical analyses

The prevalence of subsyndromal manic symptoms, based on the SADS interview, is shown in Table 2. Statistical comparisons between MDEs with vs. without subsyndromal manic symptoms (Tables 3 and 4) were made by means of analysis of variance (t-tests) for continuous variables, Chi-Squares or Fisher’s Exact Tests for categorical variables, or log–

rank Chi-Square tests on survival function distributions for time to recovery from the intake episode and time to subsequent relapse.

We took two approaches to the analysis of the impact of irritability and agitation during MDEs on all dependent variables, whether or not they were statistically different for bipolar MDEs with vs. without concurrent manic symptoms: The first was to conduct statistical tests of the significance of the additional impact each of these (alone or in combination) on each dependent variable, over and above the influence of other subsyndromal manic symptoms. We performed analysis of covariance on continuous variables, stepwise logistic regression on binary outcomes, and Cox Proportional Hazards models on time-to-event outcomes (length of intake episode and first well interval). To check that covariance was not masking important differences in naturally occurring groups (Miller and Chapman, 2001), we then *removed* MDEs with other manic symptoms (N=28) and compared remaining subjects in each of the three irritable/agitated groups to the group with purely depressive MDEs. Detailed results of the second analysis are presented in Table 5; statistically significant contrasts to the “pure” MDE group by the two methods of analysis are indicated in the footnotes.

A probability level of 0.05 (2-tailed) was used to determine statistical significance. Adjustments for multiple comparisons were not made for two reasons: First, this is an exploratory analysis of clinically important features and outcomes that *may* be associated with the presence of any concurrent subsyndromal manic symptoms, or that *may* distinguish bipolar MDEs with irritability and/or psychomotor agitation from “pure” MDEs. We make clear that the findings need to be replicated in larger samples. Second, we examine correlated subsets of variables such as alternative measures of depressive severity, suicidality during different time intervals, or various measures of the severity or chronicity of long-term course; this makes adjustments based on independent measures inappropriate.

3. Results

3.1. Prevalence and nature of clinically significant subsyndromal manic symptoms during intake MDEs

Over three-fourths (76.1%) of the intake MDEs for this bipolar sample had concurrent clinically significant subsyndromal manic symptoms. Only 23.9% of the MDEs without full concurrent mania had no manic symptoms and so can be considered to be purely depressive. Patients with BP-I and BP-II subtypes had similar rates of concurrent manic symptoms. The two analysis groups (i.e., MDEs with vs. without concurrent manic symptoms) were not associated with significant differences on any of the clinical or demographic characteristics shown in Table 1.

Table 2 shows the prevalence of individual manic symptoms, identified by the intake SADS interview. All of the DSM-IV-TR criteria for mania are covered in the SADS interview for an individual patient, subject to conditions described in the footnotes. In our sample, the most common concurrent manic spectrum symptom was overt irritability, which is a gateway (A-criterion) symptom for a diagnosis of manic episodes as well as a qualifier of MDEs; this symptom was present in 57.0% of the MDEs at intake. The next most frequent manic symptom was psychomotor agitation (part of DSM-IV-TR symptom criterion B-6 for a manic episode, as well as an MDE qualifier), which was present in 39.4% of the intake MDEs. The next most frequent manic symptom was elevated mood, an A-criterion symptom for mania (13.4%), followed by heightened energy (11.3%), and increased goal-directed activity (9.9%). Listed in Table 2 are the remaining manic symptoms, which were noted at clinically significant levels in fewer than 10% of bipolar MDEs at intake. A total of 33

subjects (23.2%) had one or more manic symptoms other than overt irritability and psychomotor agitation, including 28 who also had irritability or agitation.

3.2. Severity of intake MDE

Intake MDEs with concurrent manic symptoms were significantly more severe, as indicated in Table 3. MDEs with manic symptoms were associated with significantly lower Global Assessment Scale (GAS) scores, reflecting increased overall severity and psychosocial impairment during the worst week of the MDE prior to intake. When examined by bipolar subtype, we found that the presence of concurrent manic symptoms was associated with worse (lower) GAS scores only for BP-I MDEs [means (se)=30.9 (1.6) vs. 43.3 (2.8); $P=0.002$]. In addition, all three SADS scores measuring severity of dysphoria/depression were significantly worse (higher) for MDEs with concurrent subsyndromal manic symptoms, as compared to the pure MDEs. This was true for both BP-I and BP-II subtypes. Differences in the severity of the intake MDE were not attributable to differences in the presence of psychotic features (30.6% of MDEs with concurrent manic symptoms vs. 26.5% of pure MDEs; Fisher's Exact Test $P=0.830$).

3.3. Duration of intake MDE

Intake MDEs with concurrent subsyndromal manic symptoms were substantially longer in duration than pure MDEs (Table 3), although the overall survival distribution functions did not reach the level of statistical significance (log-rank $\chi^2=3.13$; $df=1$; $P=0.077$). Median time to recovery was approximately twice as long for MDEs with manic symptoms than for purely depressive MDEs (28 weeks vs. 14.5 weeks). MDEs with concurrent manic symptoms were more than twice as likely to last at least one or two years after the subject entered the CDS.

3.4. Polarity switch during intake MDE

We hypothesized that the presence of manic symptoms in the intake MDE would be associated with increased changes in polarity within that episode. We found that none of the "pure" MDE patients cycled to mania/hypomania during their intake episode – either before or after intake. In addition, all 17 MDEs that cycled to mania or hypomania after intake had already been polyphasic ($N=15$) or biphasic ($N=2$) prior to intake, and all 17 also had clinically significant concurrent manic symptoms during the intake MDE. Thus, the presence of concurrent manic symptoms during an MDE, combined with prior cycling in the intake episode, posed a substantial risk for additional cycling before the end of the intake MDE.

3.5. Suicidal tendencies and behavior

MDEs with concurrent subsyndromal manic symptoms were associated with significantly higher suicidal tendencies during the intake episode (Table 4). Over half of the MDEs with manic symptoms (54.6%) were rated as "severe," "extreme," or "very extreme" for suicidal tendencies, compared to just over one quarter of the purely depressive MDEs (26.5%). In terms of actual suicidal behavior, the analysis groups differed significantly in both suicide attempts, and *serious* suicide attempts, in all three time periods covered by the CDS, namely, prior to the intake MDE, during the intake MDE, and during long-term follow-up (Table 4). MDEs with some clinically significant concurrent manic symptoms were at least twice as likely as "pure" MDEs to be associated with serious suicide attempts during each of these three time periods, and had significantly more suicide attempts of any level of seriousness in each time period. This contrast in suicidal tendencies and behaviors for subjects with vs. without concurrent subsyndromal manic symptoms was present in both BP-I and BP-II subtypes.

3.6. Co-morbid diagnoses, psychosocial impairment, and long-term course

When comparing bipolar MDEs with and without concurrent manic symptoms, we found no significant differences in rates of any comorbid mental disorders, substance use disorders, or any measure of psychosocial impairment at intake or during long-term follow-up. Nor was the presence of concurrent manic symptoms associated with a significant difference in level of recovery from the intake episode (to the asymptomatic vs. residual symptom status), time to episode relapse, or any measure of the severity of the future course of illness including the percentage of follow-up with affective symptoms (at any level or at the threshold for major affective episodes), the percentage of follow-up in affective episodes, or the number of episodes within 10 or 15 years after intake.

3.7. Irritable and/or agitated bipolar major depressive episodes

Overt irritability and psychomotor agitation were the most common manic spectrum symptoms occurring during bipolar MDEs (see Table 2). Of the 142 intake bipolar MDEs examined in this paper, 57.0% were characterized by clinically significant overt expressions of irritability/anger, and 39.4% had clinically significant psychomotor agitation; 23.9% of the intake MDEs were characterized by *both* overtly expressed irritability and psychomotor agitation.

The impact of these two qualities on other clinical characteristics and outcomes is presented in Table 5. Removing MDEs with other manic symptoms, then comparing subgroups with one or both of these symptoms to purely depressive MDEs, provides a unique analysis of clinical correlates of irritability and psychomotor agitation disentangled from each other and from the possible influence of other manic symptoms. Compared to having no concurrent manic symptoms, the irritable quality of MDEs was associated with a significantly higher rate of future serious suicide attempts and impaired relationship with spouse/partner, as well as a longer duration of the intake episode. Psychomotor agitation was associated with significantly increased depressive severity, suicidal ideation, and prevalence of suicide attempts during the intake episode. A heightened risk of suicide attempts during long-term follow-up was also seen. The combination of irritable and agitated qualities of the bipolar MDE was associated with a statistically significant increase in depressive severity, intake episode duration, and history of prior suicide attempts.

4. Discussion

Although the interface of manic and depressive phases of bipolarity has been the focus of many investigations, the current findings shed light on a more subtle, less investigated, but very common form of mixed polarity — namely, the concurrent presence of subsyndromal manic symptoms during syndromal bipolar major depressive episodes. Using data from the NIMH CDS, we studied the prevalence, clinical correlates, and long-term outcomes of clinically significant subsyndromal manic symptoms occurring during bipolar MDEs.

The first conclusion from this study is that subsyndromal manic symptoms are highly prevalent during bipolar MDEs. Out of 147 patients entering the CDS with bipolar MDEs, 5 (3.4%) had a syndromal level of mania at intake, 108 (73.5%) had one or more clinically significant subsyndromal manic symptoms, and only 34 (23.1%) had purely depressive MDEs. This is consistent with the reports of others (Balázs et al., 2006; Benazzi, 2005; Benazzi and Akiskal, 2001, 2005; Goldberg et al., 2009) indicating that subsyndromal manic symptoms are the modal presentation of bipolar MDEs.

The second conclusion from this study is that the presence of any concurrent subsyndromal manic symptom(s) during bipolar MDEs represents a subtle form of mixed depressive state. Key clinical correlates, such as greater severity of the intake episode, instability of polarity,

and heightened suicidality, are similar to those reported for full manic mixed states (Balázs et al., 2006; Goldberg et al., 2009; Hawton et al., 2005; Keller et al., 1986; Swann et al., 2007).

The third conclusion from our study is that overt irritability and psychomotor agitation are the most frequent manic symptoms occurring during bipolar MDEs. Overt expression of irritability/anger and psychomotor agitation pose a particular challenge in the study of mixed manic symptoms, since they are not only symptoms of mania/hypomania, but are also qualifiers indicating specific types of MDE. Other investigators (Balázs et al., 2006; Benazzi and Akiskal, 2005; Goldberg et al., 2009) have also reported that these two MDE qualifiers are the most common subsyndromal manic symptoms occurring during bipolar MDEs. As in other studies (Benazzi, 2004; Benazzi and Akiskal, 2005, 2006; Goldberg et al., 2009; Maj et al., 2003), we found that these two characteristics have a high degree of overlap with each other and with other manic symptoms.

Our fourth conclusion is that overt irritability and psychomotor agitation appear to be markers for specific negative outcomes associated with a subsyndromal bipolar mixed state. Other investigators have reported a high association between irritability or agitation and important clinical outcomes including suicide attempts (Balázs et al., 2006; Maj et al., 2003; Swann et al., 2007) and longer intake episodes (Maj et al., 2003). Unfortunately, previous studies have examined correlates of these two characteristics without regard for their overlap with each other or with other manic symptoms during bipolar MDEs. Using CDS data, we were able to disentangle the effects of overt irritability and psychomotor agitation from the influence of their combination with each other or with other manic symptoms. We found that the quality of overt irritability (without agitation) during bipolar MDEs was associated with a significantly higher rate of serious suicide attempts during follow-up, and greater impairment in the relationship with one's spouse/partner. After controlling for the influence of other manic symptoms, psychomotor agitation was associated with greater severity of depression in the intake episode, longer intake episodes (when combined with irritability), and higher past and current suicidal tendencies. Thus, these two characteristics appear to account for much of the negative findings associated with subsyndromal manic symptoms. This is likely to be due to the fact that irritability and psychomotor agitation were the most prevalent concurrent manic symptoms during the bipolar MDEs examined, and it underscores the importance of disentangling their influence on important clinical outcomes. In their study of 1380 bipolar MDEs, Goldberg and colleagues (2009) defined and analyzed concurrent manic symptoms status *independent of the presence of irritability or psychomotor agitation*, because these symptoms have been shown to occur in both bipolar and unipolar MDEs. They report that irritability (analyzed separately from other manic symptoms) was present to at least a moderate degree in 73.1% of their overall sample, including 40.0% of MDEs meeting their definition of subsyndromal manic symptoms. Psychomotor agitation (also analyzed separately) was present in 31.2% of subjects, including 19.1% of bipolar MDEs with subsyndromal manic symptoms. Thus, the clinical correlates of concurrent subsyndromal and full manic symptoms reported by Goldberg et al. may be largely due to the presence of irritability and/or psychomotor agitation. We believe that our study is the first to attempt to disentangle the effects of these, which appear to be the most common manic spectrum symptoms occurring during bipolar MDEs.

4.1. Caveats

The SADS interview covers all DSM-IV-TR symptom criteria for manic episodes, but is not in the form of a systematic checklist. Two manic symptoms are asked only if one of 5 manic screener symptoms is present at a clinically significant level. One of these is risk-taking behavior, which has been shown in other studies to have a very low prevalence in mania. The other is racing thoughts, a prevalent symptom that is part of DSM-IV-TR criterion B-4

for mania (which also includes flight of ideas, an observational item that is rated for all CDS subjects). A particular strength of the SADS is the rating of severity of each symptom on a 6-point scale, on which a value of 3 or higher indicates clinical significance. Another advantage of the SADS is the inclusion of symptom qualities of overt irritability and psychomotor agitation which are rated for periods of the intake MDE when subjects did not have other evidence of a manic syndrome. These items may vary somewhat from the definitions of 'irritable-hostile depression' examined by Benazzi and Akiskal (2005) and Goldberg et al. (2009), and from various definitions of 'agitated' depression which may include psychic symptoms as well as psychomotor manifestations. From our data it appears that *irritable and agitated bipolar MDEs as defined in this study are the most common variants of bipolar mixed depressive state*. Our findings regarding the association of clinical characteristics and clinical outcomes are intriguing, but only suggestive, given the small number of subjects. Larger study samples are needed for more definitive analysis of the clinical importance of these characteristics, disentangled from each other and from the influence of other manic symptoms. We are presently undertaking a similar study in unipolar MDEs, in which we are testing whether qualities of overt irritability and/or psychomotor agitation are markers for underlying bipolarity.

4.2. Clinical implications

It has been reported (Goldberg et al. 2007) that for patients with bipolar MDEs and two or more concurrent manic symptoms, the addition of antidepressants to mood stabilizers was associated with significantly higher manic symptom severity at 3-month follow-up. Similarly, Frye et al. (2009) reported that the presence of minimal concurrent manic symptoms during presentation of bipolar MDEs predicted emergence or worsening of manic/hypomanic symptoms during treatment with antidepressants; this was especially true if the baseline manic symptoms were increased motor activity, racing thoughts, or pressured speech. Thus, identification of the presence of subsyndromal manic symptoms during bipolar MDEs, and particularly manic symptoms reflecting accelerated physical and mental activity, may be critical for more effective treatment of mixed bipolar MDEs. Analysis of intra-MDE symptoms in a large sample of inpatients with BP-I (Perugi et al., 2001) and outpatients with BP-II (Akiskal and Benazzi, 2004) showed strong support for two subtypes of depressive mixed states described by Kraepelin (1907): "excited depression" (marked by psychomotor agitation, talkativeness, irritable mood, and distractibility) and "depression with racing/crowded thoughts" (also characterized by risky impulsiveness). Studies are needed to validate these subtypes and determine their most effective treatment. In the meantime, skillful interviewing is needed to identify these symptoms during MDEs since they do not appear to be accompanied by euphoric/expansive manic symptoms (Benazzi et al., 2004).

We suggest that clinicians and primary physicians treating MDEs in bipolar patients use all available information from patients and those close to them to identify syndromal or subsyndromal manic symptoms present during an MDE. Patients with any concurrent manic symptoms, especially overly expressed irritability or psychomotor agitation, may need specialized treatment and particularly intensive clinical monitoring in order to avoid serious clinical outcomes such as prolonged MDEs, polarity switches within the episode, and suicidal behavior.

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Table 1

Demographic and clinical characteristics of bipolar patients (N=142) who entered the CDS in a major depressive episode without concurrent syndromal mania.

Characteristic at intake		Bipolar MDE sample (N=142)
Demographics		
Age	Mean (sd) [Range]	36.7 (13.5) [18–79]
Female gender	N (%)	83 (58.5)
Education — some college	N (%)	85 (59.9)
Marital status		
Married/living together	N (%)	60 (42.3)
Separated/widowed/divorced	N (%)	34 (23.9)
Never married	N (%)	48 (33.8)
Clinical history		
Age at onset of first affective episode	Mean (sd) [Range]	20.9 (9.6) [1–64]
Onset of first affective episode before age 21	N (%)	86 (60.6)
Four or more lifetime affective episodes (including intake)	N (%)	108 (76.1)
Lifetime bipolar diagnosis as of intake:		
Bipolar disorder, Type I (BP-I)	N (%)	52 (36.6)
Bipolar disorder, Type II (BP-II)	N (%)	90 (63.4)
Amount of follow-up (years)	Mean (sd) Median [Range]	16.2 (8.8) 20.0 [0.5–27.0]

Table 2

Frequency of specific clinically significant individual subsyndromal manic symptoms (from most to least prevalent) concurrent with intake major depressive episodes in patients with bipolar disorder (N=142).

Symptoms present at a clinically significant level concurrent with intake major depression	Bipolar MDE sample (N=142) N (%)
Irritability ^a — MDE with overt (observable) expression of irritability, annoyance and/or anger. This does not include subjective feelings of annoyance or anger, no matter how intense, unless expressed overtly in behavior.	81 (57.0)
Psychomotor agitation ^a — MDE with physical agitation lasting a few days or longer. Examples include the inability to sit still, pacing, fidgeting, movement of lips or fingers, wringing of hands, pulling at clothes, etc., which must be present other than when discussing something upsetting. It does not include subjective feelings of tension or restlessness, unless expressed overtly in behavior.	56 (39.4)
Elevated mood ^b — MDE with elevated or expansive mood and/or optimistic attitude toward the future out of proportion to the circumstances, lasting at least several hours.	19 (13.4)
Heightened Energy ^b — MDE with unusual energy (more active than usual without expected fatigue), lasting at least several days.	16 (11.3)
Increased goal-directed activity ^b — MDE with changes in involvement or activity level associated with work, family, friends, sex drive, new projects, interests, or activities as compared with usual level.	14 (9.9)
Less need for sleep than usual ^b — MDE with less need than usual to feel rested, average for several days.	12 (8.5)
Flight of ideas ^c or racing thoughts ^d — MDE with abrupt changes from topic to topic, usually based on understandable associations, distracting stimuli, or play on words; and/or thinking that is markedly accelerated.	11 (7.7)
Talkativeness (pressured speech) ^e — MDE with accelerated, pressured, or increased amount of speech.	9 (7.7) ^e
Distractibility ^c — MDE with attention too easily drawn to unimportant or irrelevant external stimuli.	9 (6.3)
Inflated self-esteem (grandiosity) ^b — MDE with increased self-esteem and appraisal of one's worth, contacts, power, or knowledge (up to grandiose delusions) as compared with usual level.	7 (4.9)
Risk-taking behavior ^e — MDE with excessive involvement in activities without recognizing the high potential for painful consequences.	2 (1.7) ^e

^aRated for all patients in the depression section of SADS, for depressed periods without evidence of full manic syndrome; also asked in the mania section if some manic screening item is >2, for the worst week prior to intake (analyzed only if the intake episode did not include a fully syndromal manic period).

^bA mania screening item, rated for all patients.

^cRated for all patients based on observation during the SADS interview.

^dRacing thoughts is asked in the mania section of SADS if some manic screening item is >2, and only for the worst week prior to intake (not also for week prior to intake). This symptom was analyzed only if the intake episode did not include a fully syndromal manic period prior to an MDE phase at intake, counting response code 2 or 3 (on 1–3 scale) as clinically significant. However, flight of ideas was rated for *all* subjects based on observation during the SADS interview.

^eAsked in the mania section of SADS if some manic screening item is >2, and only for the worst week prior to intake (not also for week prior to intake). This symptom was not counted for N=25 subjects who had a prior manic period during the intake episode, since it was not possible to know whether the worst week of the episode was during mania or MDE. The percentage shown is based on a denominator of N=117 (i.e., 142 minus 25).

Table 3

Severity and duration of intake bipolar major depressive episodes with vs. without concurrent clinically significant subsyndromal manic symptoms^a.

		MDEs with some clinically significant manic symptoms (N=108)	MDEs with no clinically significant manic symptoms (N=34)	Significance
Overall severity (symptoms and impairment) ^b				
Global assessment scale (GAS) ^c	Mean (sd)	34.1 (9.5)	38.9 (12.4)	t=2.05, df=45.9 ^d ; P=0.046
Severity of dysphoria/depression				
Depressed mood and ideation ^e	Mean (sd)	22.4 (3.7)	20.5 (5.0)	t=2.06, df=44.9 ^d ; P=0.046
Depressive-associated features ^f	Mean (sd)	50.6 (7.1)	47.1 (8.3)	t=2.45; df=140; P=0.015
Extracted Hamilton ^g	Mean (sd)	29.3 (6.8)	25.2 (7.6)	t=2.95; df=140; P=0.004
Duration of intake major depressive episode from intake to recovery (weeks) ^h	25% (95% CI)	6 (5–11)	6 (3–12)	Log-rank $\chi^2=3.13$; df=1; P=0.077
	50% (95% CI)	28 (15–52)	14.5 (7–26)	
	75% (95% CI)	112 (74–188)	46 (16–73)	
	Probability of episode Lasting:			
	1 year	0.402	0.194	
	2 years	0.253	0.108	

^aClinically significant manic symptoms are defined in Table 2.

^bBased on the worst week in the intake episode, or the past year if current episode began more than 1 year before intake.

^cPossible GAS score values range from 1 (extremely severe symptoms and impairment) to 100 (no symptoms superior functioning). Mean scores between 30 and 40 reflect major impairment, some psychoticism, and/or a suicide attempt.

^dAfter Satterthwaite adjustment for unequal group variances.

^eSum of SADS ratings of depressive mood, brooding, feelings of self-reproach, negative evaluation of self, and discouragement (SADS Score 1, with possible range 5–31).

^fSum of SADS ratings of suicidal tendencies, sleep disturbance, lack of energy, appetite/weight gain/loss, indecisiveness, difficulty concentrating, pervasive loss of interest, agitation, psychomotor retardation, depressed appearance (SADS Score 3, with possible range 14–88).

^gApproximation of 17-item Hamilton Depression Rating Score (HAM-D17) based on matching SADS items.

^hFrom survival analysis.

Table 4

Suicidal tendencies and behavior associated with intake bipolar major depressive episodes with vs. without concurrent clinically significant subsyndromal manic symptoms^a.

		MDEs with some clinically significant manic symptoms (N=108)	MDEs with no clinically significant manic symptoms (N=34)	Significance
Suicidal tendencies in intake episode ^b				
Average rating	Mean (sd)	4.6 (1.6)	3.6 (1.6)	t=2.96; df=140; P=0.004
Severe, extreme, or very extreme rating	N (%)	59 (54.6)	9 (26.5)	FET P ^c =0.006
Suicide attempt(s), by time period				
Prior to intake MDE				
Any suicide attempt	N (%)	58 (53.7)	11 (32.3)	FET P ^c =0.032
Any serious attempt ^d	N (%)	52 (48.2)	8 (23.5)	FET P ^c =0.016
During intake episode ^e				
Any suicide attempt	N (%)	42 (38.9)	4 (11.8)	FET P ^c =0.003
Any serious attempt ^d	N (%)	33 (30.6)	4 (11.8)	FET P ^c =0.042
During long-term follow-up ^f				
Any suicide attempt	N (%)	63 (58.3)	12 (35.3)	FET P ^c =0.029
Any serious attempt (or completed suicide) ^{d,g}	N (%)	44 (40.7)	7 (20.6)	FET P ^c =0.040

^aClinically significant manic symptoms are defined in Table 2.

^bSuicidal tendencies during the worst period of the intake MDE are coded (SADS 246) using the following scale: 1=not at all; 2=slight - occasional thoughts of death without suicidal thoughts; 3=mild - frequent thoughts that (s)he would be better off dead or occasional thoughts of suicide but not of a specific method; 4=moderate - often thinks of suicide or has thought of a specific method; 5=severe x often thinks of suicide and has thought of or mentally rehearsed a specific plan, OR has made a suicidal gesture of a communicative rather than a potentially medically harmful type; 6=extreme - has made preparations for a potentially serious suicidal attempt; 7=very extreme - suicidal attempt with definite intent to die or that was potentially medically harmful

^cFisher's Exact Test, 2-sided probability

^dA suicide attempt is considered serious if there is definite intent to commit suicide and/or at least moderate medical threat to life; without either condition an attempt is considered a suicide gesture.

^eCoded for the entire current episode or the past year, whichever is shorter.

^fBased on LIFE, LIFE-II, CUF, SLICE, and GRIM forms covering the period from intake to end of follow-up.

^gThere were 7 completed suicides in the manic symptom group (6.5%) and 2 in the group with no manic symptoms (5.9%) during long-term follow-up.

Table 5

Characteristics associated with clinically significant symptoms of irritability and/or agitation at intake mde isolated from the effect of other manic symptoms by removal of N=28 subjects.

	Irritable/agitated mdes without other manic symptoms				Pure MDEs (no irritable or agitated depression, or othermanic symptoms) (N=34)
	MDE with overt expression of irritability (N=37)	MDE with psychomotor agitation (N=17)	MDE with both irritability and agitation (N=21)		
Severity of dysphoria/depression in intake MDE					
Extracted Hamilton	Mean (sd)	26.6 (6.6)	31.5 (7.0) <i>a, b</i>	30.4 (6.5) <i>a, b</i>	25.2 (7.6)
Duration of intake episode (weeks from intake to recovery)	Median (95% CI)	39 ^b (15–112)	12 (5–18)	96 <i>a, b</i> (24–535)	14.5 (7–26)
	Probability of lasting 1 Year	0.460	0.057	0.538	0.194
Suicidal tendencies in intake episode — severe, extreme, or very extreme	N (%)	17 (45.9)	11 (64.7) <i>a, b</i>	8 (38.1)	9 (26.5)
Suicide attempts					
Prior to intake MDE					
Any attempt	N (%)	14 (37.8)	6 (35.3)	17 (81.0) <i>a, b</i>	11 (32.3)
Any serious attempt	N (%)	11 (29.7)	6 (35.3)	15 (71.4) <i>a, b</i>	8 (23.5)
During intake episode					
Any attempt	N (%)	11 (27.9)	8 (47.1) <i>a, b</i>	5 (23.8)	4 (11.8)
Any serious attempt	N (%)	9 (24.3)	6 (35.3) <i>a</i>	4 (19.0)	4 (11.8)
During follow-up					
Any attempt	N (%)	20 (54.1)	12 (70.6) <i>b</i>	9 (42.9)	12 (35.3)
Any serious attempt (or completed suicide) ^d	N (%)	16 (43.2) <i>a, b</i>	4 (23.5)	5 (23.8)	7 (20.6)
Impairment in relationship with spouse/partner during follow-up ^c	Mean (sd)	2.64 (0.95) <i>a, b</i>	1.90 (0.71)	1.88 (0.57)	1.95 (0.70)
	N	22	7	15	15

^aSignificantly different (2-tailed P 0.05) based on analyses of the effect of overt irritability, psychomotor agitation, or the combination vs. "Pure MDE," covarying for the influence of other manic symptoms, without 28 cases removed.

^bSignificantly different (2-tailed P 0.05) from "Pure MDE" group after removing N=28 cases with other manic symptoms, including 10 of 47 MDEs with overt irritability (21.3%), 5 of 22 MDEs with psychomotor agitation (22.7%), and 13 of 34 MDEs with both overt irritability and psychomotor agitation (38.2%).

^cThis variable was not significant in the comparison of any vs. no manic symptoms. Mean (sd) values for subjects with any (N=61) vs. no (N=15) clinically significant manic symptoms were 2.25 (0.94) and 1.95 (0.70), respectively ($t=1.19$; $df=74$; $P=0.24$).

^dThere were 3 completed suicides in the overt irritability group (8.1%), none in the psychomotor agitation group, 1 in the group with both overt irritability and psychomotor agitation (4.8%), and 2 in the group with no manic symptoms (5.9%).