Suicidal ideation and bipolar-II depression symptoms

Franco Benazzi*

E. Hecker Outpatient Psychiatry Center, Ravenna, Italy, A University of California at San Diego, USA, Collaborating Center, and Department of Psychiatry, National Health Service, Forli, Italy

Objective The FDA issued a warning about a possible risk of suicidal behaviour related to ‘newer’ antidepressants. Suicidal behaviour is common in bipolar-II (BP-II) depression, which is frequent in outpatients, and often mixed (i.e. it has concurrent hypomanic symptoms). The study aim was to find major depressive episode (MDE) and intra-MDE hypomanic symptoms associated with suicidal ideation.

Methods A total of 374 consecutive BP-II MDE outpatients were interviewed by the structured clinical interview for DSM-IV (SCID), the hypomania interview guide, and the family history screen.

Results Suicidal ideation was present in 52.6%. Suicidal ideation and lower GAF (meaning more severity), more persistent MDE symptoms, more melancholic depressions were significantly associated. Multiple logistic regression of suicidal ideation versus MDE symptoms and intra-MDE hypomanic symptoms found, as significant independent predictors, decreased self-esteem, racing/crowded thoughts, psychomotor agitation.

Discussion As expected, suicidal ideation and depression severity were associated. Racing/crowded thoughts and psychomotor agitation were independent predictors of suicidal ideation. While cross-sectional associations cannot show a causal association, some evidence from prospective studies supports the direction of the association. As BP-II depression is common and often mixed in outpatients, clinicians should assess intra-MDE racing/crowded thoughts and psychomotor agitation, as antidepressants alone may worsen these symptoms, and this may induce or increase suicidal behaviour. Mood stabilizing agents may be needed to control these excitement symptoms before using antidepressants. Copyright © 2004 John Wiley & Sons, Ltd.

Key words — bipolar II disorder; depression; suicide; agitation

INTRODUCTION

Suicidal behaviour is common in bipolar-II disorder (BP-II) (Rihmer and Pestality, 1999). Following recent reports (Healy, 2003; Healy and Whitaker, 2003), the USA FDA (Food and Drug Administration) issued a warning about a possible risk of suicidal behaviour related to the ‘newer’ antidepressants (http, 2004). This view has recently been questioned (Leon et al., 2004). It would be useful to know which cross-sectional features of BP-II depression may be related to suicidal ideation, in order to plan prevention treatments. Under-diagnosis and misdiagnosis of BP-II as major depressive disorder (MDD) is common in clinical practice (Ghaemi et al., 2002; American Psychiatric Association, 2002; Akiskal and Pinto, 1999; Angst et al., 2003; Benazzi, 2003a; Benazzi, 2004a,b; Akiskal and Benazzi, 2003; Smith et al., in press; Rybakowski et al., in press). In community and clinical samples, the BP-II to MDD ratio may be near 1 (Angst, 1998; Hantouche et al., 1998; Manning et al., 1999; Akiskal et al., 2000; Dunner, 2003; Angst et al., 2003; Benazzi, 2003b). The high frequency of BP-II depression in outpatients strongly supports its study. Mixed depression (depressive mixed state, an MDE plus concurrent intra-MDE hypomanic symptoms) was clearly described by the classics (Hecker, 1898, English translation by Koukopoulos, 2003; Kraepelin, 1921, English translation by Barclay, 1921), and has seen a rebirth of studies.
Mixed depression was found to be common in BP-II depression, suggesting the need to assess intra-MDE hypomanic symptoms. The study aim was to find major depressive episode (MDE) and intra-MDE hypomanic symptoms associated with suicidal ideation. A large database recorded for studying mixed depression was scanned to identify associations.

METHODS

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

Study setting

The study setting was a private outpatient psychiatric practice, which is more representative of the mood disorders usually seen in clinical practice in Italy (apart from the psychotic ones), because (1) it is the first or second (after family doctors) line of treatment of mood disorders, (2) the most severe and socially disadvantaged cases are usually seen in tertiary-care centres (national health service and academic centres), (3) mood disorder patients do not like to be treated in the national health service for fear of stigma, and, (4) most individuals can be treated by a private psychiatrist (fee-for-service), reducing a possible income bias.

Interviewer

The interviewer was a senior clinical (20 years in practice) and mood disorder research psychiatrist.

Patient population

A total of 374 consecutive BP-II outpatients, presenting voluntarily for major depressive episode (MDE) treatment in the past 6 years (off psychopharmacotherapy), were included. Substance-related and borderline personality disorders were excluded because they confound the diagnosis of BP-II (due to the high background mood instability related to personality and/or substances, Akiskal and Pinto, 1999), and are rare in the study setting (Benazzi, 2000). Clinically significant general medical illnesses and cognitive disorders were also excluded.

Assessment instruments

During the assessment visit (off psychoactive drugs for at least 2 weeks, apart from a few individuals on small doses of benzodiazepines, in order not to induce or suppress hypomanic symptoms) the following instruments were used: (1) the structured clinical interview for DSM-IV axis I disorders-clinician version (First et al., 1997) (SCID-CV, inter-rater reliability k = 0.70–1.0), as modified by Benazzi and Akiskal (2003b) to improve detection of BP-II by focusing the probing more on over-activity; 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) (Koukopoulos and Koukopoulos, 1999), following Kraepelin’s description (1921, English translation by Barclay, 1921) of the grading of the thought disorders of hypomania; (2) the global assessment of functioning scale (GAF, in the SCID-CV) for index MDE severity; (3) the hypomania interview guide (Williams et al., 1994) to assess intra-MDE hypomanic symptoms; (4) the structured family history screen (Weissman et al., 2000) for assessing family history of suicidal behaviour and bipolar disorders in the probands’ first-degree relatives. Often, family members or close friends supplemented clinical information during the interview, increasing the validity of BP-II diagnosis and family history (Akiskal et al., 2000; American Psychiatric Association, 2000).

Interview methods

Systematic interviews about the history of hypomanic episodes were always conducted soon after MDE diagnosis and before the assessment of study variables, in order to avoid a possible bias related to knowledge of bipolar signs (Ghaemi et al., 2002). The SCID-CV is partly semi-structured and based on clinical evaluation (not on simple yes/no answers to structured questions). Wording of the sentences can be changed to improve and to check the understanding of the interviewee. This is an important advantage versus fully structured interviews because it reduces the false-negative BP-II and mood disorders (Dunner and Tay, 1993; Brugha et al., 2001; Simpson et al., 2002; Benazzi, 2003e, 2004a). The skip out instruction of the stem question on the history of mood changes was not followed, in order to assess all past hypomanic symptoms, especially over-activity (increased goal-directed activity), following previous reports (Dunner and Tay, 1993; Akiskal et al., 2003; Angst et al., 2003; Benazzi and Akiskal, 2003b; Benazzi, 2003a,e, 2004a). This behavioural change
is easier to remember than mood changes (always required for the diagnosis of BP-II according to DSM-IV-TR, and results in being easier to remember when over-activity was reported).

**Suicidal ideation**

This was defined according to the SCID-CV question: ‘were things so bad that you were thinking a lot about death or that you would be better off dead? What about thinking of hurting yourself? Did you do anything to hurt yourself?’

**Definition of mixed depression**

Mixed depression was defined as an MDE of 3 or more concurrent intra-MDE hypomanic symptoms, according to a definition which has clinical, family history and psychometric validation (Akiskal and Benazzi, 2003; Benazzi and Akiskal, 2003a; Benazzi, 2002, 2003c, in press). Hypomanic symptoms had to appear during the MDE (i.e. a hypomanic symptom-free interval of at least 1 month before the MDE was required), to last at least 1 week, and to be present at the time of the interview (to increase reliability).

**Data analysis**

Logistic regression was used to study associations and to control for confounding. The continuous variables age, age at onset and GAF score were scaled by 10 (age, onset) or 5 (GAF), according to Hosmer and Lemeshow (2000). The p value was two-tailed, the alpha level was set at 0.05, not correcting for multiple comparisons because of the exploratory nature of the study.

**RESULTS**

Suicidal ideation was present in 52.6% of patients. Sample features are presented in Table 1. Univariate logistic regression of suicidal ideation versus clinical and family history variables is presented in Table 2. Suicidal ideation and lower GAF (meaning more severity), more persistent MDE symptoms, more melancholic depressions and fewer atypical depressions were significantly associated. Multiple logistic regression of suicidal ideation versus MDE symptoms and intra-MDE hypomanic symptoms found, as significant independent predictors, decreased self-esteem, racing/crowded thoughts, psychomotor agitation and more talkativeness.

**DISCUSSION**

As expected, suicidal ideation and depression severity were closely associated (as shown by lower GAF, more persistent depressive symptoms and more melancholic depressions). Interestingly, no association was found between suicidal ideation and a family history of suicidal behaviour.

Racing/crowded thoughts and psychomotor agitation (core symptoms of mixed depression in the present study) were found to be strong, independent predictors of suicidal ideation. In the review by Angst

---

**Table 1. Features of the bipolar-II depression sample (n = 374)**

<table>
<thead>
<tr>
<th>Variable: mean (SD); %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index age, years</td>
</tr>
<tr>
<td>Age at onset first MDE, years</td>
</tr>
<tr>
<td>Index GAF</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>≥ 5 MDEs</td>
</tr>
<tr>
<td>Index MDE symptoms &gt; 2 years</td>
</tr>
<tr>
<td>Axis I comorbidity</td>
</tr>
<tr>
<td>Index psychotic features</td>
</tr>
<tr>
<td>Index melancholic features</td>
</tr>
<tr>
<td>Index atypical features</td>
</tr>
<tr>
<td>Index mixed depression (MDE plus ≥ 3 hypomanic symptoms)</td>
</tr>
<tr>
<td>Bipolar (type 1 + 2) family history</td>
</tr>
<tr>
<td>Suicidal behaviour family history</td>
</tr>
</tbody>
</table>

**MDE symptoms**

- Depressed mood: 96.7
- Diminished interest: 95.9
- Weight loss: 34.4
- Weight gain: 22.4
- Decreased eating: 47.8
- Increased eating: 27.2
- Insomnia: 79.4
- Hypersomnia: 36.8
- Psychomotor agitation: 33.6
- Psychomotor retardation: 3.7
- Loss of energy: 86.3
- Decreased self-esteem: 66.0
- Diminished ability to concentrate: 87.1

**Intra-MDE hypomanic symptoms**

- Number of hypomanic symptoms: 3.0 (1.4)
- Elevated mood: 0.0
- Irritable mood: 60.4
- Increased self-esteem: 0.0
- Decreased need for sleep: 1.6
- More talkativeness: 23.7
- Racing/crowded thoughts: 75.6
- Distractibility: 78.6
- Increased goal-directed activity: 7.2
- Psychomotor agitation: 33.6
- Increased risky activities: 18.7

MDE, major depressive episode; GAF, global assessment of functioning scale.
et al. (1999), agitation was found to be a risk factor for suicide. In cluster and factor analyses of depression, the symptoms of bipolar and unipolar in-patient samples and of community samples, psychomotor agitation and suicidal ideation were found to be correlated (Raskin et al., 1969; Andreasen and Grove, 1982; Sullivan et al., 1998, 2002; Kendler et al., 1996; Korszun et al., 2004). Maj et al. (2003) found that bipolar-I agitated depression had significantly more suicidal ideation (and racing thoughts) than non-agitated depression. In a community sample, depression, concurrent mania and suicidal thoughts were correlated (Krabbendam et al., 2004). None of these studies, however, included BP-II depressed outpatients. While cross-sectional associations cannot show a causal association (i.e. racing thoughts and psychomotor agitation might be a cause or an effect of suicidal ideation, and these symptoms might also form a cluster), clinical observations (Koukopoulos and Koukopoulos, 1999; Akiskal and Pinto, 1999) suggest that mixed depression may become more severe when using antidepressants alone, and even be associated with new or increased suicidal ideation. Antidepressant-induced mania was found to be associated with suicidal behaviour (Slama et al., 2004). Supporting these observations, and suggesting the direction of the associations found in the present cross-sectional study, are two prospective studies showing that mixed/cycling episodes were a risk factor of future suicidal behaviour (Maser et al., 2002; Allen et al., 2004). It was also found that 50% of suicides had had agitation the week before (Busch et al., 2003), and that antidepressants could induce more switching in mixed versus non-mixed bipolar depression (Bottlender et al., 2004), further supporting the direction of the association between psychomotor agitation, racing/crowded thoughts and suicidal ideation. The FDA reported association between suicidal ideation and ‘newer’ antidepressants may be related to increasing psychomotor agitation and racing thoughts when using antidepressants alone.

It has been suggested that first treating racing thoughts and psychomotor agitation by mood stabilizing agents, before starting the antidepressants, may be the best treatment approach for mixed depression (and possibly prevent or reduce the risk of suicidal behaviour when using antidepressants alone) (Benazzi, 2003f,g). Lithium seems to have an anti-suicidal effect in bipolar disorders (Baldessarini et al., 2003). The olanzapine and fluoxetine combination was also found to be effective in reducing suicidal ideation in bipolar-I depression (Tohen et al., 2003).

Controlled trials, ideally in usual clinical practice, should be designed to compare the effects of antidepressants in mixed (including psychomotor agitation and/or racing thoughts) versus non-mixed depression, and to test if mood stabilizing agents (especially lithium) may be useful in treating the hypomanic symptoms of mixed depression (and possibly, in this way, to treat or reduce the related suicidal ideation

### Table 2. Univariate logistic regression of suicidal ideation versus clinical and family history variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index age, years</td>
<td>1.0</td>
<td>0.9–1.2</td>
<td>0.256</td>
</tr>
<tr>
<td>Age at onset first MDE, years</td>
<td>1.0</td>
<td>0.8–1.2</td>
<td>0.542</td>
</tr>
<tr>
<td>Index GAF</td>
<td>0.7</td>
<td>0.6–0.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.0</td>
<td>0.6–1.6</td>
<td>0.780</td>
</tr>
<tr>
<td>≥ 5 MDEs</td>
<td>1.0</td>
<td>0.6–1.7</td>
<td>0.896</td>
</tr>
<tr>
<td>Index MDE symptoms &gt; 2 years</td>
<td>1.6</td>
<td>1.0–2.4</td>
<td>0.029</td>
</tr>
<tr>
<td>Axis I comorbidity</td>
<td>0.8</td>
<td>0.5–1.3</td>
<td>0.543</td>
</tr>
<tr>
<td>Index psychotic features</td>
<td>1.7</td>
<td>0.8–3.9</td>
<td>0.154</td>
</tr>
<tr>
<td>Index melancholic features</td>
<td>3.4</td>
<td>1.6–7.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Index atypical features</td>
<td>0.6</td>
<td>0.4–0.9</td>
<td>0.025</td>
</tr>
<tr>
<td>Index mixed depression (MDE plus ≥ 3 hypomanic symptoms)</td>
<td>1.1</td>
<td>0.7–1.7</td>
<td>0.497</td>
</tr>
<tr>
<td>Number of hypomanic symptoms</td>
<td>1.0</td>
<td>0.8–1.1</td>
<td>0.722</td>
</tr>
<tr>
<td>Bipolar (type 1 + 2) family history</td>
<td>0.7</td>
<td>0.4–1.1</td>
<td>0.299</td>
</tr>
<tr>
<td>Suicidal behaviour family history</td>
<td>0.6</td>
<td>0.3–1.2</td>
<td>0.183</td>
</tr>
</tbody>
</table>

MDE, major depressive episode; GAF, global assessment of functioning scale; OR, odds ratio; 95% CI, 95% confidence interval.

### Table 3. Multiple logistic regression of suicidal ideation (dependent variable) versus MDE symptoms and intra-MDE hypomanic symptoms (present in more than 10% of cases, same or similar MDE and hypomanic symptoms were included only once)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDE symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>2.5</td>
<td>0.8–7.4</td>
<td>0.096</td>
</tr>
<tr>
<td>Diminished interest</td>
<td>0.5</td>
<td>0.2–1.3</td>
<td>0.171</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.8</td>
<td>0.5–1.2</td>
<td>0.410</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1.1</td>
<td>0.6–2.2</td>
<td>0.615</td>
</tr>
<tr>
<td>Decreased eating</td>
<td>1.3</td>
<td>0.8–2.0</td>
<td>0.169</td>
</tr>
<tr>
<td>Increased eating</td>
<td>0.9</td>
<td>0.4–1.6</td>
<td>0.751</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.1</td>
<td>0.7–1.7</td>
<td>0.584</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>0.8</td>
<td>0.5–1.2</td>
<td>0.327</td>
</tr>
<tr>
<td>Loss of energy</td>
<td>1.0</td>
<td>0.6–1.6</td>
<td>0.970</td>
</tr>
<tr>
<td>Decreased self-esteem</td>
<td>3.3</td>
<td>2.3–4.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Intra-MDE hypomanic symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable mood</td>
<td>1.1</td>
<td>0.8–1.6</td>
<td>0.481</td>
</tr>
<tr>
<td>More talkativeness</td>
<td>0.5</td>
<td>0.3–0.8</td>
<td>0.012</td>
</tr>
<tr>
<td>Racing/crowded thoughts</td>
<td>1.7</td>
<td>1.1–2.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Distractibility</td>
<td>0.9</td>
<td>0.6–1.4</td>
<td>0.813</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>1.9</td>
<td>1.2–2.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Increased risky activities</td>
<td>0.8</td>
<td>0.4–1.3</td>
<td>0.429</td>
</tr>
</tbody>
</table>

Log likelihood = –401.8, likelihood ratio chi-squared = 87.7, p = 0.0000.

MDE, major depressive episode; OR, odds ratio; 95% CI, 95% confidence interval.
and behaviour). Meanwhile, clinicians may find it useful to screen for hypomanic symptoms (especially psychomotor agitation and/or racing thoughts) during depression (which cannot be done by following strictly the SCID-CV), as mental and behavioural activation may be linked to suicidal ideation. The high frequency of mixed features in BP-II depressed outpatients would support such a screening.

**Limitations**

A single interviewer might bias results. However, the interviewer’s inter-rater reliability for the diagnosis of BP-II was found to be adequate (Benazzi, 2003d). An interviewer bias is unlikely as study variables were systematically recorded when the study goal was not in the mind of the interviewer. Sample features are comparable to previous studies, supporting the validity of the interview method. The reliability of BP-II diagnosis was found to be high when trained clinicians used semi-structured interviews as in the present study (Simpson et al., 2002). The interview was conducted by a clinician experienced in the study and treatment of mood disorders, systematically using validated structured and semi-structured interviews, supplemented by key informants.

**REFERENCES**


Benazzi F. in press. Family history validation of a definition of mixed depression. *Compr Psychiatry*.


Manning JS, Haykal RF, Akiskal HS. 1999. The role of bipolarity in
Manic-depressive Insanity and Paranoia
Kraepelin E. 1921.
Leon AC, Marzuk PM, Tardiff K, Teres JJ. 2004. Paroxetine, other
et al.
Hantouche EG, Akiskal HS, Lencrenon S, et al.
Koukopoulos A, Koukopoulos A. 1999. Agitated depression as a
mixed state and the problem of melancholia. Psychiatr Clin North
Am 22: 547–564.
sions of depression, mania and psychosis in the general popula-
Livingstone E & S: Edinburgh.
Leon AC, Marzuk PM, Tardiff K, Teres JJ. 2004. Paroxetine, other
antidepressants, and youth suicide in New York city: 1993 through
in bipolar I disorder: prevalence, phenomenology, and outcome.
Manning JS, Haykal RF, Akiskal HS. 1999. The role of bipolarity in
depression in the family practice setting. Psychiatr Clin North
Am 22: 689–703.
identify affectively ill patients who engage in lethal or near-lethal
suicidal behavior? A 14-year prospective study. Suicide Life
Threat Behav 32: 10–32.
of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives. J Nerv Ment Dis
Rihmer Z, Pestality P. 1999. Bipolar II disorder and suicidal beha-
Rybakowski JK, Suwalska A, Lojko D, Rymaszewska J, Kiejna A.
in press. Bipolar mood disorders among Polish psychiatric out-
patients treated for major depression. J Affect Disord.
Sato T, Bottlender R, Schroter A, Moller H-J. 2003. Frequency of
manic symptoms during a depressive episode and unipolar ‘depressive mixed state’ as bipolar spectrum. Acta Psychiatr
Scand 107: 268–274.
Serretti A, Olgiati P, in press. Profiles of ‘manic’ symptoms in
bipolar I, bipolar II and major depressive disorders. J Affect Dis-
ord.
Simpson SG, McMahon FJ, McInnis MG, et al. 2002. Diagnostic
reliability of bipolar II diagnosis. Arch Gen Psychiatry 59:
736–740.
suicidal behavior: toward the identification of a clinical subgroup.
Smith DJ, Harrison N, Muir W, Blackwood DHR, in press. The high
prevalence of bipolar spectrum disorders in young adults with
recent recurrence: toward an innovative diagnostic framework.
J Affect Disord.
Sullivan PF, Kessler RC, Kendler KS. 1998. Late latent class analysis
of lifetime depressive symptoms in the national comorbidity survey.
Sullivan PF, Prescott CA, Kendler KS. 2002. The subtypes of major
and olanzapine-fluoxetine combination in the treatment of bipo-
lar I depression. Arch Gen Psychiatry 60: 1079–1088.
Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H,
Olsson M. 2000. Brief screening for family psychiatric history.
Arch Gen Psychiatry 57: 675–682.
Hypomania interview guide (including hyperthymia). Current
Center for Environmental Therapeutics: Norwood, NJ.