Suicidal status during antidepressant treatment in 789 Sardinian patients with major affective disorder

Tondo L, Lepri B, Baldessarini RJ. Suicidal status during antidepressant treatment in 789 Sardinian patients with major affective disorder.

Objective: Relationships between antidepressant treatment and suicidality remain uncertain in major depressive disorder (MDD), and rarely evaluated in bipolar disorder (BPD).

Method: We evaluated changes in suicidality ratings (Hamilton Depression Rating Scale item-3) at the start and after 3.59 ± 2.57 months of sustained antidepressant treatment in a systematically assessed clinical sample (n = 789) of 605 patients with MDD, 103 patients with BPD-II and 81 patients with BPD-I (based on DSM-IV; 68.1% women; aged 44.3 ± 16.1 years), comparing suicidal vs. non-suicidal and recovered vs. unrecovered initially suicidal patients.

Results: Suicidal patients (103/789, 16.5%; BPD/MDD risk: 2.2) were more depressed and were ill longer. During treatment, 81.5% of suicidal patients became non-suicidal; 0.46% of 656 initially non-suicidal patients reported new suicidal thoughts, with no new attempts. Becoming non-suicidal was associated with greater depression severity and greater improvement.

Conclusion: Suicidal ideation was prevalent in patients with depressed major affective disorder, but most of the initially suicidal patients became non-suicidal with antidepressant treatment, independent of diagnosis, treatment type or dose.

Significant outcome

- During antidepressant treatment, suicidality ratings as well as other depressive symptoms improved in adults with bipolar disorder as well as major depressive disorder, independent of treatment type or dose.

Limitation

- Treatments were clinical, involved multiple modalities and suicidality was based on one item of the HDRS and may simply co-vary with recovery from acute depression.

Introduction

Suicide is a major public health challenge. Among persons with severe mood disorders, risk of suicide is as much as 20 times greater than in the general population (1), accounting for approximately 990,000 deaths and nearly 25 million attempts annually worldwide, at an international average annual suicide rate (per 100,000) of approximately 15, rate of attempts of 300–450 and estimated rate of suicidal ideation of about 3000 (2–5). Mortality, disability and morbidity associated with clinical depression and bipolar disorders, including high rates of suicides and attempts, exert major adverse effects on individuals, their families and society (6–8), as well as costing tens of billions of dollars annually in individual countries (9–14).
One would expect clinically effective treatments for mood disorders to reduce risk of suicide (4, 15). However, consistent evidence for reductions in risks of suicide and attempts in persons with major affective disorders has remained elusive. There is substantial and consistent evidence associated with long-term treatment with lithium among patients diagnosed with bipolar disorder (BPD), a mix of major affective disorders and possibly major depressive disorder (MDD), including evidence from randomized, controlled trials (4, 16–19). There is also emerging evidence that lithium may be superior in such effects to some anticonvulsants proposed as alternative mood stabilizers (4, 19–25). Surprisingly, however, evidence for a suicide risk-reducing effect of otherwise clinically effective antidepressant treatment is inconsistent and remains inconclusive (4, 5, 26–35). There have even been suggestions that risk of suicidal thinking, and perhaps suicide attempts, may be somewhat higher among juvenile and young adult patients treated with serotonin reuptake inhibitors (SRIs) or other antidepressants compared with a placebo in randomized trials (36–41). Such risks are of particular interest in juvenile depression, in which the clinical effectiveness of most antidepressants remains less well established than in adult MDD (42–44). Furthermore, the value of antidepressants for the management of long-term risk of depression in BPD remains less certain than for MDD (45, 46).

Finally, in contrast to the inconclusive evidence for a sparing effect of antidepressant treatment on suicides or attempts, there is evidence from randomized, controlled trials that antidepressant treatment is associated with greater decreases than with placebo treatment, of ratings of suicidal ideation in depressed adults, along with improvements of other symptoms of depression (47–52). However, such reduction in suicidal ideation has rarely been tested in clinical mood disorder populations, and not specifically in patients with BPD, who may have even greater risk of suicide and attempts than many patients with MDD (4, 7, 53).

Given ongoing uncertainties about potential beneficial or harmful effects of antidepressant treatment on suicidality, including ideation and suicidal acts among men vs. women of various ages, with various major affective disorders and duration and severity of illness, we have undertaken an analysis of suicidality ratings from a large sample of systematically evaluated, treated and followed-up patients at a mood disorder research center affiliated with the University of Cagliari in Sardinia. The present report is based on an analysis of item-3 (suicidal thinking and behavior) of the Hamilton Depression Rating Scale [HDRS: (54)] before and after at least 1 month of antidepressant treatment in 789 patients diagnosed with DSM-IV major affective disorder.

**Aims of the study**

We hypothesized that: (i) prevalence of elevated suicidality ratings (Hamilton Depression Rating Scale item-3 scores) would be greater in patients with BPD than in those with MDD, in severely depressed patients, in women and among the eldest or youngest patients; (ii) most patients with initially elevated suicidality ratings would show major improvement in item-3 scores as overall symptomatic ratings of depression improved during antidepressant treatment, and such improvement would vary little by sex, age, diagnosis, duration of illness or type of treatment; and (iii) newly emerging suicidality during antidepressant treatment would be rare.

**Material and methods**

**Subjects**

We analyzed information arising from systematic clinical assessments of adult patients with mood disorder at the Lucio Bini Mood Disorders Center affiliated with the University of Cagliari in Sardinia. Study subjects were drawn from a larger sample of 2826 patients diagnosed with DSM-IV major mood disorders, whose suicidal risks were reported recently (53). For the present analyses, consecutive subjects were included who met the following criteria: (i) diagnosed with a DSM-IV major affective disorder; (ii) received an antidepressant; and (iii) had at least two ratings with the 21-item Hamilton Depression Rating Scale [HDRS-21 (54)]. These ratings supported comparison of scores at intake and the first follow-up rating during treatment, 1–12 months later, so as to evaluate treatment effects. Diagnostic and assessment methods were reported previously (53, 55). All subjects underwent initial diagnostic assessments by the first author (LT), based on semi-structured interviews that followed the mood disorder components of the RDC and SCID-I, as well as extensive follow-up clinical assessments and repeated ratings with standard mood disorder rating scales during prospective, systematic follow-up. Rating scale assessments were consistently administered by the same investigator (LT), avoiding inter-rater variance. Subjects initially met DSM diagnostic criteria for major affective disorders, and diagnoses were updated to meet
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DSM-IV-TR criteria in 2007. Approximately, 1/10 subjects also underwent full, structured, SCID-I-based diagnostic assessments to confirm findings of semi-structured clinical examinations. Diagnoses [bipolar I (BP-I), bipolar II (BP-II) or major depressive disorder (MDD)] were further supported by repeated clinical assessments during follow-up. Definite suicidality was defined as an initial or follow-up score of ≥2 (range 2–4) on item-3 of the HDRS-21 rated at the start of antidepressant treatment, and at the first reassessment 1–12 months later. Ratings of suicidal status also were consistently verified by repeated and detailed clinical assessments by the principal investigator (LT).

Subjects provided written, informed consent for use of their clinical data in analyses presented anonymously in aggregate form. The project database and data management comply with US federal HIPAA regulations pertaining to confidentiality of patient records, and research use of the database for this study was approved by the Ethical Committee of the District-8 Health Agency of Cagliari (ASL8), Sardinia. Study data were entered into a computerized database by the principal investigator (LT) and a co-investigator (BL) in coded form to protect subject identity, and all authors participated in data analysis and reporting.

Treatment

Treatment was determined clinically and included use of standard antidepressants, alone or with mood stabilizing or antipsychotic drugs. We considered antidepressant types as: (i) older antidepressants [including tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), mianserin and nomifensine] vs. (ii) modern antidepressants [including serotonin-reuptake inhibitors (SRIs), duloxetine, mirtazapine or venlafaxine]. We also considered whether: (iii) a proved or proposed mood stabilizing agent (lithium carbonate or anticonvulsants including carbamazepine, divalproex, gabapentin, lamotrigine and oxcarbazepine); or (iv) an antipsychotic drug (usually haloperidol, olanzapine, quetiapine, risperidone or sulpiride) also was given; and (v) the use and duration of psychotherapy provided by an independent therapist, typically in weekly 50-min sessions. We standardized antidepressant doses (mg/day) based on relative potency (the ratio of median doses of various agents to 150 mg/day of imipramine) to provide total imipramine equivalent mg/day (36), including cases involving more than one antidepressant given simultaneously. When more than one course of antidepressant was given, only data from the most recent trial were considered.

Data analysis

Based on item-3 of HDRS-21 assessments at the start of treatment, we compared subjects initially considered ‘non-suicidal’ (item-3 score 0 or 1) with ‘definitely suicidal’ (scoring 2–4), including explicitly expressed wishes to be dead (item-3 score 2), planning (score 3) or a suicide attempt (score 4). We then compared the definitely suicidal subjects (initial item-3 score ≥2) who showed remission of suicidality (final item-3 score 0) or not, at HDRS-21 assessments following at least 1 month of antidepressant treatment. Based on within-subject analyses, we also evaluated rates of improvement (final item-3 score reduced ≥1 point), worsening (final item-3 score increased ≥1 point) and cases of emerging new suicidality (item-3 scores ≥2 during treatment, when initial scores had been 0 or 1).

We compared demographic and clinical factors, selected a priori, between the following subgroups: (i) subjects who were suicidal vs. non-suicidal at the start of antidepressant treatment; and (ii) those in whom suicidality remitted fully during treatment (item-3 score 0) or not (score ≥1). Factors considered included sex, marital status, current employment, family history of any psychiatric disorder (including substance abuse and suicidal behavior), diagnostic type (BP-I vs. BP-II vs. MDD; or all BPD vs. MDD), illness onset age, age at start of the index episode of major depression, total years of illness to the start of index treatment, any lifetime hospitalization or substance abuse, baseline total HDRS score for 20 items (not including suicidality item-3), baseline HDRS item-3 suicidality score and change in both ratings during antidepressant treatment, as well as the types and total estimated imipramine equivalent dose (mg/day) of antidepressants given, use of other psychotropic agents (mood stabilizers or antipsychotics), and use of psychotherapy.

We employed standard statistical methods, including contingency tables ($\chi^2$) for categorical comparisons, and ANOVA methods (F-test) for continuous variables or paired t-test of repeated measures, all with defined degrees of freedom (df). Based on a priori hypotheses, and following preliminary identification of potential risk factors considered individually, we used logistic regression modeling (to provide odds ratios, OR, with their 95% confidence intervals, CI) to test covariates for independent and significant association with initial suicidality or its remission during treatment. Averages are mean values with standard deviation (SD). Selected correlations were based on linear, least squares ($r$) or Spearman non-parametric regression functions ($r_s$). Statistical analyses employed
commercial computer programs (**STATVIEW-5®**: SAS Corp., Cary, NC, USA; **STATA-8®**: StataCorp, College Station, TX, USA). *A priori* hypotheses tested are outlined in the Introduction section.

**Results**

Subjects and treatments

The out-patients with antidepressant-treated major affective disorder meeting entry criteria for this study (n = 789) included 537 women and 252 men, with mean age 44.3 ± 16.1 years at the start of an index trial of antidepressant treatment. DSM-IV-TR diagnoses included: major depressive disorder (MDD, n = 605), bipolar disorder (BPD, n = 184) of type II (BP-II, n = 103) or type I (BP-I, n = 81), all in a current DSM-IV-TR major depressive episode. Age at onset averaged 34.3 ± 15.7 years, and subjects had been ill for a total of 10.2 ± 10.9 years prior to the index trial of antidepressant treatment. DSM-IV-TR diagnoses included: major depressive disorder (MDD, n = 605), bipolar disorder (BPD, n = 184) of type II (BP-II, n = 103) or type I (BP-I, n = 81), all in a current DSM-IV-TR major depressive episode. Age at onset averaged 34.3 ± 15.7 years, and subjects had been ill for a total of 10.2 ± 10.9 years prior to the index treatment. Their initial total HDRS-21 depression severity scores (including all 21 items) averaged 19.0 ± 5.5, in accordance with expected moderate severity scores (including all 21 items) averaged 19.0 ± 5.5, in accordance with expected moderate levels of illness severity among out-patients.

Over the years of data collection since the 1970s, TCAs and other older antidepressants were found to be used more often than SRIs or other modern agents (70.2% vs. 29.8%). Modern antidepressants were more likely to be given to patients with BPD than to patients with MDD [49.5% vs. 23.8%; \( \chi^2 \) (all df = 1) = 44.5, \( P < 0.0001 \)], for their greater safety among patients at high risk of mood switching and suicidal behaviors (31), and they were more often given to initially suicidal (item-3 score ≥2) vs. non-suicidal subjects (33.8% vs. 29.0%; \( \chi^2 = 1.25, P = 0.26 \)). The average total (imipramine equivalent) dose of antidepressants was 82.2 ± 58.2 mg/day, given for 3.59 ± 2.57 months between HDRS ratings. Mood stabilizing agents were given to 28.4% of patients (75.3% of BPD vs. 14.3% of MDD subjects; \( \chi^2 = 264, P < 0.0001 \)). Antipsychotic agents were given to 24.8% of patients, and their use did not differ by diagnosis. More than one antidepressant was given to 20.2% of patients, with similar rates across diagnoses. *Polytherapy* (one or more other psychotropic agents with an antidepressant) was used in 61.7% of subjects, more often among patients with BPD than among patients with MDD (88.2% vs. 11.8%; \( \chi^2 = 64.7, P < 0.0001 \)), as well as among initially suicidal vs. non-suicidal subjects (72.2% vs. 59.6%; \( \chi^2 = 7.40, P = 0.006 \)). *Psychotherapy* was included in the treatment of 22.1% of the patients, for an average duration of 51 months (3–307 months), with similar use among suicidal and non-suicidal subjects (Table 1), and among men (26.8%) and women (23.2%), with some apparent differences among patients diagnosed with MDD (16.0%), type I (27.1%) or type II BPD (35.6%), and between those who showed remission of suicidality (17.9%) or not (44.4%). In a multivariate analysis, none of these factors was significantly related to the use of psychotherapy [model-fit likelihood ratio (df = 5) = 4.56, \( P = 0.47 \)].

Baseline suicidal status

The overall average HDRS item-3 score at baseline was 0.65 ± 0.83. Initial item-3 suicidality ratings remained stable over the 30 years of subject intake (\( r = +0.064, P = 0.072 \)), suggesting consistency of ratings and patient morbidity. Based on having an item-3 score ≥2, a total of 16.9% (133/789) of subjects were initially considered to be definitely suicidal. This risk of definite suicidality was 2.2 times higher among patients with BPD (29.1% among suicidal and non-suicidal subjects (Table 1), and among men (26.8%) and women (23.2%), with some apparent differences among patients diagnosed with MDD (16.0%), type I (27.1%) or type II BPD (35.6%), and between those who showed remission of suicidality (17.9%) or not (44.4%). In a multivariate analysis, none of these factors was significantly related to the use of psychotherapy [model-fit likelihood ratio (df = 5) = 4.56, \( P = 0.47 \)].

### Table 1. Factors associated with suicidality at start of antidepressant treatment among 789 patients with major affective disorder

<table>
<thead>
<tr>
<th>Factors</th>
<th>Suicidal (%)</th>
<th>Non-suicidal (%)</th>
<th>( \chi^2 ) or ( F )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>133 (16.9%)</td>
<td>656 (83.1%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>16.9</td>
<td>83.1</td>
<td>0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>Age at treatment (years)</td>
<td>32.9 ± 14.4</td>
<td>35.5 ± 16.6</td>
<td>5.47</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>16.7</td>
<td>83.3</td>
<td>0.73</td>
<td>0.43</td>
</tr>
<tr>
<td>Ever hospitalized (%)</td>
<td>39.5</td>
<td>22.4</td>
<td>4.56</td>
<td>0.03</td>
</tr>
<tr>
<td>Substance abuse (%)</td>
<td>6.77</td>
<td>4.27</td>
<td>1.55</td>
<td>0.21</td>
</tr>
<tr>
<td>Ever hospitalized (%)</td>
<td>39.5</td>
<td>22.4</td>
<td>4.56</td>
<td>0.03</td>
</tr>
<tr>
<td>Substance abuse (%)</td>
<td>6.77</td>
<td>4.27</td>
<td>1.55</td>
<td>0.21</td>
</tr>
<tr>
<td>Initial HDRS-20†</td>
<td>19.7 ± 5.11</td>
<td>17.3 ± 5.13</td>
<td>43.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Older antidepressants (%)</td>
<td>66.2</td>
<td>71.0</td>
<td>0.17</td>
<td>0.68</td>
</tr>
<tr>
<td>Two antidepressants (%)</td>
<td>33.8</td>
<td>29.0</td>
<td>1.25</td>
<td>0.26</td>
</tr>
<tr>
<td>Antidepressant dose (mg/day)§</td>
<td>90.6 ± 58.2</td>
<td>75.0 ± 57.2</td>
<td>14.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mood stabilizer added (%)</td>
<td>44.4</td>
<td>25.2</td>
<td>20.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antipsychotic added (%)</td>
<td>25.6</td>
<td>24.7</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td>Any polytherapy (%)</td>
<td>72.2</td>
<td>59.6</td>
<td>7.40</td>
<td>0.006</td>
</tr>
<tr>
<td>Treatment (months)</td>
<td>3.5 ± 2.3</td>
<td>3.62 ± 2.64</td>
<td>0.42</td>
<td>0.51</td>
</tr>
<tr>
<td>HDRS-20 change (%)</td>
<td>55.9 ± 29.0</td>
<td>56.1 ± 32.6</td>
<td>0.01</td>
<td>0.93</td>
</tr>
</tbody>
</table>

†Required HDRS item-3 score of ≥2 at intake. Treatment (months) is time between initial and first follow-up HDRS rating after at least 1 month of antidepressant exposure.

‡For categorical comparisons (\( \chi^2 \)), df = 1; for continuous variables (\( F \)), df = 1; 787.

§Dose as imipramine equivalent mg/day for all antidepressants being taken.

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*Note:* Percentages may not add up to 100 due to rounding.

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**Statview** (SAS Institute, Cary, NC, USA) and **Statistica** (StataCorp, College Station, TX, USA).
overall; 26.2% type II, 32.1% type I) than among patients with MDD (13.2%; \( \chi^2 = 25.4, P < 0.0001 \)), whereas risk of questionable suicidal ideation (item-3 score 1) was nearly identical among patients with BPD (28.6% overall; 31.1% in type II, 24.7% in type II) and with MDD (28.8%). Observed rates at specific levels of initial suicidality (Table 2, Fig. 1) were as follows: 0 (non-suicidal: 54.5%); 1 (minimal suicidal ideation: feels life is not worth living: 28.6%); 2 (moderately severe ideation: wishes to be dead: 15.2%); 3 (severe ideation: planning for suicide: 0.76%); 4 (suicide attempt within 1 month: 0.89%). Of the 789 subjects, 227 (28.8%) were considered clinically to have been suicidal (prominent suicidal thinking, planning or attempt) at some time. This lifetime suicidal subgroup was 22.4 times more likely to have an initial suicidality rating of \( \geq 2 \) (and 3.2-fold less likely than never-suicidal patients to present with an initial item-3 score of zero).

Bivariate comparisons of initially definitely suicidal (item-3 score \( \geq 2 \)) vs. non-suicidal subjects indicated several differences in demographic and clinical factors (Table 1). Suicidal patients were more depressed at intake (higher 20-item HDRS score, with item-3 removed), more likely to be diagnosed with BPD than with MDD, ill for more years, younger at onset, more likely to receive a larger imipramine equivalent daily dose of antidepressant, and more likely to receive a mood stabilizer or any type of polytherapy (Table 1).

Multivariate logistic regression modeling for factors hypothesized to be associated with suicidality (BPD vs. MDD, greater depression severity, female sex, extremes of age) or identified in the preliminary bivariate comparisons found the following to be independently and significantly associated with being suicidal (item-3 score \( \geq 2 \)) at intake (in rank order): (i) BPD > MDD (OR 2.18, 95% CI: 1.33–3.58); (ii) use of a mood stabilizer (OR 1.67, CI: 1.03–2.71); and (iii) greater initial HDRS-20 depression severity score (OR 1.09 CI: 1.05–1.14). As expected, mood stabilizers were used less frequently in patients with MDD (14.3%) than in those with BPD (75.3%).

Changes in suicidal status with antidepressant treatment

The average HDRS item-3 (suicidality) score fell by 80.7% [from 0.65 ± 0.83 to 0.13 ± 0.40; paired \( t(df = 1; 788) = 17.9, P < 0.0001 \)]. Over the 30 years of observations, treatment-associated improvement in item-3 scores (%-change from intake) showed little change (\( r = +0.070, P = 0.18 \)), but improvement in HDRS-20 depression scores showed some gains (\( r = +0.147, P < 0.001 \)), suggesting that treatment may have more effective in recent years. At the second HDRS assessment, after an average of 3.6 ± 2.6 months
of antidepressant treatment, only 15/789 patients (1.90%) scored at ≥2 on suicidality item-3, a reduction of 8.8-fold from the initial rate of 16.9% of subjects (133/789) considered definitely suicidal [$\chi^2 (df = 1) = 43.5, P < 0.0001$; Table 1; Fig. 1]. During treatment, there were no suicide attempts among the 789 patients (vs. seven attempts at baseline), and only one case of planning suicide (compared with six at baseline; Table 2).

Among 133 initially definitely suicidal subjects, 96 (72.2%) became non-suicidal (item-3 score 0) during antidepressant treatment and another 25 had only questionable suicidal thinking (18.8%), indicating major improvements in a total of 121/133 (91.0%) subjects (Table 2). A minority of initially suicidal patients (initial item-3 score ≥2) remained unchanged during treatment (11/133, 8.27%), and only one (0.75%) worsened (Table 2). Of note, three of the 656 patients with initial item-3 scores of 0 or 1 became newly suicidal (all involving item-3 scores of 2), indicating a risk of treatment-associated, newly emerging suicidal thinking of only 0.457%, with no new suicide attempts.

Characteristics of patients who became non-suicidal with treatment

We characterized patients who shifted from being suicidal at baseline (item-3 ≥2; $n = 133$) to being non-suicidal (item-3 score 0) during antidepressant treatment ($n = 96$ ‘remitters’) with ‘non-remitters’ ($n = 40$), including three subjects who became newly suicidal (item-3 score increased from 0 to 2) during treatment, initially with bivariate comparisons of selected features. Remitters and non-remitters did not differ in age, duration of illness, history of hospitalization or substance abuse, or use and duration of psychotherapy (not shown), but remitters were 9.7% less severely depressed, had 13.5% higher initial item-3 suicidality scores and showed 2.6-fold greater improvement in total HDRS scores (minus item-3) during treatment of identical duration with similar daily antidepressant doses (Table 3). Although age was unrelated to becoming non-suicidal, the percentage decrease in item-3 scores ($r_s = +0.361, P < 0.001$), but not improvement in HDRS-20 depression severity ($r_s = +0.031, P = 0.38$), increased with age of the subject.

Multivariate logistic regression modeling also assessed the independence and significance of association with improvement in suicidality factors identified in initial bivariate comparisons, and to test $a$ priori hypotheses that improvement would vary little by sex, age, diagnosis, duration of illness or type of treatment. We found that only the initial HDRS-20 score (OR 1.06; 95% CI: 1.04–1.08; $\chi^2 = 33.4, P < 0.001$) and its percentage improvement during antidepressant treatment (OR 1.20; CI: 1.08–1.32; $\chi^2 = 11.8, P < 0.001$) were significantly and independently associated with remission of initial suicidality.

Finally, we compared changes in overall depression symptomatic ratings [HDRS total score with item-3 removed (HDRS-20)] with final suicidal status. Greatest improvements in depression severity were found: (i) among patients whose suicidality remitted (final item-3 score 0), followed (in rank order) by (ii) those who were and remained non-suicidal (item-3 = 0); (iii) subjects with initial or later questionable suicidal ideation (item-3 score 1); (iv) patients with improvement in suicidality scores (item-3 score reduced by ≥1) with (v) much less improvement in depression among those who remained suicidal or worsened; and (vi) worsening of depression among those who became newly

### Table 3. Factors associated with remission of HDRS item-3 suicidality ratings to zero during antidepressant treatment among 136 patients with major affective disorder with substantial suicidality ratings (22) at intake

<table>
<thead>
<tr>
<th>Factors</th>
<th>Remitted</th>
<th>Non-remitted</th>
<th>$\chi^2$ or $F$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>96 (67.7%)</td>
<td>40 (29.4%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Women (%)</td>
<td>67.7</td>
<td>72.5</td>
<td>0.30</td>
<td>0.58</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
<td>2.76</td>
<td>0.25</td>
</tr>
<tr>
<td>Recurrent MDD</td>
<td>56.2</td>
<td>70.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar II</td>
<td>24.0</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar I</td>
<td>19.8</td>
<td>17.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family psychiatric history (%)</td>
<td>51.0</td>
<td>45.0</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>Any substance abuse (%)</td>
<td>18.8</td>
<td>12.5</td>
<td>0.78</td>
<td>0.38</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>33.2 ± 13.9</td>
<td>33.6 ± 14.5</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Ever hospitalized (%)</td>
<td>37.9</td>
<td>44.4</td>
<td>0.12</td>
<td>0.73</td>
</tr>
<tr>
<td>Age at treatment (years)</td>
<td>45.0 ± 16.2</td>
<td>41.9 ± 12.9</td>
<td>1.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Total years ill</td>
<td>11.9 ± 12.5</td>
<td>8.81 ± 8.31</td>
<td>1.96</td>
<td>0.16</td>
</tr>
<tr>
<td>Initial HDRS-20§</td>
<td>19.5 ± 5.36</td>
<td>21.6 ± 5.82</td>
<td>4.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Initial HDRS item-3</td>
<td>2.18 ± 0.52</td>
<td>1.92 ± 0.66</td>
<td>5.62</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment type (%)</td>
<td></td>
<td></td>
<td>0.04</td>
<td>0.8</td>
</tr>
<tr>
<td>Older antidepressants</td>
<td>65.6</td>
<td>67.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modern antidepressants</td>
<td>34.4</td>
<td>32.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two antidepressants (%)§</td>
<td>24.9</td>
<td>25.0</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Antidepressant dose [mg/day]*</td>
<td>110 ± 68.7</td>
<td>122 ± 82.9</td>
<td>0.79</td>
<td>0.38</td>
</tr>
<tr>
<td>Mood stabilizer added (%)</td>
<td>46.9</td>
<td>37.5</td>
<td>1.01</td>
<td>0.32</td>
</tr>
<tr>
<td>Antipsychotic added (%)</td>
<td>28.1</td>
<td>22.5</td>
<td>0.46</td>
<td>0.50</td>
</tr>
<tr>
<td>Psychotherapy used (%)</td>
<td>55.5</td>
<td>44.4</td>
<td>2.62</td>
<td>0.11</td>
</tr>
<tr>
<td>Treatment (months)</td>
<td>3.5 ± 2.3</td>
<td>3.54 ± 2.26</td>
<td>0.32</td>
<td>0.57</td>
</tr>
<tr>
<td>HDRS-20 change (%)</td>
<td>66.5 ± 26.0</td>
<td>25.2 ± 33.6</td>
<td>66.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Remission involves subjects with initial HDRS item-3 scores ≥2 that decreased to zero during antidepressant treatment; non-remission includes similar initially suicidal patients who worsened, remained unchanged or improved only to a lower item-3 score during treatment. HDRS, Hamilton Depression Rating Scale.

*Includes three subjects who became newly suicidal during antidepressant treatment (risk: 3/656 = 0.453%).

§Two antidepressants used simultaneously.

†Total imipramine equivalent mg/day for all antidepressants taken.

| HDRS-20 change (%) | 66.5 ± 26.0 | 25.2 ± 33.6 | 66.2 | <0.0001 |
suicidal (Table 4). These findings indicate, not surprisingly, that changes in depression severity and suicidality ratings were closely associated.

**Discussion**

This naturalistic clinical study involved 789 patients with DSM-IV major affective disorders who were systematically evaluated and followed up with repeated HDRS depression and suicidality ratings backed by detailed clinical assessments. The study evaluated suicidality ratings under representative clinical conditions of treatment and observation. The main findings include a decrease in suicidality ratings at follow-up, and a novel estimate of minimum risk of newly emerging suicidality during antidepressant treatment in patients with MDD and in those with BPD.

The study has some noteworthy limitations. In addition to being naturalistic and involving multiple, uncontrolled treatments, it may involve some selection bias in that the study subjects were those who returned for follow-up and a second HDRS rating, and so may have been relatively motivated for treatment and adherent to it. It is also possible that some patients with newly emerging suicidality within the first weeks of treatment were overlooked. Ratings of suicidality were based on item-3 scores of the 21-item HDRS. This item (or item-10 of the Montgomery–Åsberg Depression Rating Scale), although used as an index of suicidality for similar research purposes (47–52), has not been validated for separate analysis from other scale items. However, the large number of patients, and the consistent clinical evaluation by the same observer to back up HDRS ratings should increase reliability of reported observations and their potential clinical relevance.

Definite suicidal ideation, planning or attempts (scores of 2–4) were found initially at a point prevalence of 16.8% of subjects, with more than twice the higher rates among patients with BPD vs. those with MDD (29.1%/13.2%), and little difference between subjects with type I (32.1%) and II (26.2%) BPD (Table 1). The high risk of suicidality among patients with types I and II BPD accords with previous findings (4, 53, 56).

In addition to BPD diagnosis, factors associated with initial definite suicidality (item-3 score ≥2; Table 1) included a higher initial 20-item HDRS depression rating (total score minus item-3), as expected, as well as younger age at onset and more total years of illness and a history of psychiatric hospitalization—all consistent with more severe affective illness. Additional support for an association of illness severity and suicidality in a depressive state is reflected in the greater likelihood of use of two or more psychotropic agents, and a higher mean total imipramine equivalent daily dose of antidepressant among suicidal patients (Table 1). Multivariate analysis confirmed that (in rank order) BP depression vs. MDD, use of a mood stabilizer and greater initial depression severity (20-item HDRS score) were independently associated with initial suicidality. Association of suicidality with severe or prolonged depression is well documented (7, 53, 57–65). The association of suicidality with ongoing use of mood stabilizers is evidently not entirely because of BPD diagnoses, but may reflect efforts to limit greater severity and recurrences of depression, and in part to limit agitation and aggression that can contribute to suicidal risk.

During treatment averaging 3.6 months, we found 8.8-fold overall reduction in the prevalence of suicidality scores initially ≥2. Only 1/133 (0.75%) initially suicidal (item-3 score ≥2) patients showed worsening of suicidality ratings during antidepressant treatment, and another 11 showed no improvement (8.3%); newly emerging suicidal thinking (second rating of item-3) occurred in three patients, and there were no new suicide attempts during treatment among all 789 subjects (Table 2; Fig. 1). It is important to acknowledge the possibility that transient early worsening of suicidality in the first days of treatment was overlooked between the start of antidepressant treatment and ratings ≥1 month later. Nevertheless, although repeat HDRS ratings were not made within the initial 4 weeks, all subjects were closely monitored clinically. Overall, mean item-3 scores decreased by an average of 81%. Such improvements are consistent with previous studies in adult major depression, including randomized, controlled trials, in which various antidepressant treatments were associated with greater decreases compared with
that in placebo (47–52). Although relationships between antidepressant treatment and suicidal risk in patients with BPD remain particularly uncertain (54), at least one large follow-up study including patients with BPD found that clinical treatment of various types was associated with reduced suicide risk and overall mortality (66).

In this study, there was no indication that several factors of interest were associated with remission of suicidality (item-3 shifting from ≥2 to 0), including age, years of illness, as well as type, dose and duration of antidepressant treatment, use of more than one psychotropic agent and use or duration of psychotherapy (Table 3). However, older current age was associated with greater percentage of improvement in suicidality ratings, although not in depression ratings. This age relationship accords with findings in controlled trials of less suicidality during treatment with an antidepressant vs. placebo with advancing age (41). Factors associated with becoming non-suicidal, and sustained in multivariate modeling, included a strong effect of greater improvement in 20-item HDRS depression severity. Moreover, changes in depression ratings and in suicidality scores were closely associated, including worsening of depression ratings selectively among the infrequent subjects of newly emerging suicidality (Table 4).

Such strong associations between changes in overall HDRS depression ratings (adjusted by deducting item-3) and in suicidality ratings suggest lack of independence of the observed improvement in item-3 scores from other rating scale items. That is, it remains unclear whether antidepressant treatment exerts a specific beneficial effect on suicidal thinking in depressed adults, or if such improvement is merely a reflection of overall clinical improvement in depression. It is important to note that suicidal behaviors rarely were involved during follow-up in the present subjects, when almost all of the item-3 scoring pertained to suicidal ideation and uncommon planning, but not suicidal acts. Indeed, evidence for a reduction in risk of suicidal behaviors (attempts and completions) with antidepressant treatment is limited (30, 32, 35), and there is more evidence of lack of such effects (26, 27, 29, 33, 34, 39, 41). By contrast, as already noted, such effects are strongly supported for long-term treatment with lithium in patients with major affective disorders (16–19), and are FDA approved for clozapine in patients with schizophrenia (67, 68).

Given the strong association of suicidal thinking and behavior with major mood disorders, especially in depressive or dysphoric-agitated phases (1, 4, 7), it is not surprising that such events may arise during treatment of acute depression, particularly before the beneficial effects of antidepressant treatment have fully evolved. Association of suicidal thinking, and less often, suicidal behaviors, with antidepressant treatment was described repeatedly (4, 57–59, 69, 70), and the risk was reported to be greater in some placebo-controlled trials of SRIs in juvenile depressive and anxiety disorders, and in depressed young adults (40, 41). The present findings provide a minimum estimate of risk of newly emerging suicidal ideation under representative clinical conditions involving a large number of observations over several months, and among patients with BPD as well as those with MDD. The observed rate was 0.46% during an average of 3.6 months of exposure to various types of antidepressants (1.5% per year). This rate may be lower than that in the general population (2), but should be considered a minimum estimate as some patients with newly emerging suicidality may have been overlooked or become lost to follow-up. Of considerable clinical importance, newly emerging suicidality appeared to be largely anticipated by association with worsening of depression (Table 3), as well as with worsening of insomnia, agitation and anger, for which treatments other than antidepressants (including mood stabilizers, antipsychotics, sedatives and additional emotional support) appear to be helpful (4, 62).

In conclusion, the present findings support expectations that suicidal thinking is highly prevalent among acutely depressed patients with a mood disorder, especially those with type II or I BPD, and that suicidal status is associated with indications of the severity of depressive illness. During treatment, suicidality ratings improved in most subjects, in close association with improvement in other symptoms of depression. These changes may well reflect overall clinical improvement rather than representing a specific therapeutic effect. We also found that newly emerging suicidal ideation as a potential adverse effect of antidepressant treatment was found at a rate below that reported in the general population, and there were no instances of new, treatment emergent suicide attempts or suicides.

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Disclosures and declaration of interests

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References

Suicidality during antidepressant treatment


