

# SUICIDAL BEHAVIOUR IN PATIENTS WITH MOOD DISORDERS

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## Abstract

The risk of suicidal behaviour in mood disorders is an inherent phenomenon and in patients with major mood disorders it strongly relates to the presence and severity of depressive episode. Suicidal behaviour in patients with mood disorders is state and severity dependent that means that suicidality markedly decreases or vanishes after clinical recovery. However, since the majority of mood disorder patients never commit and more than half of them never attempt suicide, special clinical characteristics of the illness as well as some personality, familial and psycho-social factors should also play a contributory role. Considering the clinically explorable suicide risk factors in patients with major mood disorders (family and/or personal history of suicidal behaviour, early onset of mood disorder, severe depressive episode/hopelessness, agitated/mixed depression, bipolar I or II diagnosis, rapid cycling course, comorbid Axis I and Axis II disorders, adverse life situations, lack of social and medical support, cyclothymic temperament, impulsive aggressive personality features, etc.), suicidal behaviour is predictable with a good chance. Successful acute and long-term pharmacotherapy markedly reduces the risk of attempted and completed suicide, even in this high-risk population. Supplementary psychosocial interventions (psychoeducation and targeted psychotherapies) further improve the results.

**Keywords:** Major depressive disorder, bipolar disorders, suicidal behaviour, suicide risk factors, pharmacotherapy, psychosocial interventions

## Introduction

Suicidality is one of the most alarming signs in psychiatry and it is the most hard end-point and most visible treatment outcome in patients with psychiatric disorders. Suicidal behaviour is very complex, multi-causal behaviour, involving several medical-biologic, psychosocial and cultural components, and history of untreated major mood disorders (particularly in the presence of previous suicide attempt) is the most important risk factor. However, because the majority of mood disorder patients never complete (and around 50% of them never attempt) suicide, other familial-genetic, personality, psychosocial and demographic risk factors should also play a significant contributory role<sup>1-4</sup>.

Psychological autopsy studies from different parts of the world consistently show that around 90% of consecutive suicide victims have one or more Axis I (mostly untreated) major psychiatric disorders at the time of their death, and major mood disorders (59-87%) schizophrenia/schizoaffective disorder (10-12%) and substance-use disorders (10-15%) are the most common principal diagnoses. Comorbid anxiety and personality disorders are also frequently present, but they are rare as principal (or only) diagnoses<sup>1-5</sup>. It has been estimated that 15-19% of severe (mostly hospitalized) patients with major depression would die by suicide<sup>6</sup>. In their meta-analysis of studies on suicide risk in psychiatric disorders,

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Harris and Barraclough<sup>7</sup> analysed separately the risk of suicide in unipolar major depression and in bipolar disorder. They found that the risk of suicide was about 20-fold for patients with index diagnosis of unipolar major depression, and the same figure for bipolar disorder was 15. However, these studies<sup>6,7</sup> cannot provide a precise estimation of separate suicide risk in unipolar and bipolar disorder, i.e. they overestimate the risk for unipolar depression and underestimate it for bipolar disorders. The main sources of these are that the index diagnosis frequently change during the long-term course from unipolar depression to bipolar I or bipolar II disorder<sup>8-11</sup> and in the studies (performed several decades ago) reviewed by the mentioned authors the diagnostic category of bipolar II depression (depression with hypomania but without mania) which is quite common form of bipolar disorders<sup>9,12</sup> has not been considered separately and it is very likely that the majority of bipolar II patients in these studies were included in the unipolar major depressive subgroup. Indeed, a recent long-term follow-up study showed that the rate of completed suicide was about double in bipolar disorder (types I and II combined) than in unipolar depression<sup>13</sup>. Another three recent population based epidemiological studies also found a substantially higher rate of suicide attempts in bipolar (types I and II combined) than in unipolar major depressive disorder patients<sup>14-16</sup>.

## Risk of suicidal behavior in patients with unipolar major depression or bipolar disorders

### Completed suicide

The different suicide risk in the three main subgroups of major mood disorders has been first reported by Dunner et al.<sup>17</sup> who found that 3% of the 73 unipolar, 6% of the 68 bipolar I and 18% of the 22 bipolar II patients died by suicide during their 1-9 year follow-up study. In contrast to this, in a 40 to 44 years' prospective follow-up study of 406 formerly hospitalised (186 unipolar and 220 bipolar) major mood disorder patients, in which the unipolar-bipolar conversion was carefully considered during the follow-up, Angst et al.<sup>18</sup> found that 14.5% of unipolar and 8.2% of bipolar (I + II) patients completed suicide; the SMRs for suicide in unipolar and bipolar patients were 26 and 12, respectively.

In their recent long-term prospective follow up study (average 11 years) on 1983 unipolar major depressives and 843 bipolar (I + II) patients, Tondo et al.<sup>19</sup> found five-times fold higher rate of completed suicide in bipolar I and II than in unipolar patients (0.25% of

patients/year vs. 0.05% of patients/year). This study also found that the ratio of attempted to completed suicide in bipolar II, bipolar I and unipolar depression was 5, 11, and 10, respectively, showing that the lethality of suicide attempts was far highest in bipolar II patients. The higher risk of suicide of bipolar II than bipolar I and unipolar patients has been also supported by the study of Sani et al.<sup>16</sup>. During this long-term (up to 35 years) follow-up study on 4441 formerly hospitalized psychiatric patients it has been also found that bipolar II patients had the highest risk for suicide; 2.8% of 1163 bipolar I and 4.2% of 602 bipolar II patients completed suicide while the same rate of 1142 unipolar major depressive patients was 1.9%<sup>13</sup>. Similarly, in the STEP-BD study (4360, mostly pharmacologically treated bipolar patients; mean follow-up period was 16 months) the rate of completed suicide was more than two-fold higher in bipolar II (0.34%) than in bipolar I patients (0.14%)<sup>20</sup>. Investigating the risk of completed suicide in a total Danish national cohort of patients with first psychiatric discharge (n = 176.347) Nordentoft et al.<sup>21</sup> found that the lifetime risk for suicide in bipolar disorders were 7.8% for males and 4.8% for females, while the same figures for patients with unipolar depression were 6.7% and 3.8%, respectively.

Two psychological autopsy studies where the prevalence of bipolar II, bipolar I and unipolar depression have been analysed separately show that among the 125 consecutive suicide victims with primary major depression at the time of suicide 44% had bipolar II depression, 2% had bipolar I depression and 54% had first episode or recurrent unipolar depression<sup>22,23</sup>. Because the lifetime prevalence rates of DSM-III/IV-defined bipolar illness in the population are relatively low compared with unipolar major depression (2-5% and 15-17%, respectively)<sup>24-26</sup>, these results – in agreement with other findings<sup>13,20</sup> – also suggest that among different subgroups of major mood disorders the bipolar – particularly bipolar II – types carry the highest risk of completed suicide.

### Suicide attempts

Up to fifty percent of patients with major mood disorders have at least one suicide attempt during their lifetime<sup>2,4,15</sup>. Considering only the ten studies, in which unipolar, bipolar I and bipolar II patients were analysed separately, the rate of previous suicide attempts is the lowest in unipolar major depression (13 %) highest in bipolar II patients (33%), and intermediate in bipolar I patients (28%)<sup>2</sup>. Re-analysing the ECA database, Judd and Akiskal<sup>27</sup> also reported that the rate of prior suicide attempt(s) was higher in bipolar II (34%) than

in bipolar I (24%) patients, while the same figure for unipolar major depression was only 16%<sup>28</sup>. Similarly, a study from Norway on 201 major mood disorder patients found that the lifetime history of suicide attempts in bipolar II, bipolar I and unipolar depressives were 61%, 50%, and 30%, respectively<sup>29</sup>.

A German ten-year prospective longitudinal study showed that 32% of 33 bipolar II, 17% of 65 bipolar I and 6% of 286 pure unipolar major depressive patients attempted suicide during the follow-up<sup>14</sup>. In the Finnish Jorvi Bipolar Study 16% of the 90 bipolar I and 25% of the 101 bipolar II patients have reported at least one prior suicide attempt at the index episode<sup>30</sup>. Similar findings were reported from South-Korea; 17% of the 71 bipolar I and 36% of the 34 bipolar II patients reported the history of suicide attempt<sup>31</sup>. Looking at the different diagnostic subtypes of consecutive suicide attempters with current DSM-IV major depressive episode, it has been also found that bipolar, and particularly bipolar II patients were relatively overrepresented among them both in Budapest, Hungary and in Rome, Italy<sup>32 33</sup>.

The long-term prospective study by Tondo et al.<sup>19</sup> found that the annual rate of suicide attempts during the follow-up was more than double in bipolar (I + II) than in unipolar patients and it was higher in bipolar I (1.52%), than in bipolar II (0.82%) and in unipolar (0.48%) depression. In a most recent population-based study on 935 bipolar I and 494 bipolar II patients Bega et al.<sup>34</sup> reported that lifetime suicide attempts were more common in bipolar I patients: 29% of bipolar I and 15% of bipolar II patients reported past suicide attempt. Similarly, in the STEP-BD study 4,6% of bipolar I and 3% of bipolar II patients have made suicide attempt during the 18 month follow-up<sup>20</sup>.

### ***The role of mixed (bipolar) depression in suicidal behaviour***

The majority of the studies shows that officially diagnosed DSM-IV bipolar disorders carry much higher risk of suicidal behaviour than unipolar major depressive disorder indicating that the bipolar component of major mood disorders could be one of the responsible factors. Therefore it is not surprising that subthreshold intradepressive (hypo)manic symptoms during DSM-IV unipolar major depressive disorder (mixed depression) also increase the risk of suicidal behaviour. It is important to note that mixed depressive episode (depression plus 3 or more co-occurring intradepressive hypomanic symptoms) and agitated depression are greatly overlapping conditions<sup>35 36</sup>. Analysing the NCS-Replication database Angst et

al.<sup>15</sup> also reported that the history of lifetime suicide attempts was the highest in bipolar I (66%), lower in bipolar II disorder (50%) and lowest in unipolar major depression without subthreshold bipolarity (30%). However, in patients with unipolar major depression with lifetime or current (intradepressive) subthreshold (hypo)manic symptoms, the rate of patients with prior suicide attempt was intermediate between pure unipolar major depression and bipolar II disorder (41%). Similar findings have been reported by Jabben et al.<sup>37</sup>: the lifetime history of suicide attempts in bipolar I, bipolar II and unipolar depression were 37%, 21%, and 18%, respectively, but the same rate in unipolar major depressives with subthreshold hypomanic symptoms was 38%. The importance of subthreshold bipolarity in patients with major depressive episode in suicidal behaviour is further underscored by the findings that those bipolar I or II depressives with some clinically significant intradepressive (hypo)manic symptoms showed significantly more suicide attempts at the index episode and during the long-term follow-up (54% and 58%, respectively) than those with no clinically significant (hypo)manic symptoms (32% and 35%, respectively)<sup>38</sup>. Investigating 87 young adults with DSM-IV diagnosed major depressive episode it was also found that 36% of bipolar depressives (types I and II combined) and 15% of pure unipolar depressives have made at least one prior suicide attempt, and the same rate in unipolar depressive patients with subthreshold (hypo)manic symptoms was 25%<sup>39</sup>. The elevated risk of suicidality in bipolar and bipolar spectrum patients could be the result of a complex interaction of several clinical factors, as threshold and subthreshold bipolar patients are most often mixed/agitated, show frequently rapid cycling course, predominant depressive polarity and they show a higher rate of anxiety and substance-use comorbidity.

## **Clinically detectable suicide risk factors in patients with major mood disorders**

### ***Specific clinical and personality characteristics***

Major mood disorder patients with early onset of the illness, hopelessness, insomnia as well as with comorbid anxiety, substance-use and personality disorders are also at an increased risk of attempted or completed suicide<sup>2-4 28 32 40-43</sup>. Beside the highest lethality of suicide attempts<sup>13 19</sup>, the major causes of the highest suicide risk in bipolar patients may be the high rate of comorbid anxiety disorders<sup>42 44</sup>, substance-use disorders<sup>4 45</sup> and depressive mixed states/agitated depression<sup>9 13 36 38 46-48</sup>.

Impulsivity as a personality trait increase suicide risk when combined with depression and even modest manic symptoms during bipolar depressive episodes are associated with greater level of impulsivity and higher rate of suicide attempts<sup>49-51</sup>. Current findings also show that in contrast to hyperthymic temperament cyclothymic/irritable/depressive affective temperaments, that are characteristic also for bipolar (mainly for bipolar II) disorder also increase the risk of suicidal behaviour in patients with bipolar and unipolar major depressive episode<sup>52-54</sup>.

### **Personal and family history of suicide**

Family history of suicide among first and second degree relatives<sup>17 55 56</sup> and past suicide attempt(s)<sup>2 3-5 57</sup> have been also shown as powerful risk factors for attempted or completed suicide, particularly during major depressive, mixed depressive or dysphoric manic episodes. Bipolar and unipolar patients with family history of suicidal behavior and exposed to childhood physical and/or sexual abuse are at greater risk for suicide attempts<sup>51 57</sup>. Impulsivity seems to be the link between childhood abuse and suicidal behavior particularly in the case of major depressive episode<sup>58</sup>. A study on 211 patients suffering from recurrent unipolar major depression or bipolar (I-II) disorder, hospitalized after suicide attempt, it was found that family history of suicide was significantly associated with the diagnosis of bipolar disorder and looking for the features associated with serious suicide attempt, bipolar disorder was the only associated diagnosis<sup>59</sup>.

### **Adverse life events**

Adverse life events play important role in suicidal process as predisposing (childhood events, including physical and sexual abuse) and precipitating (adulthood events) factors<sup>51</sup>. Although negative life events do not lead inevitably to suicidal behavior in healthy persons or even in the high-risk groups such as psychiatric (particularly mood disorder) patients, but they may actually trigger the suicidal process<sup>1 60 61</sup>. Over 40 percent of patients with bipolar disorder report a history of childhood physical and/or sexual abuse and depressed patients with such a history have earlier age of onset of bipolar illness, greater psychiatric comorbidity and increased rates of suicide attempts<sup>43 57</sup>. About half of all completed suicides in both bipolar I and unipolar mood disorders are associated with recent negative life events, but the stressors are commonly dependent on the victims's own behaviour, particularly in the case of bipolar I disorder<sup>60</sup>. Hypomanic and particularly manic episodes can easily lead to ag-

gressive-impulsive behavior, financial extravagance, or episodic promiscuity, thus generating several interpersonal conflicts, marital breakdown and new negative life events, all of which have a negative impact on the further course of the illness which may ultimately trigger suicidal behavior. Permanent adverse life situations (e.g., unemployment, social isolation) as well as acute psychosocial stressors (e.g., loss events, financial breakdowns) in adult patients with unipolar or bipolar disorders are useful indicators of suicidality in the clinical practice, primarily if other risk factors are also present<sup>60-63</sup>. In the majority of cases more than one suicide risk factor are present simultaneously and their effect is cumulative: the higher is the number of risk factors the higher is the suicide risk<sup>2-4 64</sup>. More than one-third of suicide victims have made at least one prior suicide attempt which indicates that the majority of suicide victims die by their first attempt<sup>1 3</sup> and since most of them have a (mainly untreated) current major depressive episode, it is very important to detect suicide risk as early as possible, particularly in depressed patients, and intervene even prior to the subject making his/her first suicide act.

### **Suicide protective factors in major mood disorder**

In contrast to numerous suicide risk factors, only a few circumstances are known to have a protective effect. Good family and social support, pregnancy and postpartum period, having a great number of children, holding strong religious beliefs, and restricting lethal suicide methods (e.g., to reduce domestic and car exhaust gas toxicity and to introduce stricter laws on gun control) whenever possible, seem to have some protective effect<sup>65-67</sup>. Recent studies have found that hyperthymic temperament may be also a protective factor<sup>52 53 68 69</sup>. However, one of the most extensively studied and changeable suicide protective factor in major mood disorders is the acute and long-term pharmacological treatment<sup>4 18 43 70 71</sup>.

### **Medical contact before suicidal events**

Despite of the fact that up to 66% of suicide victims contact different levels of health care (mostly GPs and psychiatrists) during the 4-week period before their suicide, the rate of adequate pharmacotherapy among depressed suicide victims is disturbingly low<sup>1 22 72 73</sup>. While the current prevalence of DSM-III/DSM-IV or ICD-10 major depression in the primary care practice is around 8-10%, the majority of depressed patients

are not recognised by their GPs. Moreover, the rate of adequate antidepressant pharmacotherapy among diagnosed depressives was less than 20%. However, studies performed 5-10 years later, reported much higher rates of recognition and treatment of depression in primary care practice (62-85%) and 33-50% of them were treated with antidepressants<sup>69 74</sup>.

Since successful acute and long-term pharmacotherapy of mood disorders relieves not only the clinical symptoms, but parallel with this also decreases or vanishes suicidality, the appropriate treatment of mood disorders is a key issue in suicide prevention<sup>3 4 23 43 69 71 72 75 76</sup>.

Table I shows the clinically most important suicide risk factors in patients with major mood disorders.

### The role of underlying bipolarity in antidepressant-resistance and antidepressant-associated suicidal behaviour

One of the most common sources of antidepressant-resistance is the unrecognized bipolar nature of the “unipolar” major depressive episode<sup>71 77-79</sup>. Unrecog-

**Table I.** Clinically detectable suicide risk factors in patients with mood disorders.

• Diagnostic subtype: Bipolar II = Bipolar I > Unipolar
• Early onset of the illness (< 25 years)
• Previous/current suicidal ideation
• Previous suicide attempt
• Current clinical features: <ul style="list-style-type: none"> <li>- Severe depression, hopelessness, insomnia, guilt;</li> <li>- Mixed depressive episode/agitated depression;</li> <li>- Dysphoric (mixed) mania or hypomania;</li> <li>- Mixed affective episode;</li> <li>- Rapid cycling course;</li> <li>- First episode depression, predominantly depressive polarity;</li> <li>- Comorbid anxiety/anxiety disorders, substance-use and personality disorders;</li> <li>- Cyclothymic/irritable/depressive affective temperaments;</li> <li>- Impulsive/aggressive personality features</li> </ul>
• Family history of suicide in first- and second degree relatives
• History of childhood physical and/or sexual abuse
• Permanent adverse life situations, acute psychosocial stressors
• Lacking adequate acute and/or long-term treatment/care
• Noncompliance with the acute and/or long-term treatment

nized bipolar depressives (mainly bipolar II depressives in the daily clinical practice) and mixed “unipolar” depressed patients with intradepressive (hypo) manic symptoms in the randomized controlled trials on unipolar major depression are considered as “unipolar” major depressives that means that these patients receive antidepressants and co-administered anxiolytics but not mood stabilizers<sup>14 15</sup>. This can result in a high rate of treatment resistance, which is about two-times higher in patient groups mentioned above compared to patients with true unipolar major depression. In open clinical studies the frequency of antidepressant-resistance ranges from 41-65% in bipolar (types I and II combined) depression and between 18-27% in unipolar depression<sup>71 77 78</sup>. Another study have shown that 80% of AD-resistant “unipolar” depressives have threshold or subthreshold bipolar disorder<sup>80</sup>. In addition, it has been found that the rate of the bipolar spectrum disorder among the 212 DSM-IV defined antidepressant responsive unipolar major depressive disorder inpatients was 3.8% but the same figure in 68 antidepressant-resistant inpatients was 47.1% indicating that the underlying bipolar diathesis was important contributor to antidepressant nonresponse. Similarly, a significantly higher rate of antidepressant nonresponse in „pre-bipolar” major depressives than in pure major depressives have been also reported by Li et al.<sup>79</sup>.

Moreover, antidepressant monotherapy – without the coadministration of mood stabilizers or atypical antipsychotics – in bipolar and bipolar spectrum depressive subjects can worsen the cross-sectional picture of depression (particularly in adolescents and young adults) not only by causing (hypo)manic switch, but also via inducing or aggravating depressive mixed state/agitation, that is the major substrate of suicidal behaviour<sup>9 47 70 71 78 81</sup>. The retrospective chart-review of 17 patients with “pre-bipolar” major depression (i.e., patients who become bipolar I and II during the follow-up) and of another 17 patients with pure unipolar depression showed that family history of completed suicide and bipolar disorder, early onset of major depressive episode as well as treatment-emergent mixed depression, mood lability, psychomotor activation, suicidality and non-response to antidepressant monotherapy were significantly more common in “pre-bipolar” than in pure unipolar depressives<sup>78</sup>. Initial antidepressant monotherapy of patients subsequently diagnosed as bipolar disorder may result in higher switch rate and more frequent suicidal behaviour<sup>81</sup>.

However, recent results show that a significant part (30-40%) of DSM-IV diagnosed unipolar major de-

pressive disorder patients have clinically significant lifetime or current subthreshold (hypo)manic symptoms (mixed depression), as well as other basic clinical features (family history of bipolar disorder, early onset, bipolar conversion, etc.) that are characteristic and external validators for bipolar disorder<sup>14 15 35 82</sup>. This means that more than one-third of DSM-IV diagnosed unipolar depressives are in fact subthreshold bipolar depressives and beside the antidepressant resistance primarily these patients are the subjects of bipolar conversion<sup>14 82</sup>. The slightly elevated (but in absolute sense quite low) risk of suicidal behaviour among patients taking antidepressants compared to those taking placebo in randomised controlled antidepressant trials on DSM-IV diagnosed unipolar major depressive disorder might be the consequence of the depression-worsening potential of antidepressant monotherapy in subthreshold and mixed bipolar depressed patients who were included into these trials falsely diagnosed as suffering from unipolar depression<sup>70 71 76</sup>. Antidepressants can worsen depression but it is not the case for placebo and worsening of depression is the “final cause” of suicidal behaviour even in drug-free patients. In other words, when antidepressants worsen depression in a few patients, its psychopathological substrate might well reside in an agitated, excited, mentally overstimulated, anxious (bipolar) depressive mixed state<sup>9 70 71</sup>.

Successful acute and long-term treatment of unipolar major depression and bipolar disorders markedly reduces the suicide morbidity and mortality even in this high-risk population but – as mentioned above – antidepressants can worsen depression and can lead to suicidal behavior in a small vulnerable subpopulation<sup>18 43 70 76</sup>. However, in the everyday clinical practice, the suicide preventive effect of antidepressants highly overshadows this unwanted iatrogeny. As the consequence of the FDA Black Box Warning (BBW) in 2004, the recently decreased use of antidepressants in children and adolescents seen in some countries has been accompanied by a concurrent increase in suicide rates in that age-groups while in middle-aged and old persons, where the utiliza-

tion of antidepressants increased continuously the suicide rates decreased. These findings provided further support that the BBW, contrary to its intention, resulted in the increasing number of untreated young depressives and – ultimately – the markedly increased suicide mortality of this age group. This increase occurred among young persons without antidepressant treatment<sup>83 84</sup>. The formal recognition of depressive mixed states in our official diagnostic system (a mixed features specifier across all mood syndromes in the DSM-V) will help to mark out those pseudo-unipolar mixed depressives for whom mood stabilizer and/or atypical antipsychotic is the appropriate treatment (at the same time antidepressant monotherapy is contraindicated for these patients).

## Suicide prevention in mood disorders – Pharmacological and psychosocial treatments

As suicidal behavior in unipolar and bipolar patients occur mostly during severe pure or mixed depressive episodes and less frequently in the frame of dysphoric (mixed) mania, but practically never during euphoric mania and euthymia<sup>2 3 43 47</sup>, it is not surprising that effective acute and long-term treatment of mood disorders have a strong protective effect against suicidal behaviour<sup>18 76</sup> and probably against other complications such as secondary substance-use disorders, marital instability, loss of job, cardiovascular morbidity/mortality, violent behaviour, etc.

Recently, effective psychosocial interventions in the field of mood disorders were developed primarily for patients who show insufficient response to acute and long-term pharmacotherapy, who cannot tolerate drugs or who are noncompliant with the treatment<sup>85 86</sup>. The interaction between pharmacotherapy and psychosocial interventions is quite complex as successful episode-preventive medication counteracts dysfunctional cognitions (including low self-esteem) and adjunctive cognitive therapy helps to optimize the long-term course<sup>87</sup>.

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