

# Suicide Risk in Patients With Major Depressive Disorder

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Understanding the origins of suicide is the first step in preventing it. Review of the current literature has revealed only limited data from general practice and community samples; most research has been performed on inpatient psychiatric populations, and extended follow-ups are rare. Mood disorders were found to be highly associated with suicide, especially in patients with major depressive disorder. Depression is an important factor in suicides of adolescents and the elderly, but those with late-onset depression are at higher risk. Both comorbidity with other disorders, such as anxiety and agitation, and rapid changes in the depressive state, for instance after release from the hospital, increase the risk for suicide. *(J Clin Psychiatry 1999;60[suppl 2]:57-62)*

The reviews of Guze and Robins<sup>1</sup> and of Goodwin and Jamison<sup>2</sup> summarizing a large number of follow-up studies of patients with major depressive disorders (MDD) came to the well-known conclusion that between 12% and 19%, or on average about 15%, of the patients died by suicide. It was also concluded "that early in the course of the illness, before other causes of death come fully into play, the relative risk of suicide increases."<sup>1</sup> An elevated suicide risk at the early stage of the illness was also suggested by the studies carried out in Iowa<sup>3,4</sup> and in St. Louis, Missouri.<sup>5</sup> A high rate of suicide among major depressive patients was observed shortly after discharge from hospital, when the episode was still ongoing. Fawcett et al.,<sup>6</sup> in the NIMH Collaborative Programme of Psychobiology of Depression, found 25 suicides in a mean of 4 years of follow-up of 921 patients, 32% of which had occurred within the first 6 months and 62% within the first 12 months after discharge. Roy<sup>7</sup> found that 65% of suicides occurred within 6 months of discharge from hospital. Of course, such figures depend on the length of follow-up. It is plausible that the suicide risk increases during the waxing and waning periods in the rapid-cycling state.

But we have to remember that Guze and Robins<sup>1</sup> were not uncritical and stressed the following: "in none of the cited investigations were the necessary data presented that

would permit an estimate of the risk of suicide as a function of time since onset of illness, corrected for the age of onset of the illness. And if such data are available, it is difficult to evaluate the significance of an increased relative risk of suicide, particularly since 'early in the course of illness' is defined as 'before many patients in a sample have died.'"

In 1997, Blair-West et al.<sup>8</sup> challenged the 15% lifetime suicide risk of major depressive patients. On the basis of the suicide risks of total populations and prevalence rates of major depression in the community, they concluded that a 15% suicide risk would far exceed the observed suicide rates in the population. Blair-West and colleagues<sup>8</sup> stressed that studies based on hospitalized major depressive patients cannot be representative for studies of the suicide risk of all depressives, as suicidality is one of the primary indications for admission. They say: "A serious bias has occurred wherein the variable being studied (suicidality) actually selected out those with the highest risk of suicide for inclusion in the studies! We see this sampling bias as the greatest contributor to the spuriously high reported risk of suicide in MDD." As a consequence, they criticize the studies reviewed by Guze and Robins,<sup>1</sup> as well as by Goodwin and Jamison,<sup>2</sup> for failing to separate the critical dyadic groupings into inpatients and outpatients, most severe and least severe cases of MDD, primary and secondary depression, and bipolar and unipolar depression.

## METHODOLOGICAL CONSIDERATIONS

There is no doubt that the definitions of major depressive disorder given by DSM and ICD embrace a large spectrum of depressive states varying considerably in severity and length. Only a minority of these patients are hospitalized. Therefore, studies of hospitalized patients cannot be representative of the total population of major

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**Table 1. Standardized Mortality Ratio (SMR)**

Study	Sample <sup>a</sup>	Diagnoses	Years of Observation	SMR		Total M + F	
				Males	Females	SMR	N
Eastwood et al, 1982 <sup>9</sup>	4	Affective disorders	9.5	1.14	1.55	1.37	585
Murphy et al, 1987 <sup>10</sup>	1	Affective disorders	16	2.10	1.20	1.50	1003
Angst et al, 1998 <sup>11,12</sup>	4	Unipolar or bipolar	34–38	1.64	1.59	1.61	406
Weeke, 1979 <sup>13</sup>	4	Unipolar or bipolar	1–8	1.95	1.55	1.69	8136
Weeke and Vaeth, 1986 <sup>14</sup>	4	Unipolar or bipolar	5–7	2.17	1.45	1.73	2168
Lee and Murray, 1988 <sup>15</sup>	4	Depression	22	...	...	1.90	89
Zheng et al, 1997 <sup>16</sup>	1	Depression	2.5	3.10	1.70	2.49	1499
Schwalb and Schwalb, 1987 <sup>17</sup>	4	All psychiatric disorders	10	1.30	1.44	1.36	1239
Murphy et al, 1989 <sup>18</sup>	2	All psychiatric disorders	16	1.54	1.65	1.59	142
Rörsman, 1974 <sup>19</sup>	3 + 4	All psychiatric disorders	6	1.79	1.43	1.60	3623
Martin et al, 1985 <sup>20</sup>	3	All psychiatric disorders	6–12	2.18	1.90	2.01	331

<sup>a</sup>Samples (1) community sample, (2) general practice patients, (3) psychiatric outpatients (4) psychiatric inpatients.

**Table 2. Meta-Analysis of Suicide Risk in Affective Disorder\***

Diagnosis	Standardized Mortality Ratio	95% Confidence Interval	Number of Studies	Number of Suicides
Bipolar disorder	15.05	12.25 to 18.44	23	93
Major depressive disorder/ major depressive episode	20.35	18.27 to 22.59	14	351
Dysthymia	12.12	11.50 to 12.77	9	1436
Mood disorders not otherwise specified	16.10	14.52 to 17.81	12	377
Total <sup>a</sup>	13.65	13.08 to 14.21	58	2257

<sup>a</sup>Computed by Felix Angst.  
\*Adapted from reference 22, with permission.

depressive patients. When reviewing studies on mortality of these patients, we have to distinguish between studies based on psychiatric inpatient or outpatient samples, studies of general practice samples and, finally, studies of community samples. Furthermore, we have to distinguish between retrospective studies (to which all psychological autopsy studies have to be allocated) and between prospective or follow-up studies, where the length of the follow-up is an important variable. Finally, there are record linkage studies of total populations covering large geographic areas, which link, for instance, records of hospital admissions with mortality data.

**Mortality**

Table 1 summarizes data on mortality of patients with affective disorders by means of standardized mortality ratios (SMR) of 11 studies (including our own).<sup>9–20</sup> They all confirm an elevation of the mortality to a varying extent between a factor of 1.36 to 2.49 compared to the general population. Most studies give an SMR ranging from 1.5 to 2.0. These findings are stable across community, general practice, and psychiatric inpatient and outpatient samples. In addition, there is some trend toward a higher SMR among males than females, especially in the community study of Zheng et al.<sup>16</sup> and Murphy et al.<sup>10</sup> Table 1 demonstrates that the studies reported vary considerably in length. The longest follow-up study—over 34 to 38 years—is our own and is based on a hospitalized sample.

We found no difference in overall mortality by gender in patients suffering from major depression or bipolar disorder.

The specific standardized mortality ratio for suicide among depressive patients varies within a wide range: from 8<sup>3,19,21</sup> to 35. Black et al.<sup>4</sup> found a lower specific suicide SMR of 3.3 for bipolar disorder than for depression, which had an SMR of 9.5. A superb meta-analysis of the suicide risk of affective disorders was recently published by Harris and Barraclough.<sup>22</sup> Surprisingly,

they came to the conclusion that the specific suicide SMR for bipolar disorder was lower (15 based on 23 studies) than that for a mixed group with major depressive episodes and major depressive disorders: 14 studies gave an SMR of 20.35 (Table 2). Dysthymia was definitely lower with 12.12. By using the data of Harris and Barraclough,<sup>22</sup> we computed a total SMR of 13.65 for all 58 studies, which represented a total of 2257 suicides. The authors could not give the SMR separately by gender. Weeke and Vaeth<sup>14</sup> found an SMR for suicide of 22.2 for males and 12.5 for females, whereas we found the opposite 21.87 (95% confidence interval [CI] = 14.64 to 31.40) for females and 12.59 (95% CI = 6.88 to 21.12) for males.

Apart from suicide, there is evidence for an increased mortality by cardiovascular disorders.<sup>14,23–25</sup> Ahrens et al.<sup>25</sup> reported a reduction of this modality by long-term treatment with lithium. Other causes of elevated mortality are respiratory disorders, pneumonia, bronchitis, asthma/hay fever, hyperthyroidism, hypothyroidism, and head injuries.<sup>23</sup>

**Psychological Autopsy Studies**

An important source of information are psychological autopsy studies of representative samples of suicides. Some of them are listed in Table 3. After the classical studies of Barraclough et al.,<sup>27</sup> which came up with a very high rate of 86% depressed subjects among all suicides, many other studies were carried out, but they indicate lower

Table 3. Suicides: Autopsy Studies

Study	N	Country	Groups	% Depressed	Diagnosis
Dorpat and Ripley, 1960 <sup>26</sup>	114	United States		18	Psychotic depression
				12	Other depression
Barracough et al, 1974 <sup>27</sup>	100	United Kingdom		86	Depression
Rich et al, 1986 <sup>28</sup>	204	United States	< 30 y	9	Major depressive disorder
			> 30 y	29	Major depressive disorder
			< 30 y	47	Affective disorder
			> 30 y	82	Affective disorder
Rich et al, 1988 <sup>29</sup>	204	United States	Males	7	Major depressive disorder
			Females	17	Major depressive disorder
Arato et al, 1988 <sup>30</sup>	217	Hungary		24	Unipolar depression (RDC)
				22	Bipolar depression
Asgard, 1990 <sup>31</sup>	104	Sweden	Females	35	Major depressive disorder (RDC)
				24	Other depression
Marttunen et al, 1991 <sup>32</sup>	53	Finland	Adolescents	51	Depression (comorbid)
Brent et al, 1993 <sup>21</sup>	67	United States	Adolescents	51	Major depressive disorder
Henriksson et al, 1993 <sup>33</sup>	229	Finland		31	Major depressive disorder (comorbid)

rates of depressed subjects. Among adolescents studied in Finland<sup>32</sup> and in the United States,<sup>21</sup> 50% of suicides could be explained by depression. According to the Finnish study, comorbidity was an additional risk factor. Several other studies published over the past decade found that only about a fifth to a third of suicides in the general population could be explained by major depressive disorders. The largest study, published by Henriksson et al.<sup>33</sup> from Finland, found a 31% rate of major depression in 229 subjects (again, many of them were comorbid). A Hungarian study by Arato et al.<sup>30</sup> found that 24% of the 217 suicides had major depression, and the American study by Rich et al.<sup>29</sup> of 204 subjects identified 7% of the male suicides and 17% of the female suicides as patients with major depressive disorder. The study by Rich et al.<sup>28</sup> also indicated that the proportion of major depressive patients might be higher among subjects committing suicide after age 30, a finding that is difficult to explain in view of the studies of adolescent samples. On the whole, the modern studies seem to be compatible with one of the first studies of Dorpat and Ripley,<sup>26</sup> which identified 25% of all suicides as a consequence of some kind of depression, half of which was psychotic depression. In summary, there are sound data supporting the assumption that about 20% to 35% of suicides are a consequence of major depressive disorders.<sup>34</sup>

#### FOLLOW-UP STUDIES ON THE SUICIDE RISK OF HOSPITALIZED PATIENTS WITH MAJOR DEPRESSION

Little can be added in this respect to the excellent reviews of Guze and Robins<sup>1</sup> and Goodwin and Jamison.<sup>2</sup>

One of the largest and longest follow-up studies is the Iowa 500 study.<sup>35</sup> In a 30- to 40-year follow-up of 182 depressive patients, 10.6% had died by suicide.<sup>35</sup> In a smaller, 7-year study of 50 patients, Bronisch et al.<sup>36</sup> found a rate of 12% suicides among patients with RDC major de-

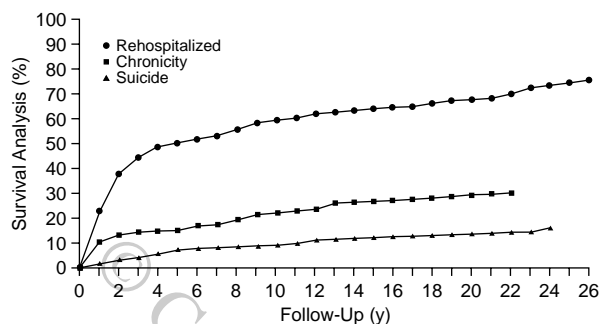
pression. Two studies, from the United Kingdom<sup>15</sup> and Australia,<sup>37</sup> suggested suicide rates of 4% and 7% over observation periods of 18 and 15 years, respectively. It is obvious that the rate is dependent on the length of follow-up, and for this reason only long-term follow-up studies are conclusive. The impact of treatment was not taken into account in these studies.

#### The Zurich Follow-Up Study of 406 Hospitalized Patients With Mood Disorders

Our own study, initiated between 1959 and 1963, comprised all 406 hospitalized admissions over 5 years with a diagnosis of unipolar depression (N = 186) or bipolar disorder (N = 220). Over lifetime, 61% of these had at some time been psychotic. They were followed up every 5 years until 1985. In 1991, mortality data were gathered, and by that time, 64.0% (unipolar = 68.8%, bipolar = 60.0%) of the sample had died. Currently, we are updating the mortality data: 75.7% (unipolar = 79.0%, bipolar = 71.8%) of the sample is dead, and the overall SMR of 1.61 (Table 1), with a specific suicide SMR of 17.63, is based on these new data. The SMR for unipolar depression was definitely higher (26.72; 26 observed deaths) than that for bipolar illness (12.28; 18 observed deaths) ( $p < .001$ ). The suicide SMR for males was 12.59; for females, 21.87 ( $p < .001$ ).

The SMR is a static measure and indicates neither the suicide risk as a function of age or the suicide risk as a function of time after onset of illness. Undoubtedly, this time-dependence of suicide risk is of great practical and therapeutic interest. If there were a high risk soon after onset of illness with a significantly lower risk thereafter, as suggested by some authors (e.g., Tondo et al.<sup>38</sup>), patients would have little chance of benefitting from maintenance treatment. Unfortunately, the question of how to determine the time-dependence of suicide risk throughout the time course of depression is a largely unsolved methodological issue. Specifically, Poisson-distribution-based approaches may be actually misleading as they implicitly

**Figure 1. Risk of Suicide for 186 Patients Who Had Unipolar Depression\***



\*Based on data from references 39 and 40.

assume an equal and constant risk for all patients and controls in the population under investigation. Patients who withdraw from longitudinal suicide studies (“dropouts”), as well as sampling biases due, for example, to the fact that the sample under consideration encompasses an overproportionately large number of depressive patients, hospitalized because of acute suicidal actions, aggravate the methodological difficulties. In contrast, survival-analytical methods are well suited to model the time to some particular event under the inclusion of dropouts as so-called censored observations. The methodological problem inherent to this type of analysis lies in the crucial assumption that the 2 processes that lead to a censored observation or to the event of interest must be uncorrelated.

The application of survival-analytical methods to (1) the 406 patients of our prospective study of depression, (2) a 20-year catamnestic study of 502 schizophrenic patients, and (3) a sample of 49 completed suicides from a prospective study of patients with borderline personality disorder revealed an almost constant suicide risk that persisted throughout lifetime for all diagnostic groups.<sup>39,40</sup> Figure 1 shows an approximately linear risk function for the depressive patients of our sample, thus suggesting that the suicide risk remained at high levels over the follow-up period of 20 to 30 years. Our findings indicate that there exists a diagnosis-independent “core” group of psychiatric patients who are at constant high suicide risk and are clearly in need of long-term treatment for the prevention of suicide attempts and, ultimately, completed suicide.

### Suicide Among Outpatient and Community Samples

The large outpatient study of Martin et al.<sup>20,41</sup> disputes the assumption of high suicide rates in milder forms of depression. In a 7-year follow-up study carried out in St. Louis, Missouri, only 5 of 253 patients with mood disorders had experienced unnatural deaths. None of the 137 patients with primary depression had committed suicide. Another, relatively small, study by Morrison<sup>42</sup> of 42 unipolar depressive patients in private practice concluded that

**Table 4. Patient Studies: Unipolar vs. Bipolar Depression**

Study	Follow-Up	% Suicides		Sample	
		Unipolar	Bipolar	Unipolar	Bipolar
Black et al, 1987 <sup>4</sup>	2–13 y	3.3	1.2	1007	586
Angst, 1998 <sup>11</sup>	34–38 y	14.0	8.2	186	220

the suicide rate was only slightly higher than that in the general population.

Follow-up studies in the community are still rare. In a 2-year follow-up of the Piedmont sample of the Epidemiologic Catchment Area study, 2.7% of subjects with major depressive episodes had committed suicide.<sup>43</sup> The relative risk was only 0.9 (95% CI = 0.5 to 1.4). In another American 2-year follow-up of a large household sample (N = 45,711), 30 of 615 major depressive patients had committed suicide. An elevated hazard ratio of 3.1 for males and 1.7 for females was reported.<sup>16</sup>

### ILLNESS-DEPENDENT RISK FACTORS FOR SUICIDE AMONG PATIENTS WITH MOOD DISORDER

Whether gender is a risk factor for suicide in major depressive disorder is uncertain. Hanna and Grant’s,<sup>44</sup> and Weeke and Vaeth’s<sup>14</sup> studies would suggest a higher risk of suicide among women, which was confirmed by our data. But one has to keep in mind that in the general population, the base rate of suicide is considerably higher for males than for females. There is basic agreement that the presence of psychotic symptoms does not increase the suicide risk according to the studies of Coryell and Tsuang,<sup>45</sup> Dilsaver et al.,<sup>34</sup> and our own study.

The diagnosis of unipolar major depression is always a bit uncertain; we observed a diagnostic change from unipolar to bipolar disorder of 1% per year of follow-up. Data on major depressive disorder without a long follow-up is therefore based on a potentially heterogeneous sample. Together with our data, the studies of Black et al.<sup>4</sup> from Iowa, our own data (Table 4), and the meta-analysis of Harris and Barraclough<sup>22</sup> support the assumption that patients with unipolar depression may have a clearly higher risk of suicide than those with bipolar depression. This is not the case for studies of suicide attempts. For instance, in the Epidemiologic Catchment Area study reported by Chen and Dilsaver,<sup>46</sup> the odds ratio for lifetime suicide attempts for patients with bipolar disorder was 2-fold higher at 6.2 versus 3.1 among those with unipolar depression. This finding is not easy to interpret because there is a correlation between suicide and a previous history of suicide attempts<sup>47</sup> as well as with a history of suicide ideation/attempts.<sup>48</sup> Higher rates of suicides among patients with bipolar disorder were also reported by Dunner et al.<sup>49</sup> and Perris and D’Elia.<sup>50</sup> In contrast, the outpatient study of Martin et al.<sup>20</sup> could not identify differences in suicide mortality between

unipolar and bipolar patients, but the number of 19 bipolar patients was too small to be conclusive.

There is good agreement between studies that patients who suffer from major depression comorbid with other psychiatric disorders are at increased risk for suicide. Fawcett<sup>51</sup> identified symptoms and diagnosis of anxiety and agitation as risk factors, and Isometsä et al.<sup>52</sup> considered comorbidity in general to be a risk factor; this was also found by Brent et al.<sup>53</sup> among the suicides of adolescents. It is impressive that Isometsä and colleagues,<sup>52</sup> in the psychological autopsy study of patients with major depression who completed suicide, found that 85% of cases had a comorbid psychiatric illness, 52% had a physical illness, 34% had personality disorder, 31% had psychoactive substance use disorder, and 17% had anxiety disorder.

### CAN WE REDUCE MORTALITY BY LONG-TERM MEDICATION?

Prophylactic medication with lithium has been reported to reduce suicide rates<sup>25,54</sup> and may even reduce general mortality<sup>55,56</sup> and cardiovascular mortality.

Are these favorable effects limited to lithium, or can they be expected from other prophylactic treatments? In our own long-term study of 186 unipolar depressive patients, only 70 (37.6%) had been treated between episodes by long-term medication whereas 116 were not. Table 5 demonstrates that the treated group had a better outcome in terms of suicide rates. Only 5.7% of treated versus 18.1% of untreated subjects committed suicide. Rates of death, recovery, and chronicity and Global Assessment Scale mean values did not clearly differ between the 2 groups.

The favorable effect of long-term medication was analyzed for all patients, bipolar and unipolar together (N = 406), and demonstrated a reduction of suicides when neuroleptics and/or antidepressants were used with or without lithium. These studies therefore suggest that the reduction of mortality is not limited to long-term lithium prophylaxis; it may be very interesting to study other drugs in this respect (e.g., antiepileptics and atypical neuroleptics).

### CONCLUSIONS

The mortality of patients with mood disorders is 42% to 150% higher than that in the general population.

Suicide as a consequence of depressive episodes is one of the main causes of the increased mortality. The specific risk associated with affective disorders is elevated 12-fold to 20-fold. Depression plays a major role in the suicide of adolescents (50%) and the elderly.

Psychological autopsy studies of suicide victims identified high rates of major depressive disorders within the range of about 20% to 35%.

**Table 5. Outcome of Treated vs. Untreated Unipolar Depressives**

Characteristic	Unipolar Disorder (N = 186)	
	Untreated (N = 116)	Treated (N = 70)
Age at last observation, y (mean)	70.0	71.5
Dead (%)	71.6	64.3
Suicide (%)	18.1	5.7 <sup>a</sup>
Recovered (%)	30.2	18.6
Chronic (%)	9.5	18.6
Global Assessment Scale, last interval (mean)	77.5	62.0

<sup>a</sup>p < .05.

A number of illness-dependent risk factors were investigated. It is uncertain whether the suicide rates differ between bipolar and major depressive patients and between depressive males and females. Comorbidity increases suicide risks substantially. Further risk factors are anxiety and agitation. Rapid changes at the beginning and toward the end of a depressive episode constitute an increased suicide risk, especially in the 6 to 12 months after discharge from hospital. Every new episode brings along a new potential for suicide, and depression is, in the majority of cases, recurrent. The long-term risk therefore remains constant over decades after onset of the illness. Patients with late-onset major depression are at higher risk than those with early-onset depression.

Long-term medication of lithium has been shown to reduce significantly the suicide risk of patients with mood disorders, and there are tentative data suggesting that neuroleptics and/or antidepressants may have similar beneficial effects.

Methodologically, one has to consider that most studies on major depressive disorders and suicide were carried out on psychiatric inpatients. The generally assumed suicide risk of 15% probably applies only to inpatients. Little is known about the suicide risk of patients from general practice or community samples; it seems to be much lower.

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