Research report

Mortality of patients with mood disorders: follow-up over 34–38 years

F. Angst, H.H. Stassen, P.J. Clayton, J. Angst

Institute of Social and Preventive Medicine, Zurich University, Zurich, Switzerland

Santa Fe, NM, USA

Zurich University Psychiatric Hospital, Lengstrasse 31 Mail Box 68, 8029 Zurich, Switzerland

Received 29 February 2000; accepted 3 April 2001

Abstract

Background: All follow-up studies of causes of death in affective disordered patients have found they have markedly elevated suicide rates and a less reproducible increased mortality from other causes. The reported rates by gender, disorder type and treatment are more variable. Methods: Hospitalised affective disordered patients \( n = 406 \) were followed prospectively for 22 years or more. Later, mortality was assessed for 99\% of them at which time 76\% had died. Results: Standardised Mortality Rates (observed deaths/expected deaths) for patients were elevated especially for suicide and circulatory disorders in both men and women. Women actually had higher suicide rates but that did not take into account the twofold increase in general population rates for men. Unipolar patients had significantly higher rates of suicide than bipolar Is or IIs. In all groups long term medication treatment with antidepressants alone or with a neuroleptic, or with lithium in combination with antidepressants and/or neuroleptics significantly lowered suicide rates even though the treated were more severely ill. Although at the age of onset the suicide rates were most elevated, from ages 30 to 70 the rates were remarkably constant despite the different courses of illness. Limitations: The patients were identified as inpatients and followed prospectively. The treatments were uncontrolled and are not quantifiable but were documented during the follow-up. Conclusions: Men and women hospitalised for affective disorders have elevated mortality rates from suicide and circulatory disorders. Unipolars have higher suicide rates than bipolar Is or IIs. Long term medication treatment lowers the suicide rates, despite the fact that it was the more severely ill who were treated. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Mortality; Unipolar; Bipolar disorder; Suicide; Gender; Treatment

1. Introduction

It is well known that psychiatric patients have elevated mortality rates that vary between 36 and 100\% compared to the general population (Rorsman, 1974; Martin et al., 1985a,b; Schwalb and Schwalb, 1987; Murphy et al., 1989). This was also demonstrated specifically for patients with mood disorders (Table 1) in clinical and epidemiological samples (Murphy et al., 1987; Zheng et al., 1997). The
Table 1
Studies on overall mortality of patients with affective disorders standardised mortality ratio (SMR)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Diagnoses</th>
<th>Observation period (years)</th>
<th>Males SMR</th>
<th>Females SMR</th>
<th>Total m+f SMR</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berglund and Nilsson (1987)</td>
<td>4</td>
<td>Unipolar or bipolar</td>
<td>14–27</td>
<td>1.29</td>
<td>1.20</td>
<td>1.23</td>
<td>1206</td>
</tr>
<tr>
<td>Eastwood et al. (1982)</td>
<td>4</td>
<td>Affective disorders</td>
<td>9.5</td>
<td>1.14</td>
<td>1.55</td>
<td>1.37</td>
<td>585</td>
</tr>
<tr>
<td>Murphy et al. (1987)</td>
<td>1</td>
<td>Affective disorders</td>
<td>16</td>
<td>2.10</td>
<td>1.20</td>
<td>1.50</td>
<td>1003</td>
</tr>
<tr>
<td>Black (1998)</td>
<td>4</td>
<td>Unipolar or bipolar</td>
<td>30–40</td>
<td>1.41</td>
<td>1.82</td>
<td>1.61</td>
<td>1593</td>
</tr>
<tr>
<td>Angst (1998)</td>
<td>4</td>
<td>Unipolar or bipolar</td>
<td>34–38</td>
<td>1.64</td>
<td>1.59</td>
<td>1.61</td>
<td>406</td>
</tr>
<tr>
<td>Weeke (1979)</td>
<td>4</td>
<td>Unipolar or bipolar</td>
<td>1–8</td>
<td>1.95</td>
<td>1.55</td>
<td>1.69</td>
<td>8136</td>
</tr>
<tr>
<td>Weeke and Vaeth (1986)</td>
<td>4</td>
<td>Unipolar or bipolar</td>
<td>5–7</td>
<td>2.17</td>
<td>1.45</td>
<td>1.73</td>
<td>2168</td>
</tr>
<tr>
<td>Ciompi and Medvecka (1976)</td>
<td>4</td>
<td>Depression</td>
<td>22–47</td>
<td>1.69</td>
<td>1.95</td>
<td>1.85</td>
<td>523</td>
</tr>
<tr>
<td>Lee and Murray (1988)</td>
<td>4</td>
<td>Depression</td>
<td>22</td>
<td>—</td>
<td>—</td>
<td>1.90</td>
<td>89</td>
</tr>
<tr>
<td>Hoyer et al. (2000)</td>
<td>4</td>
<td>Depression</td>
<td>5–25</td>
<td>2.18</td>
<td>1.81</td>
<td>1.94</td>
<td>54 103</td>
</tr>
<tr>
<td>Zheng et al. (1997)</td>
<td>4</td>
<td>Depression</td>
<td>2.5</td>
<td>3.10</td>
<td>1.70</td>
<td>2.49</td>
<td>1499</td>
</tr>
<tr>
<td>Brodersen et al. (2000)</td>
<td>4</td>
<td>Unipolar or bipolar</td>
<td>16</td>
<td>2.42</td>
<td>2.56</td>
<td>2.50</td>
<td>133</td>
</tr>
</tbody>
</table>

Criteria for inclusion: either large sample (n > 5000) or long observation period (>5 years) and expected deaths calculated out of all years of observation period.

As reference for calculation of expected deaths: median year.

Samples: (1) community sample, (2) GP patients, (3) psychiatric outpatients, (4) psychiatric inpatients.

Elevated mortality is mainly explained by suicide, but a number of other causes contribute to this elevation: death by accidents (Tsuang and Woolson, 1978; Weeke and Vaeth, 1986; Murphy et al., 1987, 1989), secondary substance abuse (Eastwood et al., 1982), coronary heart disease (Weeke and Vaeth, 1986; Murphy et al., 1989; Sharma and Markar, 1994), cerebrovascular disorders (Baldwin, 1980; Schwalb and Schwalb, 1987; Zheng et al., 1997), respiratory infections (Baldwin, 1980; Schwalb and Schwalb, 1987; Sharma and Markar, 1994), thyroid disorders (Baldwin, 1980) and homicide (Hoyer et al., 2000). Mortality from neoplasms was not found to be elevated (Rorsman, 1974; Baldwin, 1980; Schwalb and Schwalb, 1987; Murphy et al., 1989).

The true suicide mortality is difficult to evaluate because an unknown number of patients may commit suicide at the onset of their illness before a diagnosis can be made. In this context psychological autopsy studies of suicides in the general population are of great interest. A classic paper of Robins et al. (1959) found that of 194 suicides, 101 had psychotic diagnoses. The most common diagnosis was manic-depressive illness in 60%. Barraclough et al. (1974) reported a very high rate of 86% and Coppen (1994) found among all suicides, 70% were depressed. Other studies found considerably lower rates: among adolescents studied in Finland (Marttunen et al., 1991) and in the USA (Brent et al., 1993) 50% of suicides were explained by depression; in adults only 20–30% of suicides were reported to be a consequence of depression (Dorpat and Ripley, 1960; Arato et al., 1988; Henriksson et al., 1993; Dilsaver et al., 1994).

Traditionally follow-up studies on mortality and suicide of patients with mood disorders were from hospitalised samples. Since the classic review of such studies by Guze and Robins (1970) it was generally assumed that on the average about 15% (range 12–19%) of depressed patients would commit suicide. But doubts were recently raised by Blair-West et al. (1997) who stressed on the basis of the prevalence of depression in the general population that such high suicide rates would far exceed the observed incidence figures. They pointed out that studies of inpatients carried an inherent bias in favour of high suicide rates: inpatients cannot be representative of all depressives as suicidality is one of the primary indications for admission. They estimated a much lower theoretical suicide rate of 3.5% for patients with affective disorders. In a new analysis they estimated a lifetime suicide rate of 3.4%, with a high preponderance of male suicides (6.9%) over female suicides (1.1%) as a consequence of major depression (Blair-West et al., 1999). Based on hospitalised samples several long-term follow-up studies of major depressives were carried out over 10 or more years applying identical criteria...
Table 2
Long-term follow-up studies of depressive inpatients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Follow-up (years)</th>
<th>Readmitted (%)</th>
<th>Poor outcome (%)</th>
<th>Suicide (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiloh et al. (1988)</td>
<td>1988</td>
<td>133</td>
<td>15</td>
<td>56</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Thornicroft et al. (1993)</td>
<td>1993</td>
<td>439</td>
<td>10</td>
<td>35</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Surtees and Barkley (1994)</td>
<td>1994</td>
<td>80†</td>
<td>12</td>
<td>60</td>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>

† Including probable suicide/suspect unnatural deaths.
‡ 62.8% inpatients.
§ 87.5% inpatients.

(Table 2). The suicide rates varied between 4 and 7% (Lee and Murray, 1988; Kiloh et al., 1988) or 10.6% (Winokur and Tsuang, 1975). Our preliminary results (Angst and Preisig, 1995) showed 13% suicides.

Still uncertain is the question of whether suicides would occur more frequently among bipolar patients or unipolar patients (Morrison, 1982). Most studies found no differences (Stallone et al., 1980) or even a higher mortality among unipolar depressives (Brent et al., 1993), this was recently confirmed by the large meta-analysis of Harris and Barraclough (1997).

1.1. Suicide in outpatients or community samples

Prospective community studies are still very rare and long-term follow-up studies on suicides do not exist with the exception of two investigations. The 25-year follow-up Lundby study of Hagnell et al. (1982) found 28 suicides (23 m, 5 f) among 3563 persons. Of these, 15 who committed suicide had suffered from depression. The age-standardised suicide rate in men with depression was 13-fold higher than that of the total cohort. In a much more restricted (age, follow-up) study, in a 2-year follow-up of the Piedmont sample of the epidemiologic catchment area study only 2.7% of elderly subjects (60 years and older) with major depressive episodes had committed suicide (Fredman et al., 1989). Compared to the normal population the relative risk was not elevated [0.9 (95% CI: 0.5–1.4)]. Because the Lundby study counted treated depressives rather than relying on diagnoses made by interviews of community samples, the diagnoses of both subjects and controls seem more valid and the results more dependable even though the numbers were small.

A large outpatient random sample study of Martin et al. (1985a,b) found only five cases of unnatural deaths among 253 patients with mood disorders followed-up over 7 years. None of the 137 patients with primary depression had committed suicide, all were in treatment. A private practice study of 42 unipolar depressive outpatients followed over 8.5 years (Morrison, 1982) estimated that the suicide rate was only slightly higher than in the general population.

From these data it is obvious that studies of community and outpatient samples give much lower suicide rates than studies of hospitalised patients.

Our investigation on suicide in affective disorders is limited to severe depressed or manic hospitalised patients. The purpose of the long-term follow-up is to analyse the mortality of unipolar depressives and bipolar patients compared to the normal population and to analyse the impact of an interval medication, given under naturalistic conditions between episodes, on mortality. The present analysis is an extensive up-date of earlier analyses (Angst, 1998, 1999; Angst et al., 1998).

2. Methods

2.1. Sample

The sample consists of 186 unipolar and 220 bipolar depressive or manic patients who were hospitalised between 1959 and 1963 in the Psychiatric Hospital University of Zurich with a diagnosis of mania or endogenous depression, endo-reactive depression, manic-depressive disorder or affective disorder with mood-congruent or mood-incongruent
psychotic features (hallucinations or delusions) including schizoaffectives. Sixty-one percent of patients met criteria for psychosis over lifetime. Bipolarity was assumed as soon as hypomania occurred for a few days without considering whether it seemed to be drug-induced or not.

Psychopathology was assessed between 1959 and 1963 by a rating scale for mood disorder (Angst et al., 1964), which included the items agitation, retardation, hypochondriasis, suicidal thoughts and suicide attempts. Furthermore, a family history of psychiatric disorders and suicidality was taken from the probands and at least one first degree relative.

Follow-ups by telephone were carried out in 1963, 1965, 1970, 1975, 1980 and in person interviews in 1985. Furthermore in 1991 and at the end of 1997 the mortality was determined according to ICD-8 codes on the basis of information from the Federal Office of Statistics of Switzerland. A detailed description of the sample of which all qualify for modern criteria for major depression and mania or hypomania can be found in Angst and Preisig (1995). The diagnoses of bipolar I vs. bipolar II disorders were made according the original criteria of Dunner et al. (1976). The follow-up of the clinical course and outcome ended in 1985. The mortality follow-up continued until 1997 over 34–38 years; 76% of the patients had died by the end of 1997.

An attempt was also made to assess the long-term treatment during the intervals between episodes. All treating physicians were called and all records were assessed. In order to be considered as treated the patient had to be medicated at least over 6 months or, if shorter, for the whole time period between two episodes. The treatment was specified for each interval up to 1985 distinguishing between neuroleptics, antidepressants and lithium without assessment of the dosage and precise length of the treatment (shortcoming of the study).

2.2. Statistics

Survival analyses according to Kaplan and Meier (1958) were carried out using SAS software, other calculations (SMR etc.) using EXCEL programs. Differences between survival functions were tested by log-rank tests.

While survival analysis allows one to assess the risk of committing suicide as a function of time, the standard mortality ratio (SMR) is an integral quantification of the gender-, age- and birth cohort specific mortality. For each gender, each 5-year age group, each observation year (1959–1997) and each cause of death the specific mortality rate (per 100 000 living) of the Swiss population was determined out of the Swiss National Death Registry and multiplied by the count of living of the sample in the specific strata. The sum of these products resulted in the expected deaths (E) and the ratio of the observed deaths (O) divided by E determined the SMR = O/E. If the patients had died earlier and/or more frequent by a specific cause of death than the people of the local population, the SMR was >1.0. Thus, the SMR not only quantifies the over- or under-mortality compared to the general population but allows also a comparison of the mortality among different samples which is not confounded by different frequency distribution of gender, age and observation period.

The 95% confidence interval was computed according to Lindell (1984) assuming a Poisson distribution. An elevated SMR was regarded as significant at the 5% level if the respective 95% confidence interval did not include the value of 1. A comparison between different SMRs was carried out by t-tests, based on normal approximation of Poisson distribution.

3. Results

Of the 406 patients 99.3% could be followed-up to the end of 1997. Three persons were lost by emigration. Table 3 gives a summary of the deaths: 83% of males and 72% of females had died. Persons still

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sample</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Drop-outs</td>
</tr>
<tr>
<td>Alive</td>
</tr>
<tr>
<td>Dead</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Age at last obs. (median)</td>
</tr>
<tr>
<td>Age at death (median)</td>
</tr>
</tbody>
</table>
alive had a median age of 70 years and those who died a median age of 74 years.

3.1. Overall mortality of patients with affective disorders by gender

Table 4 demonstrates an elevated overall mortality (SMR) of patients with affective disorders of 1.61 (1.64 for males and 1.59 for females). Most impressive are the SMR of 18.04 for suicide (males 13.49, females 21.87). There was also an increased risk of death by cardiovascular disorders (SMR = 1.61), which was most clearly present among females [SMR 1.70 (95% CI: 1.34–2.14)]. Among males, deaths from cerebrovascular and other vascular disorders were elevated (SMR = 2.21) as well as deaths by accidents and intoxications (SMR = 2.95). Taken together for all circulatory diseases, both sexes show elevated SMRs (males 1.63, females 1.47).

3.2. Overall mortality of unipolar vs. bipolar patients

Table 5 gives the SMR of unipolar and bipolar patients. Unipolar depressives had a SMR of 1.63, bipo- "lar of 1.58, which means that the total mortality was elevated by 63 and 58%, respectively; the difference between the two groups was small but statistically significant.

Most impressive are the relative SMRs for suicide, which was 26.7 for UP and 12.3 for BP; the difference between the two disorders was large and highly significant. Apart from suicides, cardiovascular disorders were significantly elevated. In bipo- lars death from cardiovascular diseases and all vascular diseases was significantly elevated. More details of the results were reported in the thesis of Angst (1998).

Comparing uni- and bipolar patients a survival analysis of non-suicidal and suicidal deaths did not show significant differences.
Table 5
Standardised mortality ratio (SMR) of unipolar (UP, n = 147) versus bipolar (BP, n = 158) of total male and female patients

<table>
<thead>
<tr>
<th></th>
<th>UP</th>
<th>BP</th>
<th>UP vs. BP (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>SMR</td>
<td>O</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>23</td>
<td>1.05</td>
<td>22</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>40</td>
<td>1.36</td>
<td>59</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>20</td>
<td>1.30</td>
<td>21</td>
</tr>
<tr>
<td>Accident, intoxication</td>
<td>7</td>
<td>1.96</td>
<td>8</td>
</tr>
<tr>
<td>Suicide</td>
<td>26</td>
<td>26.72*</td>
<td>18</td>
</tr>
<tr>
<td>Other causes</td>
<td>31</td>
<td>1.64*</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>147</td>
<td>1.63*</td>
<td>158</td>
</tr>
<tr>
<td>All vascular diseases</td>
<td>60</td>
<td>1.34*</td>
<td>80</td>
</tr>
<tr>
<td>All non-suicide</td>
<td>121</td>
<td>1.36*</td>
<td>140</td>
</tr>
</tbody>
</table>

Ns, not significant (t-test); O, observed deaths.
* With P<0.05 (two-tailed) different from 1.0 (Poisson-distribution).

3.3. Risk factors for suicide

Symptoms of depression including agitation, retardation, hypochondriasis suicide thoughts and suicide attempts were examined to see if they correlated with completed suicide. In the univariate analysis, the depressive symptoms, suicidal thoughts and retrospective suicide attempts were not associated with suicide, but more recent suicide attempts (during the prospective observation since 1959) were associated (OR 2.05; CI: 1.1–4.0). In the multivariate logistic regression, both, suicidal thoughts (OR 2.34) and suicide attempts (OR 3.76) predicted suicides; sex was not predictive.

3.4. Time characteristics of suicide risk

Analysis of the suicide risk as a function of age of onset yielded essentially linear and parallel curves for the completed suicides and the natural deaths, thus suggesting that there is a constant risk of suicide, independent of the onset of depression. However, it is important to note that (1) patients die from suicide, on average, 10 years earlier than from...
natural causes (Fig. 1) and (2) there is a non-linearity with a significantly elevated suicide risk around the age of onset of 20 years (Fig. 2).

In a further analysis we focused our interest on the age distribution of suicide risk in comparison to the risk of dying a natural death. To this end we used the Kaplan–Meier product-limit estimator for the construction of the cumulative curve of completed suicides and natural deaths, respectively. In order to make the time characteristics of the cumulative curves directly comparable, all patients who were alive by the end of the observation period were excluded from the analysis and calculations were carried out separately for the subgroups of completed suicides \((n = 44/10.8\% )\) and natural deaths \((n = 261/64.3\% )\). The resulting cumulative curves turned out to be remarkably different (Fig. 1). In fact, the rates of completed suicides were almost constant between the ages of 30 and 70 as indicated by a linear curve characteristics, while natural deaths occurred in their majority at higher ages \((> 60\) years\), as indicated by a clearly non-linear (exponential) cumulative curve. The irregularities of the curve characteristics are clearly artifactual, due to the relatively small number of observed suicides. Similarly, the non-linearities below the age of 30 and beyond the age of 70 can be attributed to the fact that there were too few observations in these age periods.

When analyzing the suicide risk as a function of the duration of illness we found again a clearly linear relationship that underlined our finding of a constant suicide risk over a lifetime among depressive patients.

3.5. Mortality of unipolar and bipolar patients under long-term medication

The patients who were originally hospitalised between 1959 and 1963 were, after discharge, mainly treated by the referring doctors: GPs, internists and psychiatrists. A treatment during the intervals was more frequently given to patients with incomplete remission after the episodes and much more frequent in the case of bipolar patients. Table 6 shows the treatment rates and outcomes of unipolar and bipolar patients. Unipolars were treated in 38%, bipolars in 62% of cases. Recovery was achieved among both subgroups of mood disorders much less frequently in the treated sub-samples. Also chronicity was slightly more frequent among treated than untreated cases, especially in unipolars. In addition unipolar depressives, who were treated, had more residual symptoms and social consequences, illustrated by significantly lower Global Assessment Scale score (median), than those who were not treated. The data of this naturalistic study indicate that the treated patients certainly were not those in which the disorder, over decades, took a better course and outcome. In
contrast to their poorer outcome, treated patients tended to live longer and to have a 2.5-fold lower suicide rate ($P=0.04$) than the untreated samples in both unipolar (18.1 vs. 7.1%) and bipolar disorder (13.1 vs. 5.2%). The marked reduction of suicides in the treated sub-samples is also shown significantly by survival-analyses for both unipolar and bipolar disorders.

A more precise analysis of the mortality can be obtained by SMRs. The data are given for both subtypes of affective disorder together and separately. Two kinds of statistics were carried out: $t$-tests over the SMR comparing non-treated with treated subgroups and tests of significance based on Poisson distribution comparing the SMR of the patients with the general population. The results are shown in Tables 7 and 8 for unipolar and bipolar affective disorders, respectively.

Treated unipolar depressives vs. untreated patients had a significantly lower suicide mortality (SMR 11.86 vs. 38.07) and in addition a slightly lower total mortality (1.56 vs. 1.67). But overall treated depressives died more frequently from cerebrovascular disorders.

Treated bipolar patients subjects had a considerably lower SMR for suicide (6.43) compared to the non-treated subjects (26.54). This difference is spectacular. Furthermore cardiovascular deaths were less

### Table 6
Outcome of treated versus untreated unipolar and bipolar patients

<table>
<thead>
<tr>
<th></th>
<th>Unipolar</th>
<th></th>
<th>Bipolar</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Treated</td>
<td></td>
<td>Untreated</td>
<td>Treated</td>
</tr>
<tr>
<td>$n$</td>
<td>116</td>
<td>70</td>
<td>84</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Recovered (%)</td>
<td>30.2</td>
<td>18.6</td>
<td>0.08</td>
<td>20.2</td>
<td>13.2</td>
</tr>
<tr>
<td>Chronic (%)</td>
<td>9.5</td>
<td>18.6</td>
<td>0.07</td>
<td>15.5</td>
<td>16.2</td>
</tr>
<tr>
<td>GAS (last interval, median)</td>
<td>78</td>
<td>62</td>
<td>0.01</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Age at last observation (median)</td>
<td>70</td>
<td>72</td>
<td>Ns</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Alive (%)</td>
<td>22.4</td>
<td>18.6</td>
<td>Ns</td>
<td>23.8</td>
<td>30.9</td>
</tr>
<tr>
<td>Suicide (%)</td>
<td>18.1</td>
<td>7.1</td>
<td>0.04</td>
<td>13.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Other deaths (%)</td>
<td>59.5</td>
<td>74.3</td>
<td>10.04</td>
<td>63.1</td>
<td>64.0</td>
</tr>
</tbody>
</table>

Ns, not significant.

* $\chi^2$ test.

** Wilcoxon test.

### Table 7
SMR of unipolar (UP, $n=147$ deaths) depressed inpatients: untreated versus prophylactically treated

<table>
<thead>
<tr>
<th></th>
<th>UP total M+F</th>
<th>Untreated</th>
<th>SMR</th>
<th>Treated</th>
<th>SMR</th>
<th>$P&lt;$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$O$</td>
<td>SMR</td>
<td>$O$</td>
<td>SMR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td>16</td>
<td>1.26</td>
<td>7</td>
<td>0.76</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>25</td>
<td>1.42</td>
<td>15</td>
<td>1.26</td>
<td></td>
<td>Ns</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>8</td>
<td>0.85</td>
<td>12</td>
<td>2.02</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Accident, intoxication</td>
<td>4</td>
<td>1.91</td>
<td>3</td>
<td>2.03</td>
<td></td>
<td>Ns</td>
</tr>
<tr>
<td>Suicide</td>
<td>21</td>
<td>38.07</td>
<td>5</td>
<td>11.86</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Other causes</td>
<td>16</td>
<td>1.40</td>
<td>15</td>
<td>2.01</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>1.67</td>
<td>57</td>
<td>1.56</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>All vascular diseases</td>
<td>33</td>
<td>1.22</td>
<td>27</td>
<td>1.51</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>All non-suicide</td>
<td>69</td>
<td>1.30</td>
<td>52</td>
<td>1.44</td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

$O$, observed deaths; ns, non significant ($t$-test).

* With $P<0.05$ (two-tailed) different from 1.0 (Poisson-distribution).
often observed among treated (SMR 1.68) than among untreated subjects (SMR 2.23). Overall the mortality in the treated bipolar group (SMR 1.33) was considerably lower than in the untreated group (SMR 2.18). In contrast to unipolar depressives, there was no increase of cerebrovascular deaths under treatment in the bipolar sample.

In both diagnostic subgroups, however, the treated subjects still had an elevated mortality; this was mainly due to suicides but also due to other deaths especially cardiovascular (bipolars) and cerebrovascular disorders (unipolar depressives).

The remarkable differences in mortality between treated and non-treated subjects raises the question of which type of drugs may have been responsible for these effects? In this context we have to stress that the drug treatment was given under natural conditions by doctors based on the prevailing symptoms. In many cases psychotic symptoms (delusions or hallucinations), which had been present in 61% at least once over lifetime, had to be treated by neuroleptics and in many cases the neuroleptic may have been clozapine as it was available in Switzerland continuously from 1961 to the present.

Of the unipolar depressives 3.8% received lithium plus neuroleptics or antidepressants and 1.6% lithium alone and 9.7% neuroleptics plus antidepressants. In contrast, 27.8% of the bipolars received lithium plus neuroleptics or antidepressants, 9.6% lithium alone and 8.2% neuroleptics plus antidepressants. A monotherapy of antidepressants was given in 15.6% of the unipolars and in 9.1% of the bipolars, while the proportion of patients with a monotherapy of neuroleptics was 7% in both diagnostic groups.

All drug-treated subgroups showed a significant reduction of suicides on the basis of the SMR. The effect was very strong in patients treated by antidepressants, by antidepressants plus neuroleptics, or by lithium plus antidepressants and/or neuroleptics. In all these cases the SMR for suicide is close to one, but the number of cases are small. A decrease of cardiovascular mortality was also observed under antidepressants as well as lithium plus antidepressants/neuroleptics. On the other hand an increased mortality for cerebrovascular disorder was found with neuroleptic treatment (SMR 4.24) and elevated cardiovascular deaths (SMR 2.20) under a combination of neuroleptics and antidepressants.

In order to separate the effects of the different subgroups of drugs we carried out logistic regression. The logistic regression over all unipolar and bipolar patients, who had died (n = 305) showed a significant suicide reducing effect of antidepressants. Lithium alone did not have any effect, but did in combination with antidepressants and/or neuroleptics.

In addition to suicide as a dependent variable we analysed by logistic regression also cardiovascular deaths as a function of subtypes of drug treatment in order to test the hypothesis that antidepressants

### Table 8

<table>
<thead>
<tr>
<th>BP total M+F</th>
<th>Untreated O</th>
<th>SMR</th>
<th>Treated O</th>
<th>SMR</th>
<th>Untreated vs. treated P&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasm</td>
<td>10</td>
<td>1.39</td>
<td>12</td>
<td>0.63</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>21</td>
<td>2.23*</td>
<td>38</td>
<td>1.68*</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>8</td>
<td>1.62</td>
<td>13</td>
<td>1.25</td>
<td>0.05*</td>
</tr>
<tr>
<td>Accident, intoxication</td>
<td>2</td>
<td>1.59</td>
<td>6</td>
<td>1.98</td>
<td>ns</td>
</tr>
<tr>
<td>Suicide</td>
<td>11</td>
<td>29.19*</td>
<td>7</td>
<td>6.43*</td>
<td>0.001</td>
</tr>
<tr>
<td>Other causes</td>
<td>12</td>
<td>1.94</td>
<td>18</td>
<td>1.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>2.18*</td>
<td>94</td>
<td>1.33*</td>
<td>0.001</td>
</tr>
<tr>
<td>All vascular diseases</td>
<td>29</td>
<td>2.02*</td>
<td>51</td>
<td>1.54*</td>
<td>0.001</td>
</tr>
<tr>
<td>All non-suicide</td>
<td>53</td>
<td>1.83*</td>
<td>87</td>
<td>1.25</td>
<td>0.001</td>
</tr>
</tbody>
</table>

O, observed deaths; ns, not significant (t-test).
* With P < 0.05 (two-tailed) different from 1.0 (Poisson-distribution).
* One-tailed P < 0.05 (t-test).
would increase mortality. The results were negative for the total group and for both unipolar and bipolar subgroups.

3.6. Overall mortality of bipolar I vs. bipolar II patients

Bipolar I (n = 113) could be compared with bipolar II (n = 46) patients who had died (Table 9). Overall the SMR was significantly higher for BP I (1.86) compared to BP II (1.18) patients. The difference is not explained by the suicide rates as these do not differ significantly (SMR BP I: 11.53, BP II: 14.15). A total of 8% of BP I vs. 9% of BP II patients had committed suicide. The difference is mainly due to cerebrovascular deaths among BP I patients with a SMR of 2.04 compared to an SMR of 0.61 among BP II patients (P < 0.001), but the number of observed deaths was small in BP II (n = 4).

3.7. Mortality of bipolar I and bipolar II patients under long-term medication

Considering only subjects who had died, an interval treatment analysis was carried out in 58.4% of 113 BP I and 63.0% of 46 BP II patients. In both patient groups treated subjects had a significantly lower general mortality and especially a strongly reduced suicide mortality. Among untreated BP I patients 17.0% committed suicide versus 6.1% in treated subjects. The analogue figures for BP II patients were 17.6 and 10.3%, respectively. Compared to untreated BP I patients (SMR = 27.63), treated patients had an SMR of only 9.51; but this is based on very few cases and statistical comparisons are not conclusive. Nevertheless our findings on both BP I and BP II patients point in the same direction.

4. Discussion

The present study is the longest recorded prospective follow-up (over 34–38 years) of a large sample of hospitalised patients with mood disorders. There is no similar study, in which the majority of subjects (76%) were followed-up repeatedly until their deaths. Therefore the data on mortality are probably representative for a severely ill patient population, of which 61% had manifested psychotic symptoms (mood congruent or mood-incongruent delusions or hallucinations) at least once over lifetime. Published studies indicate clearly that hospitalised patients with mood disorders may have considerably higher suicide rates than those treated as outpatients or identified in the community (Martin et al., 1985a,b;
Fredman et al., 1989). Our finding of a high general and a high suicide mortality is in line with the follow-up studies of hospitalised patients. From that point of view our result is not surprising. Overall the standardised mortality ratio was 1.61 and the SMR for suicide 18-fold higher than expected.

Of further interest is the suicide mortality by gender. Men had a 13.5-times higher suicide rate, women 21.9 times. To interpret these gender differences one has to be aware that they are dependent on the suicide mortality of the general population, which is twofold higher among males (Angst, 1992). A new 16-year follow-up study from Denmark also reported higher SMR for suicides among women (29.4) than men (13.4) (Brodersen et al., 2000). These differences do not mean that women committed suicide more frequently than men because the base rate for suicides in the general population is twofold higher for men than women. Still in these disorders women have at least equal suicide rates.

A multivariate logistic regression identified suicidal thoughts and suicide attempts as predictors of suicide; these findings confirm the conclusions of Goldstein et al. (1991), who followed-up 1906 patients admitted with affective disorders.

The suicide mortality (SMR 18.04) of our study is compatible with the result of the large meta-analysis of Harris and Barraclough (1997) (SMR 13.65) in which milder depression was included. In line with this meta-analysis we also found higher SMRs for suicides of unipolar depressives (26.7) than of bipolars (12.3). In our study the difference in suicide rates between unipolar and bipolar patients is also demonstrated by survival analysis.

Rhimer and Pestality (1999) reported that suicidal behaviour is particularly high for patients with BP II disorders although it has not yet been firmly established that they have higher completed suicide rates than BP I. In our data there were no differences in suicide mortality between BP I and BP II disorders. Although our study provides a lifelong follow-up and subjects with ‘drug-induced’ hypomanic symptoms were classified as BP II disorders there is still a possibility that some unipolars would belong to the BP II spectrum. The expanding classification of BP II disorders, including fewer symptoms than that required for hypomania or including personality designations such as hyperthymia (Akiskal et al., 2000) might change the numbers somewhat, but the lifelong follow-up assures that this group of patients is fairly well classified.

Our study also confirmed an increased risk of death by cardiovascular and cerebrovascular disorders and by accidents and intoxications. Similar findings had been reported by other authors (Baldwin, 1980; Weeke and Vaeth, 1986; Schwab and Schwab, 1987; Murphy et al., 1989; Sharma and Markar, 1994; Zheng et al., 1997). In our study BP I patients had a significantly higher mortality due to cerebrovascular diseases than BP II patients.

4.1. In which stage of the illness does suicide occur?

Based on retrospective studies, Guze and Robins (1970) reported that suicide would occur early in the course of the illness, before other causes of death come fully into play, a finding which was also confirmed prospectively by Tsuang and Woolson, Clayton and Black and colleagues (Tsuang and Woolson, 1978; Clayton, 1983; Black et al., 1987). It is well documented (Fawcett et al., 1987; Roy, 1993) that a large number of suicides occur during the first 6–12 months after discharge from the hospital. These findings are compatible with our follow-up data. We hypothesised (Angst, 1999) that the suicide risk may increase during periods of rapid changes of the depressive state and would therefore occur mainly at the beginning and at the end of episodes.

Another question, in addition to the suicides in the early stage of the disorder (Baldessarini et al., 1999) is whether the suicide risk waxes and wanes with each new episode of the disorder and is therefore also a function of the overall course and number of episodes. Survival analyses by Angst and Stassen (1987) and Angst et al. (1990) found a constant risk for suicide over decades of follow-up as a consequence of the recurrence of mood disorders. Our new data (Figs. 1 and 2) showed again a linear constant relationship when the suicide risk was analysed as a function of age of onset or age. This underlines the fact that there exists a subgroup of depressives with a constant suicide risk over their lifetimes. The nature of this risk is unknown but may be attributed to a specific biological factor, or genetic predisposition, that is present in 10–15% of both severe unipolar...
and bipolar depressives. Given this constant risk, life long therapeutic precautions appear to be mandatory.

Furthermore we reported that recurrence is overwhelmingly frequent among both unipolar and bipolar disorders, and bipolars experienced about twice as many episodes as unipolar depressives (Angst, 1986; Angst and Preisig, 1995). The finding of a persistent high suicide risk over decades is in line with the high suicide risk observed in the depressed elderly. Our finding would suggest that patients with severe recurrent mood disorders require treatment as long as recurrences or residual symptoms are observed. This conclusion can only be drawn for severely ill patients with mood disorders who required hospitalisation in 1959–1963. This group is especially prone to commit suicide because some of them are hospitalised for their suicide risk as noted by Blair-West et al. (1997) in their criticism of the assumed suicide risk of 15% for all depressed patients.

An important finding of our study is the fact that patients under long-term medication had a significantly lower overall mortality due to both a reduction of non-suicidal mortality and a remarkable reduction of suicide mortality compared to untreated patients. The treated groups, unipolars and bipolars, had a 2.5-fold lower suicide rate than the untreated patients. The difference is confirmed by the results of survival analysis and standardised mortality ratios. In the case of bipolar patients, who were much more frequently treated than unipolar depressives, the difference of treated bipolar subjects (SMR = 6.43) versus non-treated subjects (SMR = 26.54) was even higher than among unipolar depressives (SMR = 11.86 versus 38.07). Within bipolar I vs. bipolar II subgroups the reduction of suicides tended to be equal. An earlier shorter follow-up study of Black et al. (1989) could not find a relationship between type of treatment during the index admission an later mortality including suicide. In contrast to their study our study correlated the long-term medication during the intervals between episodes with the mortality and did not take into account the treatment at the index episode.

These findings require some reflection and cautious interpretation. One has to be aware that we are dealing with a naturalistic study and that the patients were not randomised into a treated and an untreated group. Furthermore, the differences may be biased by selection processes, since patients who see their doctors on a regular basis and comply with treatment over a long time period are generally regarded as being less ‘complicated’ cases and may have a lower ‘endogenous’ suicide risk than patients who lack compliance. Our analysis of the outcome of the two subgroups demonstrated that treated subjects developed more chronicity and more residual states during the intervals between episodes, which may be interpreted as an indicator of severity, e.g. that those subjects who received treatment had more persistent symptoms. Two third of bipolar patients and one third of unipolar depressives received long-term medications. The reduction of suicides is more marked in the bipolar subgroup than in the unipolar. This might be explained by the more intensive treatment.

An even more difficult question to consider is related to the type of long-term medication given. It is a weakness of this study that prospectively this treatment was not documented systematically and that we cannot give precise data on the dosage and the length of treatments. We can only stress that the treatment had to be given over a full cycle (time from one episode to the subsequent episode) or longer than 6 months after full or incomplete remission from an episode; of course, in the majority of cases the treatment lasted many years. Another weakness of the study is that the treatments were not given according to any defined criteria but the prescription was up to the treating doctor who was a psychiatrist, a GP or an internist. We subclassified the administered drugs into three categories, antidepressants, neuroleptics and lithium or combinations of them and did not consider the administration of benzodiazepines. Both unipolar and bipolar patients, who had been treated with antidepressants, showed much lower suicide rates than untreated patients. Such a correlation was also observed between antidepressants plus neuroleptics as well as this combination together with lithium, whereas lithium alone did not show a correlation. The observed standardised mortality ratios for suicide among these treated groups did not differ any more significantly from the normal population but the SMRs were still a bit higher but were based on small numbers.

These results do not prove directly that the
decrease of suicide in subjects with long-term medication was strictly caused by the medication itself. Such a conclusion could only be drawn from a well designed experimental prospective trial. But the data are suggestive for a positive drug effect and certainly raise the hypothesis of a positive effect of a long-term medication with antidepressants or of a combination of antidepressants with neuroleptics or lithium. Several studies have shown that lithium and long-term medication can decrease suicide rates (Coppen et al., 1991; Müller-Oerlinghausen et al., 1992; Müller-Oerlinghausen and Berghöfer, 1999; Ahrens et al., 1995; Felber and Kyber, 1994; Nilsson, 1995, 1999) whereas the results of one study with the antidepressant maprotiline was negative: Rouillon et al. (1992) showed a trend to an increased risk for suicide compared to placebo (small n). It may be surprising that in our study lithium alone did not correlate with a decrease of suicide mortality; but one has to be aware that the sample receiving lithium alone was rather small and that on the other hand the subsample receiving lithium plus other drugs (antidepressants or neuroleptics) had a substantially reduced suicide rate.

One might also argue that the reduction of mortality is more a consequence of self-selection for the medication and also a consequence of compliance. The Aarhus follow-up study of Brodersen et al. (2000) showed that lithium compliant patients committed significantly less suicide than lithium non-compliers. Patients treated over years with medication may also be treated better for physical disorders (cardiovascular disorders, diabetes, etc.) and therefore live longer and commit less suicide because of a continuous relationship with the doctor and better general care. We cannot rule out this possibility completely, but in this case all subgroups of medicated patients should have an equal reduction of their suicide risk, which was not the case. If one would try to explain the findings by such an unspecific therapeutic effect, then one would have to explain why so many other treatment programs failed to reduce the suicide rates, except the program of Rutz et al. (1989), which was based on systematic education of general practitioners and better pharmacotherapy, which can also consist in the administration of low dose neuroleptics, e.g. flupenthixol (Montgomery et al., 1983).

Finally, it may be surprising that antidepressants, even given to bipolar patients, were correlated so strongly with lower suicide rates. But is it really so surprising that antidepressants can reduce suicide risk if they can improve depression? Isaacson et al. (1996) found, on the basis of epidemiological data, the risk for suicide among depressed patients who were treated with antidepressants in Sweden as 141 per 100 000 person years and, among the untreated, 259 per 100 000 person years (i.e. 1.8 times higher among the untreated).

In conclusion, our findings support the administration of a long-term prophylactic medication in patients with affective disorders. It also seriously supports the conclusion that coadministration of antidepressants even in bipolars is useful. Furthermore, the positive effect of a combination of antidepressants and neuroleptics found in this study may also be of special interest in view of the rapid development of atypical neuroleptics. In this context we have to remember that the suicide risk in schizophrenics is remarkably reduced by a long-term medication with clozapine (Meltzer and Okayli, 1995; Walker et al., 1997). If we assume that suicidality is a phenomenon, which is not specific for a certain diagnosis but a manifestation of a very specific biological and psychological constellation across different diagnostic classes, it may be worthwhile to investigate further the effect of antidepressants, atypical neuroleptics and mood stabilisers on the risk of suicides. Preventing suicides is certainly a primary goal of long-term treatment.

References


Angst, F., 1998. Mortalität und Prophylaxe bei Patienten mit...
affektiven Störungen nach 34–38 Jahren Follow-up. University of Zurich, Zurich.

Angst, J., 1986. Verlauf und Ausgang affektiver und schizo- 
offene Fragen. 2. Jans Weitbrecht-Symposium, Bonn 22,

113–116.

Angst, J., Battegay, R., Pooldinger, W., 1964. Zur Methodik der
statistischen Bearbeitung des Therapieverlaufs depressiver

Angst, J., Preisig, M., 1995. Course of a clinical cohort of
unipolar, bipolar and schizoaffective patients. Results of a
Psychiatr. 146, 5–16.

Angst, J., Sellaro, R., Angst, F., 1998. Long-term outcome and
mortality of treated versus untreated bipolar and depressed
115–119.

Angst, J., Stassen, H.H., 1987. Verlaufsaspekte affektiver Psycho-
Fortschritte in der Psychosenforschung? 7. Weissenaer Schizo-
phrenie-Symposium, Bonn 1986. Schattauer, Stuttgart, New
York, pp. 145–164.

Suicide in affective and schizoaffective disorders. In: Mar-
neros, A., Tsuang, M.T. (Eds.), Affective and Schizoaffective
185.

Arato, M., Demeter, E., Röhmer, Z., Somogyi, E., 1988. Re-
gressive psychiatric assessment of 200 suicides in Budapest.

Balderessarin, R.J., Tondo, L., Hennen, J., 1999. Effects of lithium
treatment and its discontinuation on suicidal behavior in
bipolar manic-depressive disorders. J. Clin. Psychiatry 60,
77–84.

Baldwin, J.A., 1980. Schizophrenia and physical disease: A
preliminary analysis of the data from the Oxford Record

hundred cases of suicide: Clinical aspects. Br. J. Psychiatry
125, 355–373.

76, 372–380.

Black, D.W., 1998. Iowa record-linkage study: death rates in
psychiatric patients. J. Affect. Disord. 50, 277–282.

Black, D.W., Winokur, G., Mohandas, E., Woolson, R.F., Nasral-
lah, A., 1989. Does treatment influence mortality in depre-
sives? A follow-up of 1976 patients with major affective

of major affective disorder. A comparison with general popula-

Blair-West, G.W., Cantor, C.H., Mellsop, G.W., Eyeson-Annan,
M.L., 1999. Lifetime suicide risk in major depression; sex and

Down-rating lifetime suicide risk in major depression. Acta
Psychiatr. Scand. 95, 259–263.

Brent, D.A., Perper, J., Moritz, G., Allmann, C., Friend, A., Roth,
risk factors for adolescent suicide: a case-control study. J. Am.

Brodersen, A., Licht, R.W., Vestergaard, P., Olesen, A.V., Morten-
sen, P.B., 2000. Sixteen-year mortality in patients with affect-
ive disorder commenced on lithium. Br. J. Psychiatr. 176,
429–433.

Ciompi, L., Medvecka, J., 1976. Etude comparative de la mortalité
a long terme dans les maladies mentales. Schweiz Arch.

Clayton, P.J., 1983. Epidemiologic and risk factors in suicide. In:
Grinspoon, L. (Ed.), Psychiatry Update. American Psychiatric

Coppen, A., 1994. Depression as a lethal disease: prevention

Coppen, A., Standaish-Barry, H., Bailey, J., Houston, G., Silcocks,
P., Hermon, C., 1991. Does lithium reduce the mortality of

Dilsaver, S.C., Chen, Y.W., Swann, A.C, Shoaib, A.M., Kra-
jewski, K.J., 1994. Suicidality in patients with pure and
depressive mania. Am. J. Psychiatry 151, 1312–1315.


Dunne, D., Fleiss, J.L., Fieve, R.R., 1976. The course of
development of mania in patients with recurrent depression.
Am. J. Psychiatry 133, 905–908.


Fawcett, J., Scheftner, W., Hedeker, D.D., Gibbons, R., Coryell,
affective disorders: A controlled prospective study. Am. J.
Psychiatry 144, 35–40.

Felber, W., Kyber, A., 1994. Suizide und Parasuizide während
dausserhalb einer Lithiumprophylaxe. In: Muller-Oerlinghausen,

Friedman, L., Schoenbach, V.J., Kaplan, B.H., Blazer, D.G., James,
between depressive symptoms and mortality among older
patients with treatment-resistant depression. J. Gerontol. 44,
S149–S156.

The predictin of suicide: sensitivity, specificity, and predictiv-
value of a multivariate model applied to suicide among 1906
patients with affective disorders. Arch. Gen. Psychiatry 48,
418–422.

Guze, S.B., Robins, E., 1970. Suicide and primary affective

Hagnell, O., Lanke, J., Rorsman, B., 1982. Suicide and depression
in the male part of the Lundby Study. Changes over time


