Outcome of Patients With Major Depressive Disorder After Serious Suicide Attempt

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Objective: To investigate the outcome of subjects with major depressive disorder after serious suicide attempt and to examine the effect of psychotic symptoms on their outcome.

Method: The study population included all individuals aged 16 years or older in Finland who were hospitalized with *ICD-10* diagnoses of major depressive disorder and attempted suicide from 1996 to 2003 (N = 1,820). The main outcome measures were completed suicides, overall mortality, and repeated suicide attempts during drug treatment versus no treatment.

Results: During the 4-year follow-up period, 13% of patients died, 6% completed suicide, and 31% made a repeat suicide attempt. Subjects with major depression with psychotic features completed suicide more often than subjects without psychotic features during the follow-up (hazard ratio [HR] 3.32; 95% CI, 1.95–5.67). Antidepressant treatment reduced all-cause mortality by 24% (HR 0.74; 95% CI, 0.56–0.97) but did not reduce suicide mortality (HR 1.06; 95% CI, 0.71–1.58).

Conclusions: Psychotic symptoms during major depressive episode increase the risk of completed suicide after serious suicide attempt. The quality of treatment for major depression with psychotic features after attempted suicide should be improved to prevent suicide.

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Both serious suicide attempt and depressive disorder are well-known predictors of high suicide risk.[1] More than half of suicides occur in the context of depressive disorder.[2–6] A particularly high risk group for eventual suicide is mood disorder patients with a current suicide attempt.[7] Patients with major depressive disorder have about 20-fold risk of suicide[1,8,9] and about 7-fold risk of attempted suicide.[10] The risk of attempted or completed suicide in patients with psychiatric admissions is highest during the first 2 years after discharge.[6,7,10–15] Future suicidal acts among patients with major depressive episode have been associated with a history of attempted suicide, severe depression, cigarette smoking, familial and genetic factors, early-loss experiences, and comorbid alcoholism.[16,17] There are few previous studies investigating the effect of the presence of psychotic symptoms and the severity of depression on the outcomes of suicide attempters with major depressive disorder.[18,19] Furthermore, the frequency of antidepressant treatment received after hospitalization following a suicide attempt among subjects with major depressive disorder is not well known, although suicide attempters with major depression should be a high priority subgroup for treatment.[20]

The aims of the present study were to investigate the outcome of subjects with major depressive disorder following a serious suicide attempt and to examine the effect of psychotic symptoms and severity of depression on outcomes in a large, nationwide 8-year cohort. An additional aim was to examine the frequency of antidepressant treatment after the index attempt and its effect on mortality.

METHOD

Main Outcome Measures

The hazard ratio of completed suicides, overall mortality, and repeated suicide attempts during drug treatment versus no treatment was calculated by adjusting the effect of confounding variables.

Study Population and Procedures

The study was approved by the internal ethical committee of the National Public Health Institute, Helsinki, Finland. Approval was also obtained from all the institutions involved, and from the Ministry of Health and Social Welfare. The study population included all individuals in Finland who had been hospitalized with a diagnosis of suicide attempt (*International Statistical Classification of Diseases, Tenth Revision* [*ICD-10*] code X60–X84, Z72.8, or Z91.5) from January 1, 1996, to December 31, 2003, and who were diagnosed as depressed (F32 or F33) at the moment of the first (index) suicide attempt[20] (serious suicide attempt). Severity of depression was defined as mild (F32.0, F 33.0), moderate (F32.1, F33.1), severe (F32.2, F33.2), psychotic (F32.3, F33.3), or other (F32.8, F32.9, F33.8, F33.9)

Table 1. Demographic and Clinical Characteristics of Patients Included in the Study Who Were Hospitalized With a Diagnosis of Suicide Attempt and Major Depressive Disorder

Variable	Male Patients (n = 710)	Female Patients (n = 1,110)	All Patients (N = 1,820)
Age, mean ± SD, y	42.3 ± 14.2	41.4 ± 16.0	41.7 ± 15.4
Duration of index hospitalization, mean ± SD, d	6.5 ± 13.3	5.3 ± 10.8	5.8 ± 11.8
Single depressive episode (F32.0[a]), n (%)	617 (87)	933 (84)	1,550 (85)
Recurrent depressive disorder (F33.0[a]), n (%)	93 (13)	177 (16)	270 (15)
Severity of depressive disorder at the index hospitalization, n (%)			
Mild	25 (4)	63 (6)	88 (5)
Medium	136 (19)	211 (19)	347 (19)
Severe	198 (28)	279 (25)	477 (26)
Severe, psychotic	45 (6)	65 (6)	110 (6)
Other	306 (43)	492 (44)	798 (44)
Initial antidepressant treatment (in first 2 weeks), n (%)			
Total	381 (54)	668 (60)	1,049 (58)
Single episode	330 (87)	546 (82)	876 (84)
Recurrent	51 (13)	122 (18)	173 (16)
Mild	17 (4)	35 (5)	52 (5)
Medium	74 (19)	124 (19)	198 (19)
Severe	122 (32)	183 (27)	305 (29)
Severe, psychotic	27 (7)	42 (6)	69 (6)
Other	141 (37)	284 (42)	425 (41)
Initial antipsychotic treatment (in first 2 weeks), n (%)			
Total	131 (18)	207 (19)	338 (19)
Single episode	103 (79)	164 (79)	267 (79)
Recurrent	28 (21)	43 (21)	71 (21)
Mild	3 (2)	9 (4)	12 (4)
Medium	25 (19)	27 (13)	52 (15)
Severe	41 (31)	58 (28)	99 (29)
Severe, psychotic	17 (13)	25 (12)	42 (12)
Other	45 (34)	88 (43)	133 (39)

[a]*International Classification of Diseases, Tenth Revision*, code.

according to *ICD-10*. Psychotic features during index hospitalization were defined as *psychotic depression*. Only individuals at least 16 years old when the index hospitalization began were included.

The following information was obtained from the study population by register linkage via the unique personal identification codes routinely used in Finnish registers. Index hospitalization data were obtained from the National Hospital Discharge Register and included the admission and discharge dates of hospitalization and the diagnosis code. Date and cause of death were obtained from Statistics Finland. Cause of death was classified as suicide, other unnatural cause, or other cause. Data on use of antidepressant medication from a nationwide prescription register were also included. This register tracks medication purchased from a pharmacy. For convenience, *medication use* refers to repeated purchasing of medication from a pharmacy (although not all patients actually take the medication as instructed). In Finland, prescriptions for antidepressant medications are filed by the National Social Insurance Scheme. The available data included the date of purchase and the dose, stated as the international standard–defined daily dose.[21] Medication was classified according to the anatomic therapeutic chemical classification system.[22]

The following information was eventually obtained for each individual included in the study population: sex, age at index hospitalization, date and duration of index hospitalization, number of hospitalizations because of attempted suicide, and use of antipsychotic (anatomic therapeutic chemical: N05A*) or antidepressant (N06A*) medicine after the index hospitalization. Duration of drug treatment was calculated according to the purchased defined daily dose. For each individual, the follow-up was divided into periods during which the value of time-dependent variables (ie, medication and suicide attempts) was constant. Thus, the follow-up of each individual consisted of several contiguous periods, each defined with specific entry and exit times.

Data Analysis

The main outcomes of interest were suicide, all-cause death, and repeated suicide attempts during the follow-up period, with the end of follow-up as censoring time. First, we carried out univariate analysis using Poisson regression model. Next, we used Cox proportional hazards multivariate models with a counting process approach to estimate effects of baseline characteristics on outcome variables. To take into account the multiple periods for each individual, we calculated robust variance estimators based on a grouped jackknife method.[23] In all models, we used sex, age, and severity of depression at the index hospitalization as background variables. Next, in order to estimate the average causal effect of time-dependent medication, we applied marginal structural models (MSMs) approach with the Cox models.[24,25]

Marginal structural models aim to appropriately control for the effects of time-dependent confounders affected by previous treatment. This model can be used to adjust for confounding and selection bias due to measured time-varying covariates affected by exposure. We used inverse probability weights in the Cox model to estimate MSMs. Weighting creates a pseudopopulation in which the exposure is independent of the measured confounders. The pseudopopulation is the result of assignment of a weight to each participant that is, informally, proportional to the patient's probability of receiving their own exposure history. The parameters of weighted regression models, which equal the parameters of MSMs, can be used to estimate the average causal effect of exposure in the original study population. Marginal structural models assume no unmeasured confounding that is not empirically verifiable. We used stabilized weights in MSMs.[24] The numerator of weights in MSMs consisted of sex, age, and severity of depression at the index hospitalization. Denominators were sex, age, and severity of depression at the index hospitalization, time-dependent utilization of antipsychotic, time-dependent utilization of antidepressant, and time-dependent number of subsequent attempted suicides during the follow-up period.

All statistical data analyses were carried out using R software.[26]

RESULTS

The study population included 1,820 individuals (Table 1), with 7,640 cumulated person-years and a mean duration of 4.2 years' follow-up. One thousand four hundred eighty-two individuals were common with study population in Tiihonen et al.[27] During the follow-up period, 233 patients (13%) died, 106 (6%) completed suicide, and 570 (31%) made a total of 1,008 suicide attempts (Table 2). Thirty-six unnatural deaths other than suicide (2%) and 91 deaths from other causes (5%) were observed. Of the suicide attempts, 105 (6%) were violent and 1,715 (94%), nonviolent. Three (3%) of the patients who made a violent attempt had mild depressive disorder; 19 (18%), moderate depressive disorder; 55 (52%), severe depressive disorder with or without psychotic symptoms; and 28 (27%), other depressive disorder.

Table 2. All-Cause and Suicide Mortality and Incidence of Attempted Suicide After a Serious Suicide Attempt[a]

Variable	All Cause Mortality			Mortality Due to Suicide			Incidence of Subsequent Attempted Suicide		
	Deaths/Person-Years	Mortality	Relative Risk (95% CI)	Deaths/Person-Years	Suicide Mortality	Relative Risk (95% CI)	Attempts/Person-Years	Incidence	Relative Risk (95% CI)
Gender									
Male	128/2,844	0.0450	1.00 (1.00–1.00)	58/2,844	0.0204	1.00 (1.00–1.00)	358/2,761	0.1297	1.00 (1.00–1.00)
Female	105/4,796	0.0219	0.49 (0.38–0.63)	48/4,796	0.0100	0.49 (0.33–0.72)	650/4,631	0.1404	1.08 (0.95–1.23)
Time-varying antidepressant utilization									
No	129/4,188	0.0308	1.00 (1.00–1.00)	47/4,188	0.0112	1.00 (1.00–1.00)	378/4,073	0.0928	1.00 (1.00–1.00)
Yes	104/3,452	0.0301	0.98 (0.76–1.27)	59/3,452	0.0171	1.52 (1.04–2.23)	630/3,319	0.1898	2.05 (1.80–2.32)
Time-varying antipsychotic utilization									
No	177/6,161	0.0287	1.00 (1.00–1.00)	77/6,161	0.0125	1.00 (1.00–1.00)	709/5,993	0.1183	1.00 (1.00–1.00)
Yes	56/1,479	0.0379	1.32 (0.98–1.78)	29/1,479	0.0196	1.57 (1.02–2.41)	299/1,399	0.2138	1.81 (1.58–2.07)
Antidepressant during first 2 weeks									
No	102/3,369	0.0303	1.00 (1.00–1.00)	40/3,369	0.0119	1.00 (1.00–1.00)	434/3,283	0.1322	1.00 (1.00–1.00)
Yes	131/4,271	0.0307	1.01 (0.78–1.31)	66/4,271	0.0155	1.30 (0.88–1.93)	574/4,109	0.1397	1.06 (0.93–1.20)
Antipsychotic during first 2 weeks									
No	182/6,158	0.0296	1.00 (1.00–1.00)	81/6,158	0.0132	1.00 (1.00–1.00)	764/5,983	0.1277	1.00 (1.00–1.00)
Yes	51/1,482	0.0344	1.16 (0.85–1.59)	25/1,482	0.0169	1.28 (0.82–2.01)	244/1,408	0.1732	1.36 (1.17–1.57)
Duration of index hospitalization, d									
1	86/3,656	0.0235	1.00 (1.00–1.00)	38/3,656	0.0104	1.00 (1.00–1.00)	486/3,560	0.1365	1.00 (1.00–1.00)
>1–5	81/2,374	0.0341	1.45 (1.07–1.96)	34/2,374	0.0143	1.38 (0.87–2.19)	298/2,305	0.1293	0.95 (0.82–1.09)
>5	66/1,609	0.0410	1.74 (1.27–2.40)	34/1,609	0.0211	2.03 (1.28–3.23)	224/1,526	0.1468	1.08 (0.92–1.26)
Severity of the depression at index hospitalization									
Mild	9/313	0.0288	1.00 (1.00–1.00)	2/313	0.0064	1.00 (1.00–1.00)	26/307	0.0846	1.00 (1.00–1.00)
Medium	46/1,467	0.0314	1.09 (0.53–2.23)	11/1,467	0.0075	1.17 (0.26–5.29)	207/1,415	0.1463	1.73 (1.15–2.60)
Severe	68/2,022	0.0336	1.17 (0.58–2.34)	40/2,022	0.0198	3.10 (0.75–12.81)	291/1,941	0.1500	1.77 (1.19–2.65)
Severe with psychotic features	28/393	0.0712	2.48 (1.17–5.25)	19/393	0.0483	7.56 (1.76–32.45)	39/368	0.1060	1.25 (0.76–2.06)
Other	82/3,445	0.0238	0.83 (0.42–1.65)	34/3,445	0.0099	1.54 (0.37–6.43)	445/3,361	0.1324	1.56 (1.05–2.32)

[a]Number of cases, person-years, mortality and suicide attempts; relative risk values are based on univariate Poisson regression models with respect to time-varying antidepressant or antipsychotic utilization, initial 2-week antidepressant or antipsychotic utilization, duration of index hospitalization, and severity of depression at index hospitalization.

Figure 1. Cumulative Events With Respect to the First Attempted Suicide During Follow-Up: All-Cause Mortality, Suicide Mortality, and Mortality Due to Unnatural Causes or Other Causes in Patients With Major Depressive Disorder
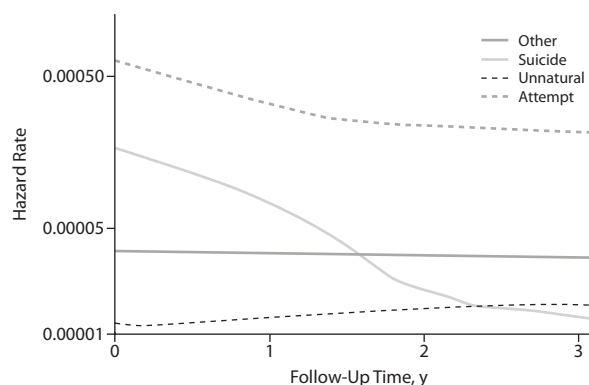

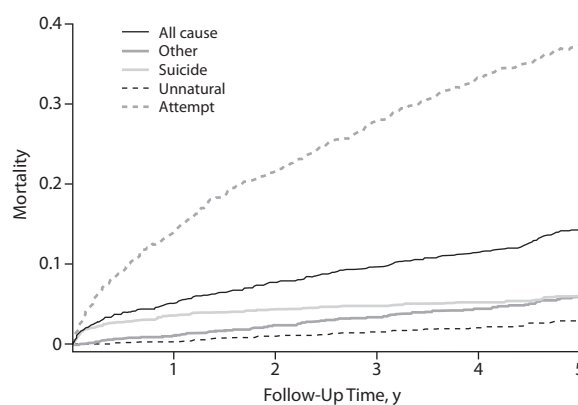Figure 2. Hazard Rate Since Start of the Follow-Up Period

Table 3. Hazard Ratio (HR) With 95% CI From Cox Models With Baseline Explanatory Variables (initial 2-week antidepressant or antipsychotic utilization, duration of index hospitalization, and severity of depression at index hospitalization)

Variable	All-Cause, HR (95% CI)	Suicide, HR (95% CI)	Attempted Suicide, HR (95% CI)
Initial antipsychotic (in first 2 weeks)			
No	(reference)	(reference)	(reference)
Yes	1.18 (0.85–1.62)	1.31 (0.84–2.06)	1.54 (1.23–1.90)
Initial antidepressant (in first 2 weeks)			
No	(reference)	(reference)	(reference)
Yes	0.74 (0.56–0.97)	1.06 (0.71–1.58)	1.80 (1.52–2.14)
Gender			
Male	(reference)	(reference)	(reference)
Female	0.49 (0.38–0.64)	0.52 (0.35–0.77)	1.07 (0.88–1.29)
Age, y			
< 20	(reference)	(reference)	(reference)
20–30	1.64 (0.48–5.55)	3.47 (0.46–26.24)	1.33 (0.86–2.07)
31–40	2.22 (0.68–7.22)	4.25 (0.58–31.05)	1.34 (0.88–2.06)
41–50	3.97 (1.24–12.71)	5.16 (0.71–37.70)	1.16 (0.75–1.79)
51–60	5.95 (1.84–19.19)	8.11 (1.10–59.73)	0.98 (0.62–1.54)
61–100	11.71 (3.65–37.59)	5.65 (0.74–43.40)	0.65 (0.39–1.07)
Index depression			
No psychotic features	(reference)	(reference)	(reference)
Psychotic features	2.00 (1.30–3.07)	3.32 (1.95–5.67)	0.67 (0.44–1.02)

The mean ± SD duration of index hospitalization was shorter among female than male patients (5.3 ± 10.8 days vs 6.5 ± 13.3 days; $P = .036$). There was no gender difference in severity of depression distribution at the index hospitalization. Mean ± SD age for severe depressive episode with psychotic symptoms was 43.2 ± 15.7 years versus 39.6 ± 15.1 years for severe depressive episode without psychotic features (not significant). Altogether, 58% of subjects received antidepressants and 19%, antipsychotics (Table 1). Women received antidepressants more often than men during the 2 weeks following the attempt (60% vs 54%, $\chi^2 = 7.27$, $P = .007$). Sixty-three percent of patients with severe depressive episode with psychotic symptoms were treated with antidepressants, while 38% were given antipsychotics. During follow-up, 35 patients (38%) received both antidepressants and antipsychotics.

Men died more often than women during the follow-up due to all causes and to suicide (Table 2). Subjects who attempted or completed suicide during the follow-up were more likely to have received antidepressants or antipsychotics during the study period. Subjects with major depression with psychotic features had higher mortality due to all causes and to suicide than those without psychotic features during the follow-up, while psychotic features had no impact on suicide attempts.

The hazard rate of suicide was high immediately after first admission and then declined to a steady level after about 2 years (Figure 1). The mortality hazard from other causes remained steady throughout the follow-up period (Figure 2).

Initial treatment with antidepressants during the first 2 weeks after admission reduced all-cause mortality but increased the risk of a further suicide attempt (Table 3). Psychotic features during the index episode increased all-cause mortality 2-fold and increased mortality due to suicide over 3-fold.

Table 4. Results From Marginal Structural Models (adjusted for age, sex, and severity of the initial depression diagnosis)

Variable	HR From Marginal Structural Model (95% CI)
All-cause mortality	
Antipsychotic	1.08 (0.86–1.61)
Antidepressant	0.75 (0.55–0.96)
Suicide or unnatural deaths	
Antipsychotic	1.34 (0.94–2.04)
Antidepressant	0.87 (0.58–1.16)
Suicides	
Antipsychotic	1.32 (0.80–1.97)
Antidepressant	1.12 (0.69–1.54)

Abbreviation: HR = hazard ratio.

The MSM of all-cause mortality gives the most reliable estimate of the causal effect of medication, showing that antidepressant treatment lowered all-cause mortality by 25% (hazard ratio [HR], 0.75; 95% CI, 0.55–0.96) during the follow-up (Table 4). Altogether, 43 deaths with cause of death I00–I99 (diseases of the circulatory system) were observed (adjusted MSM HR, 0.52; 95% CI, 0.27–0.97 for antidepressant treatment and HR, 0.80; 95% CI, 0.40–1.66 for antipsychotic treatment).

DISCUSSION

We found that psychotic symptoms during major depressive episode elevated the risk of eventual suicide after a serious suicide attempt 3-fold. Only half of hospitalized suicide attempters with depressive disorder received antidepressant treatment soon after the attempt, although this type of medication decreased overall mortality by 25%.

To our knowledge, this is the first study investigating the effect of psychotic symptoms and severe depression on the outcome of all hospitalized attempted suicide patients with depressive disorder in a large, nationwide 8-year cohort. Our cohort included follow-up data from all hospitalized suicide attempters with depressive disorder in Finland from 1996 to 2003.[20,27] In addition, we were able to investigate both repeated suicide attempts and overall deaths, including eventual suicides and violent deaths, whereas most previous outcome studies have concentrated only on fatal outcome. Because all psychiatric inpatient treatment in Finland is free of charge and there are no private psychiatric inpatient facilities, these findings are not biased by socioeconomic differences.

Overall, the accuracy of the National Hospital Discharge Register is good.[28–33] However, we cannot exclude the possibility of some underreporting of attempted suicide in the present study. Another limitation is that the diagnoses of mental disorders were not based on standardized diagnostic interview schedules but were clinical diagnoses by the physicians treating the patients. The severity of depressive disorder was assessed by the treating clinician, and the ratings "other" and "unspecified" (F32.8, F32.9, F33.8, F33.9)

covered 43% of the cases. Our finding that 6% of hospitalized suicide attempters with a diagnosis of major depressive disorder had psychotic symptoms accords with a previous finding that the lifetime prevalence of major depressive disorder with psychotic features is 0.35%.[33] However, the association of treatment with suicide is difficult to interpret as it is likely that suicide is more frequent among most symptomatic patients and that they are more likely to get treatment than those with less severe cases.

In the present study, the risk of suicide was 6% and the risk of repeated suicide attempt was 31% among hospitalized suicide attempters with depressive disorder over almost 4 years of follow-up. A systematic review has estimated that 16% of all suicide attempters repeat their attempt and 2% commit suicide within 1 year of nonfatal suicidal behavior.[34] After more than 9 years' follow-up of attempted suicide in observational and experimental studies including all suicide attempters, around 7% commit suicide.[34] Our cohort was a high-risk group for eventual suicide because of attempted suicide's leading to both hospitalization and major depressive disorder. General mortality and suicide rate in severe depression have been found to remain elevated in over 15–42 years of follow-up.[35,36] In our study, the risk of suicide was highest just after first admission and declined over the 2 years following admission in accordance with previous studies.[6,7,10–15] Moreover, although the risk of attempted suicide was highest just after first admission, it remained elevated throughout the follow-up. Psychotic features associated with major depression at hospitalization increased both all-cause mortality and suicide mortality, but this increase was not associated with repeated attempts. One reason for seemingly low risk of attempted suicides in psychotic patients is that their risk of death during follow-up is high, which leads to underestimation of attempted suicides, because after death it is not possible to have attempted suicide.

Mortality due to suicides and all-cause mortality were associated in univariate analyses with male gender, severe depressive episode with psychotic features, and longer hospital stay. The finding that longer hospital stay was associated with higher suicide risk is explained by a longer period of hospital treatment for psychotic depression than for depression without psychotic features. Mortality due to suicide was associated with antidepressant and antipsychotic utilization. This finding might be explained by the fact that subjects with more severe disorder are treated more rigorously. Suicide attempts were associated with moderate or severe depressive disorder and antidepressant and antipsychotic utilization, whereas psychotic features, longer hospital stay, or male gender were not associated with suicide attempts in univariate analyses. In other words, the risk factors associated with suicide attempts and completed suicides seemed to be somewhat different but overlapping.

All-cause mortality and mortality due to suicides were independently associated with male gender. A gender difference in suicide risk was expected and is well known in

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suicidology. As expected, mortality due to suicides was independently associated with the age group 51–60 years, whereas all-cause mortality was predicted by older age after adjusting for possible confounding factors. Both completed suicide and all-cause mortality were predicted by psychotic depression. Few previous studies[18,19] have investigated the effect of psychotic symptoms on mortality among subjects with major depressive disorder. None of these studies have examined the effect of psychotic symptoms on outcome after serious suicide attempt. In previous studies involving unipolar patients[37] and unipolar and bipolar affective patients,[38] those with and without psychotic symptoms had a similar risk of suicide, although these patients had not recently been hospitalized because of a suicide attempt. However, the risk for relapse of depressive episode leading to readmission was greater for patients with rather than without psychotic symptoms.[37] Moreover, severity of depression has been found to increase the risk of relapse and of suicide.[39,40]

We found that less than two-thirds of patients with psychotic depression received antidepressants after the index episode, although current use of antidepressant medication was associated with markedly decreased all-cause mortality. Furthermore, less than half of patients with psychotic depression received antipsychotics. It has been previously reported that both suicide attempters[41,42] and completers[43,44] with major depression are undertreated. Several recent studies have found an inverse correlation between the use of antidepressants and suicidal behavior.[45–51] The finding that antidepressant medication was associated with markedly decreased all-cause mortality accords with research indicating that antidepressant treatment may reduce cardiovascular mortality,[52] which may explain the finding. In line with our findings, previous studies have found a reduction of 30%–40% in total mortality among patients using SSRIs versus those not using antidepressants.[27,52] Repeated suicide attempts during follow-up were not associated with psychotic features at intake but were independently associated with antidepressant and antipsychotic utilization. This may be explained by an elevated risk of intoxication due to easy availability of means (ie, medication) resulting in an increase in nonfatal suicidal behavior and a decrease in more violent and fatal suicide methods.

In conclusion, psychotic symptoms during major depressive episode following a serious suicide attempt increase the risk of completed suicide. The quality of treatment for major depression with psychotic features after attempted suicide should be improved to prevent suicide.

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