ORIGINAL ARTICLE

Antidepressants and the Risk of Suicide, Attempted Suicide, and Overall Mortality in a Nationwide Cohort

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Background: It is unknown if antidepressant treatment is associated with either increased or decreased risk of suicide.

Objective: To estimate the risk of suicide, attempted suicide, and overall mortality during antidepressant treatments in a real-life setting with high statistical power.

Design and Setting: A cohort study in which all subjects without psychosis, hospitalized because of a suicide attempt from January 1, 1997, to December 31, 2003, in Finland, were followed up through a nationwide computerized database.

Participants: A total of 15 390 patients with a mean follow-up of 3.4 years.

Main Outcome Measures: The propensity score–adjusted relative risks (RRs) during monotherapy with the most frequently used antidepressants compared with no antidepressant treatment.

Results: In the entire cohort, fluoxetine use was associated with the lowest risk (RR, 0.52; 95% confidence interval [CI], 0.30-0.93), and venlafaxine hydrochloride use with the highest risk (RR, 1.61; 95% CI, 1.01-2.57), of suicide. A substantially lower mortality was observed during selective serotonin reuptake inhibitor use (RR, 0.59; 95% CI, 0.49-0.71; $P<.001$), and this was attributable to a decrease in cardiovascular- and cerebrovascular-related deaths (RR, 0.42; 95% CI, 0.24-0.71; $P=.001$). Among subjects who had ever used any antidepressant, the current use of medication was associated with a markedly increased risk of attempted suicide (39%, $P<.001$), but also with a markedly decreased risk of completed suicide (–32%, $P=.002$) and mortality (–49%, $P<.001$), when compared with no current use of medication. The results for subjects aged 10 to 19 years were basically the same as those in the total population, except for an increased risk of death with paroxetine hydrochloride use (RR, 5.44; 95% CI, 2.15-13.70; $P<.001$).

Conclusions: Among suicidal subjects who had ever used antidepressants, the current use of any antidepressant was associated with a markedly increased risk of attempted suicide and, at the same time, with a markedly decreased risk of completed suicide and death. Lower mortality was attributable to a decrease in cardiovascular- and cerebrovascular-related deaths during selective serotonin reuptake inhibitor use.

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THE USE OF ANTIDEPRESSANTS and the risk of suicidal behavior have been under widespread public discussion.[1-5] The greatest concern has been the putative causal relationship between selective serotonin reuptake inhibitor (SSRI) treatment and increased risk of suicide among children and adolescents. Major depression is the most important medical condition that exists as a risk factor for suicidal behavior, and the role of antidepressants in suicide prevention is a major public health issue. Despite extensive research, it has not been possible to demonstrate that the use of any antidepressant medication decreases the risk of suicide. Although several ecological studies[6-9] have shown an inverse correlation between the use of novel antidepressants and suicide mortality, large meta-analyses[10-12] of randomized controlled trials (RCTs) have indicated a trend suggesting that patients who receive active medication may have a higher risk of suicidal behavior than patients receiving placebo. Moreover, Fergusson et al[13] recently observed a significant increase in the risk of suicide attempts among patients receiving SSRIs vs placebo. One possible rea-

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son for this apparent discrepancy between observational correlation studies and meta-analyses based on RCTs might be that antidepressants may increase nonfatal suicidal behavior and, at the same time, decrease fatal suicidal behavior. Because suicidal patients are usually excluded from RCTs, and the number of subjects is relatively small, to our knowledge, no effects from antidepressant treatment on fatal suicidal behavior have been detected in RCTs. This is explained by the fact that suicide is a relatively rare phenomenon and, therefore, an effective study population should include tens of thousands of patients and follow-up times should be up to several years to achieve a sufficient level of statistical power that can properly investigate a putative link between antidepressants and the risk of suicide. One possible way to overcome this obstacle is to study high-risk populations in which suicidal behavior is more common. Because previous suicide attempts are the most important risk factor for predicting suicide,[14] a large cohort of suicidal patients would be an obvious choice to investigate the association between antidepressant treatment and the risk of suicide. However, to our knowledge, no such studies have been published. It is not known if antidepressant treatment is associated with either an increased or a decreased risk of suicide.

In Finland, it is possible to identify all subjects treated in a hospital since 1967 by using the National Hospital Discharge Register, and the accuracy of the National Hospital Discharge Register data is very good.[15-18] Information on mortality and cause of death is recorded by Statistics Finland, and all reimbursed medication prescriptions purchased from a pharmacy are registered by the Social Insurance Institution of Finland, which covers all patients who are alive and residing in Finland. The aim of this study was to investigate, with high statistical power in a nationwide cohort of suicidal subjects, how the risk of suicide, severe suicide attempts, and mortality differs between subjects receiving SSRIs, tricyclic antidepressants (TCAs), or serotonergic-noradrenergic antidepressants (SNAs) vs no antidepressant treatment.

METHODS

MAIN OUTCOME MEASURES

The relative risk (RR) of completed suicides, suicide attempts leading to hospitalization, and overall mortality during TCA (amitriptyline or doxepin hydrochloride), SSRI (fluoxetine, citalopram hydrobromide, paroxetine hydrochloride, sertraline, or fluvoxamine maleate), and SNA (mianserin hydrochloride, mirtazapine, or venlafaxine hydrochloride) treatment vs no antidepressant use was calculated by adjusting the effect of confounding variables.

STUDY POPULATION AND PROCEDURES

No ethical committee approval was obtained (because this was a register-based study). Approval was obtained from all institutions involved, and from the Ministry of Health and Social Welfare. The study population included all individuals in Finland who were hospitalized with a diagnosis of suicide attempt (*International Statistical Classification of Diseases, 10th Revision* code X60-X84, Z72.8, or Z91.5) from January 1, 1997, to December 31, 2003 (the first hospital treatment period was considered as the index period). These patients had no hospitalization registered in the National Hospital Discharge Register with a psychosis diagnosis (*International Statistical Classification of Diseases, 10th Revision* code F20-F29 or F30-F31), and were at least 10 years old when the index hospitalization began.

The following information was obtained from the study population by register linkage through unique personal identification codes, which are routinely used in Finnish registers. Index hospitalization data were obtained from the National Hospital Discharge Register. These data included the admission and discharge dates of hospitalization and the diagnosis code. Date and cause of death were obtained from Statistics Finland. Data on use of antidepressant medication from a nationwide prescription register were also included. This register tracks medication that has been purchased from a pharmacy. For convenience, "medication use" refers to repeated purchasing of medication from a pharmacy (although not all patients who have purchased medication actually take the medication as instructed). In Finland, prescriptions for antidepressant medications are filed by the National Social Insurance Scheme. The available data contained information on the day of purchase and dose, stated as the international standard daily defined dose.[19] The medication was classified according to the anatomic-therapeutic-chemical classification system.[20]

The following information was eventually obtained for each individual in the study population: sex, age at the index hospitalization (10-14, 15-19, 20-29, 30-64, or >65 years), geographical location (22 hospital districts covering the whole country), number of antidepressant prescriptions during the year before the index date (0, 1-2, or >2), number of severe suicide attempts leading to hospitalizations during the 5 years before the index hospitalization (0, 1, 2, 3-4, or >4), date of the index hospitalization, number of hospitalizations because of attempted suicide (1, 2, 3, 4-6, or >6), and use of antidepressant medications after the index hospitalization. The duration of the antidepressant treatment was calculated according to the purchased daily defined dose.[21] The following classification was used. The 10 most frequently used substances (amitriptyline, doxepin, fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, mianserin, mirtazapine, and venlafaxine) were determined, and individuals who used only 1 drug category were assigned to the respective group. Mixed use (ie, several antidepressant medications) or rarely used drugs were assigned to a separate group ("other"), and no use of medications composed a separate group. The hazard of suicide, suicide attempts, and mortality during the use of TCAs (amitriptyline or doxepin), SSRIs (fluoxetine, citalopram, paroxetine, sertraline, or fluvoxamine), and SNAs (mianserin, mirtazapine, or venlafaxine) or other antidepressants was compared with the hazard during no antidepressant use, by taking into account the effect of the background variables of each individual. For each individual, the follow-up was cut into periods, in which the value of time-dependent variables (ie, antidepressant 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

Cox proportional hazards analyses with a counting process approach[22] were conducted using the outcome variables previously mentioned, by using the end of follow-up as a censoring time. To take into account the fact that there were multiple periods for one individual, we calculated the robust variance estimators based on a grouped jackknife method.[22] Because those

Table 1. Baseline Characteristics and Histories of Antidepressant Use and Severe Suicide Attempts Leading to Hospitalization Before the Index Suicide Attempt (Before the Start of Follow-up)*

Variable	All Participants	Participants According to Antidepressant Use During Follow-up		*P* Value
		None	Any	
Male-female ratio	7466:7924	3936:3451	3530:4473	<.001
Age, y	38.8 ± 15.5	38.5 ± 16.6	39.1 ± 14.4	.008
No. of purchased antidepressant prescriptions during the year before follow-up	0.41 ± 0.74	0.28 ± 0.62	0.54 ± 0.81	<.001
No. of suicide attempts during the 5 years before follow-up	0.12 ± 0.63	0.03 ± 0.23	0.20 ± 0.84	<.001

*Data are given as mean ± SD unless otherwise indicated.

Table 2. Data for Suicides, Suicide Attempts, and Mortality

Variable	Person-Years	No. of Suicides	Suicide RR (95% CI)*	No. of Suicide Attempts	Suicide Attempts RR (95% CI)*	No. of Deaths	Total Mortality RR (95% CI)*
Sex							
Male	24 687	385	1.00	3410	1.00	1021	1.00
Female	27 900	217	0.50 (0.42-0.59)	3726	0.97 (0.92-1.01)	562	0.49 (0.44-0.54)
Age, y							
10-14	978	2	1.00	58	1.00	2	1.00
15-19	4611	26	2.76 (0.66-11.62)	446	1.63 (1.24-2.15)	42	4.46 (1.08-18.41)
20-29	11 296	112	4.85 (1.20-19.63)	1500	2.24 (1.72-2.91)	181	7.84 (1.95-31.58)
30-64	33 245	422	6.21 (1.55-24.91)	4879	2.48 (1.91-3.21)	1046	15.39 (3.84-61.62)
65-100	2457	40	7.96 (1.92-32.94)	253	1.74 (1.31-2.31)	312	62.10 (15.46-249.40)
No. of suicide attempts before the index hospitalization							
0	40 776	337	1.00	4243	1.00	1062	1.00
1	8009	171	2.58 (2.15-3.11)	1382	1.66 (1.56-1.76)	356	1.71 (1.51-1.92)
2	2172	45	2.51 (1.84-3.42)	641	2.84 (2.61-3.08)	83	1.47 (1.17-1.83)
3-4	1374	39	3.43 (2.47-4.78)	627	4.39 (4.03-4.77)	62	1.73 (1.34-2.24)
≥5	256	10	4.73 (2.52-8.87)	243	9.13 (8.02-10.39)	20	3.00 (1.93-4.67)
Multiple antidepressant medications							
No	49 599	542	1.00	6332	1.00	1476	1.00
Yes	2988	60	1.84 (1.41-2.40)	804	2.11 (1.96-2.27)	107	1.20 (0.99-1.46)
No. of previous purchased antidepressant prescriptions							
0	37 099	351	1.00	4095	1.00	1048	1.00
1	11 105	158	1.50 (1.25-1.81)	1998	1.63 (1.55-1.72)	372	1.19 (1.05-1.34)
2	3368	64	2.01 (1.54-2.62)	765	2.06 (1.91-2.22)	116	1.22 (1.01-1.48)
3-8	1015	29	3.02 (2.07-4.41)	278	2.48 (2.20-2.80)	47	1.64 (1.22-2.20)

Abbreviations: CI, confidence interval; RR, relative risk.
*The CIs are based on univariate Poisson regression models.

patients who never used an antidepressant during follow-up may differ from those who did, we also analyzed the risk of attempted suicide, completed suicide, and death among patients who had never used antidepressants, those who had stopped using medication, and those who were using medication. This analysis is analogous to that used in the Million Women Study.[23]

In all models, we used sex, age, number of purchased antidepressant prescriptions during the year before the index date, use of multiple antidepressant medications, number of severe suicide attempts leading to hospitalization during the 5 years before the index hospitalization, and number of subsequent hospitalizations because of suicide attempts as background variables. In all, the model's hospital district was used as stratum, with its own baseline hazard. We estimated the hazards ratio for the medication groups by using 2 different sets of models: 1 with quintiles of propensity scores[24] as an additional background variable and 1 without a propensity score adjustment. The propensity scores for each medication group were calculated using sex, age, number of previous antidepressant prescriptions, and number of previous suicide attempts as explanatory variables. All statistical data analyses were carried out using R software.[25]

RESULTS

STUDY COHORT

The entire cohort included 15 390 patients (7466 males and 7924 females). A total of 602 suicides, 7136 suicide

attempts leading to hospitalization, and 1583 deaths were recorded during the follow-up (mean, 3.4 years). **Table 1** shows the sociodemographic and clinical data of patients with vs those without antidepressant use during follow-up, and the relative effect of background variables on the risk of suicides, suicide attempts, and mortality is shown in **Table 2**. The number of previous suicide attempts was the strongest predictor of suicide attempt, and age was the strongest predictor of death and suicide.

SUICIDES

The risks of suicide associated with the use of each type of TCA, SSRI, and SNA vs no antidepressant use are shown in **Figure 1** and **Table 3**. The adjusted RR for suicide with the use of any antidepressant vs no use was 0.91. Selective serotonin reuptake inhibitor use was associated with a slightly lower, and SNA use with a slightly higher, risk of suicide than no antidepressant use, but these differences were not statistically significant. Fluoxetine use was associated with significantly decreased risk, and venlafaxine use with increased risk, of suicide. In the subpopulation of subjects aged 10 to 19 years, 28 suicides were recorded (7 during any antidepressant use and 21 during no antidepressant use) (RR, 1.33; 95% confidence interval [CI], 0.50-3.51). No significant differences ($P>.18$) were observed between the antidepressant groups (TCA, SSRI, and SNA) or specific antidepressants vs no use.

SUICIDE ATTEMPTS

The RR of suicide attempts leading to hospitalization was markedly increased during the use of all antidepressants when compared with no antidepressant use (**Figure 2** and **Table 4**). The results among the subgroup of subjects aged 10 to 19 years indicated a slightly higher risk increase than in the total population during the use of SSRIs (**Figure 3** and **Table 5**).

TOTAL MORTALITY

Mortality was substantially (31%-41%) lower during the use of all antidepressants in the group comparison (TCA, SSRI, or SNA vs no antidepressant use), and the RR for the use of any antidepressant (vs no antidepressant use) was 0.64, corresponding to a population-attributable fraction of 12%. In the analysis of specific medications, fluoxetine, citalopram, sertraline, mianserin, and mirtazapine use differed significantly from the mortality during no antidepressant use (**Figure 4** and **Table 6**). Only 44 deaths were detected among subjects aged 10 to 19 years, and no significant differences were observed between antidepressant use and no use, except for paroxetine (RR, 5.44; 95% CI, 2.15-13.73; $P<.001$) (4 deaths per 99 person-years). The causes of death during paroxetine use were suicide (n=1), drowning (n=1), and unintentional injuries (n=2). Also, fluvoxamine (RR, 10.13; 95% CI, 2.14-47.95) was associated with an increased risk of death, but this was based on only 1 death during 45 person-years.

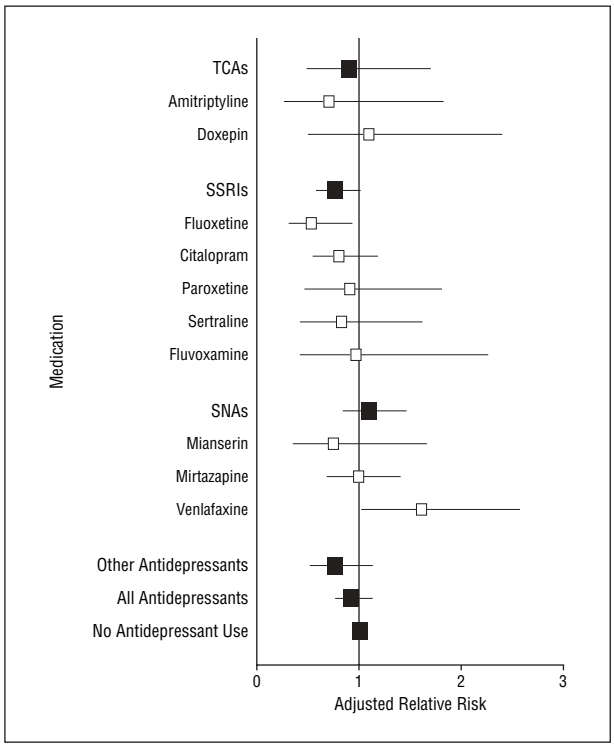

Figure 1. Relative risk and 95% confidence interval of suicides obtained by using medication as a time-dependent variable. The relative risks were adjusted with the propensity score method, and by including sex, age, geographical location (as strata), number of suicide attempts before the index hospitalization, number of suicide attempts during follow-up, use of multiple antidepressant medications, and number of purchased antidepressant prescriptions during the previous year in the model. SNA indicates serotonergic-noradrenergic antidepressant; SSRI, selective serotonin reuptake inhibitor; and TCA, tricyclic antidepressant. Citalopram was given as citalopram hydrobromide; doxepin, as doxepin hydrochloride; fluvoxamine, as fluvoxamine maleate; mianserin, as mianserin hydrochloride; paroxetine, as paroxetine hydrochloride; and venlafaxine, as venlafaxine hydrochloride.

The risk of death during antidepressant use vs no use was further studied in a secondary analysis on the causes of death by analyzing mortality in the 4 most frequent categories (unintentional injuries and violence, n=825; diseases of the circulatory system, n=256; neoplasms, n=97; and diseases of the respiratory system, n=49).[26] Antidepressant medication (any medication vs no medication) was associated with a significantly lower mortality in the category of diseases of the circulatory system (RR, 0.48; 95% CI, 0.34-0.68; $P=.002$), but not in other categories. Selective serotonin reuptake inhibitor use was associated with substantially decreased risk of all cardiovascular- and cerebrovascular-related deaths (RR, 0.42; 95% CI, 0.24-0.71; $P=.001$) (RR for the risk of cardiovascular-related death, 0.37 [95% CI, 0.17-0.78]; and RR for the risk of cerebrovascular-related death, 0.13 [95% CI, 0.02-1.06]). Serotonergic-noradrenergic antidepressant use was associated with a borderline significant decrease of all cardiovascular- and cerebrovascular-related deaths (RR, 0.53; 95% CI, 0.29-0.98; $P=.043$). No statistically significant ($P>.23$) effects were observed for any other class of antidepressants or causes of deaths.

Table 3. Data for Suicides Obtained by Using Medication as a Time-Dependent Variable*

Medication	No. of Person-Years	No. of Suicides	Incidence per 1000 Person-Years	RR (95% CI)		*P* Value
				Crude	Adjusted	
TCAs	923	12	13.0	1.14 (0.64-2.02)	0.90 (0.48-1.70)	.76
Amitriptyline	469	5	10.7	0.93 (0.89-2.25)	0.69 (0.26-1.83)	.46
Doxepin hydrochloride	454	7	15.4	1.35 (0.64-2.85)	1.09 (0.49-2.39)	.84
SSRIs	6946	66	9.5	0.81 (0.63-1.05)	0.76 (0.57-1.01)	.06
Fluoxetine	2081	14	6.7	0.58 (0.34-0.98)	0.52 (0.30-0.93)	.03
Citalopram hydrobromide	2752	29	10.5	0.92 (0.63-1.33)	0.80 (0.54-1.19)	.26
Paroxetine hydrochloride	845	9	10.7	0.93 (0.48-1.80)	0.90 (0.45-1.81)	.78
Sertraline	850	9	10.6	0.92 (0.48-1.78)	0.82 (0.41-1.61)	.56
Fluvoxamine maleate	418	5	12.0	1.04 (0.43-2.52)	0.95 (0.40-2.26)	.90
SNAs	3736	65	17.4	1.58 (1.22-2.05)	1.09 (0.82-1.47)	.54
Mianserin hydrochloride	600	7	11.7	1.02 (0.48-2.15)	0.74 (0.33-1.65)	.46
Mirtazapine	2113	35	16.6	1.47 (1.05-2.07)	0.98 (0.68-1.41)	.91
Venlafaxine hydrochloride	1022	23	22.5	2.00 (1.32-3.04)	1.61 (1.01-2.57)	.04
Other antidepressants	4146	55	13.3	1.18 (0.89-1.55)	0.76 (0.51-1.13)	.18
All antidepressants	15 751	198	12.6	1.15 (0.97-1.36)	0.91 (0.75-1.11)	.36
No antidepressant use	36 836	404	11.0	1.00	1.00	NA

Abbreviations: CI, confidence interval; NA, data not applicable; RR, relative risk; SNA, serotonergic-noradrenergic antidepressant; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

*The RRs were adjusted with the propensity score method, and by including sex, age, geographical location (as strata), number of suicide attempts before the index hospitalization, number of suicide attempts during follow-up, use of multiple antidepressant medications, and number of purchased antidepressant prescriptions during the previous year in the model.

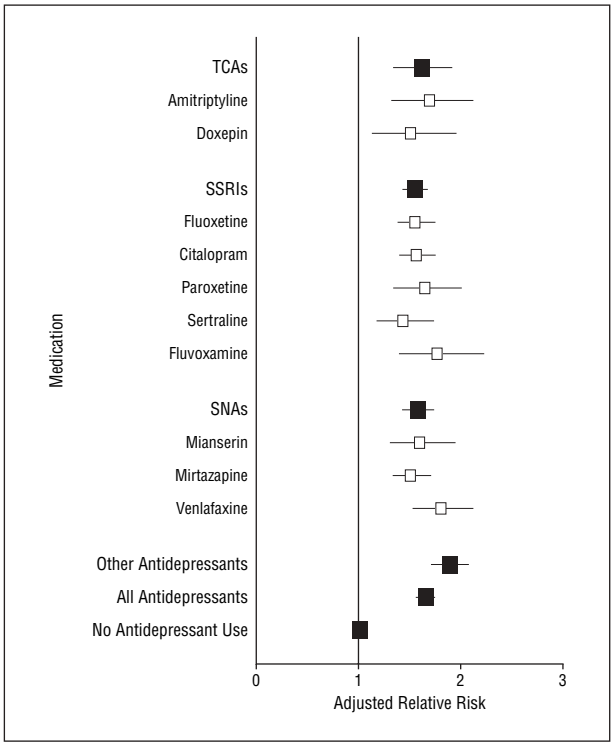

Figure 2. Relative risk and 95% confidence interval of suicide attempts obtained by using medication as a time-dependent variable. The relative risks were adjusted as explained in the legend to Figure 1. Abbreviations and complete drug names are also given in the legend to Figure 1.

ANALYSIS OF NEVER VS EVER USE AND CURRENT VS PREVIOUS USE OF ANTIDEPRESSANTS

Table 7 shows the risk of suicide, attempted suicide, and mortality among patients who had not used antidepressant medication vs those who had used any antidepressant medication, and the comparison between current vs previous use of medication. Among patients who had ever used any antidepressant, the current use of medication was associated with a markedly increased risk of attempted suicide (39%, $P<.001$), but, at the same time, also with a markedly decreased risk of completed suicide (–32%, $P=.002$) and mortality (–49%, $P<.001$) when compared with no current use of medication. The adjusted RR of cardiovascular-related death was 1.91 (95% CI, 1.38-2.65) during no current use of an antidepressant and 0.60 (95% CI, 0.42-0.86) during current use of an antidepressant, when compared with patients who had never used medication. In the comparison of current vs no current use, current use of antidepressants was associated with 68% lower cardiovascular- and cerebrovascular-related mortality ($P<.001$).

COMMENT

Our results indicate that in a comprehensive nationwide suicidal patient population (1) risk of suicide attempts is definitely increased during all antidepressant treatments when compared with no antidepressant use; (2) the use of antidepressants is not associated with an increased risk of suicide; (3) antidepressant and, especially, SSRI use is associated with a marked reduction in total mortality, mostly attributable to a decrease in cardiovascular-related deaths; and (4) among subjects who had ever used any antidepressant, the current use of medication was associated with markedly increased risk of attempted suicide, but also with markedly decreased risk of completed suicide and mortality when compared with no current use of medication. To our knowledge, no solid evidence has been previously reported on any of these

Table 4. Data for Suicide Attempts Obtained by Using Medication as a Time-Dependent Variable*

Medication	No. of Person-Years	No. of Suicide Attempts	Incidence per 1000 Person-Years	RR (95% CI)		*P* Value
				Crude	Adjusted	
TCAs	923	159	172.3	1.28 (1.09-1.49)	1.60 (1.33-1.91)	<.001
Amitriptyline	469	89	189.8	1.40 (1.14-1.73)	1.67 (1.31-2.11)	<.001
Doxepin hydrochloride	454	70	154.2	1.14 (0.90-1.44)	1.49 (1.13-1.95)	.004
SSRIs	6946	1224	176.2	1.36 (1.28-1.48)	1.54 (1.42-1.66)	<.001
Fluoxetine	2081	394	189.3	1.42 (1.28-1.57)	1.54 (1.37-1.74)	<.001
Citalopram hydrobromide	2752	478	173.7	1.30 (1.19-1.43)	1.55 (1.38-1.74)	<.001
Paroxetine hydrochloride	845	139	164.5	1.22 (1.03-1.44)	1.63 (1.33-1.99)	<.001
Sertraline	850	126	148.2	1.09 (0.92-1.30)	1.41 (1.15-1.72)	.002
Fluvoxamine maleate	418	87	207.9	1.54 (1.25-1.90)	1.75 (1.38-2.22)	<.001
SNAs	3736	663	177.5	1.34 (1.24-1.45)	1.57 (1.42-1.73)	<.001
Mianserin hydrochloride	600	107	178.2	1.32 (1.09-1.60)	1.58 (1.29-1.94)	<.001
Mirtazapine	2113	362	171.3	1.28 (1.15-1.42)	1.50 (1.32-1.70)	<.001
Venlafaxine hydrochloride	1022	194	189.8	1.41 (1.22-1.63)	1.79 (1.52-2.11)	<.001
Other antidepressants	4146	1178	284.2	2.31 (2.17-2.46)	1.87 (1.70-2.06)	<.001
All antidepressants	15 751	3224	204.7	1.93 (1.84-2.20)	1.64 (1.54-1.74)	<.001
No antidepressant use	36 836	3912	106.2	1.00	1.00	NA

Abbreviations: See Table 3.
*The RRs were adjusted as explained in the second footnote to Table 3.

issues, partly because deaths and severe suicidal behavior are too infrequent incidents to be detected in sufficient numbers for statistical analyses. Our database included follow-up data from 100% of all hospital-treated survivors of attempted suicide in Finland from 1997 to 2003. Thus, it was possible to detect more than 600 suicides and 7000 severe suicide attempts leading to hospitalization. Both of these numbers are more than 5-fold greater than the figures of any previous studies.[10,12-14,27] Our results suggest that the discrepancy between RCTs[10-12] (showing an increase in suicide attempts) and observational studies[6-9] (showing a decrease in completed suicides) can be explained by the fact that antidepressant use is associated with an increased risk of nonfatal suicidal behavior and, at the same time, a decreased risk of fatal suicidal behavior. This opposite type of effect on fatal vs nonfatal suicidal behavior may be explained by an increased risk of intoxication because of easy availability of means (antidepressant medication), resulting in an increase in nonfatal suicidal behavior, and by a decrease in the incidence of violent and more fatal methods of suicide attempts, such as hanging and shooting.

It is not possible to adjust all confounding factors in a nonrandomized observational study. Our results show that previous suicide attempts and antidepressant treatment were the most important background variables contributing to the risk of forthcoming suicidal behavior, as previously observed by Jick et al.[14] In our study, it was not possible to obtain information on psychiatric diagnoses (except a psychosis diagnosis, which was an exclusion criterion). The main results were not affected by adjustment of these and numerous other background variables (ie, the crude and adjusted RRs were basically the same, except for the risk of suicide during SNA use and for the risk of death during TCA and SNA use). However, it is possible that despite an adjustment of the most important confounding factors,[14] there may be the possibility of residual bias, which could contribute to an increased risk of suicide attempts among patients with medication. To minimize the residual confounding caused by patient selection, we analyzed the risk of attempted suicide, completed suicide, and death (Table 7) among patients who had never used antidepressants, those who had

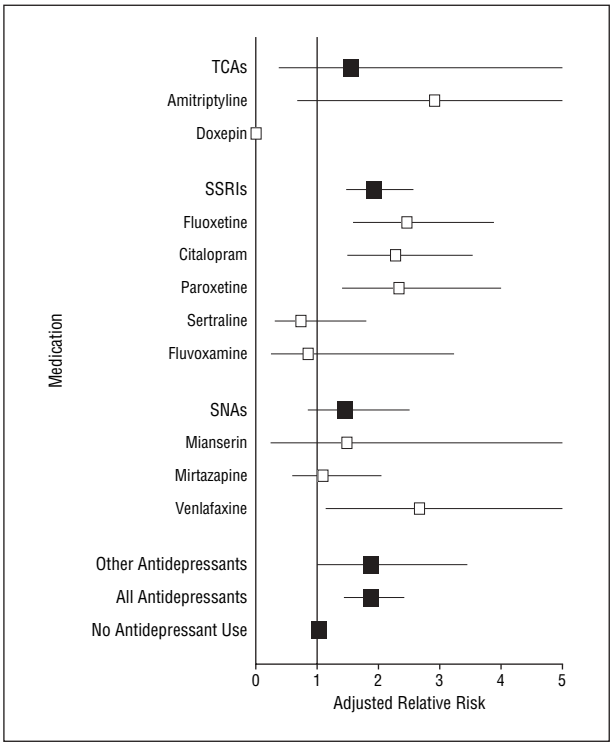

Figure 3. Relative risk and 95% confidence interval of suicide attempts among subjects aged 10 to 19 years obtained by using medication as a time-dependent variable. The relative risks were adjusted as explained in the legend to Figure 1. Because of the restricted scale of the figure, the upper ends of the confidence intervals for TCAs, amitriptyline, mianserin, and venlafaxine are not shown. Abbreviations and complete drug names are given in the legend to Figure 1.

Table 5. Data for Suicide Attempts Among Subjects Aged 10 to 19 Years Only, Obtained by Using Medication as a Time-Dependent Variable*

Medication	No. of Person-Years	No. of Suicide Attempts	Incidence per 1000 Person-Years	RR (95% CI)		*P* Value
				Crude	Adjusted	
TCAs	9	2	227.0	2.52 (0.63-10.12)	1.53 (0.34-6.86)	.15
Amitriptyline	3	2	588.9	6.55 (1.63-26.27)	2.90 (0.65-13.00)	.16
Doxepin hydrochloride	5	0	0	0	0	NA
SSRIs	535	70	130.9	1.53 (1.19-1.96)	1.91 (1.43-2.55)	<.001
Fluoxetine	132	21	159.2	1.80 (1.16-2.78)	2.44 (1.54-3.86)	<.001
Citalopram hydrobromide	174	27	155.5	1.77 (1.20-2.60)	2.27 (1.47-3.52)	<.001
Paroxetine hydrochloride	99	16	161.4	1.82 (1.10-2.99)	2.32 (1.36-3.99)	.002
Sertraline	85	4	46.8	0.52 (0.19-1.38)	0.71 (0.28-1.80)	.47
Fluvoxamine maleate	45	2	44.9	0.50 (0.12-1.99)	0.82 (0.21-3.23)	.78
SNAs	172	22	128.1	1.44 (0.94-2.21)	1.43 (0.82-2.51)	.02
Mianserin hydrochloride	10	1	97.9	1.09 (0.15-7.72)	1.46 (0.17-12.86)	.73
Mirtazapine	108	11	101.9	1.13 (0.62-2.06)	1.06 (0.56-2.01)	.85
Venlafaxine hydrochloride	54	10	186.6	2.09 (1.12-3.91)	2.65 (1.14-6.20)	.02
Other antidepressants	106	15	141.1	1.58 (0.95-2.65)	1.82 (0.97-3.43)	.06
All antidepressants	821	109	132.7	1.60 (1.30-1.98)	1.84 (1.40-2.42)	<.001
No antidepressant use	4767	395	82.9	1.00	1.00	NA

Abbreviations: See Table 3.
*The RRs were adjusted as explained in the second footnote to Table 3.

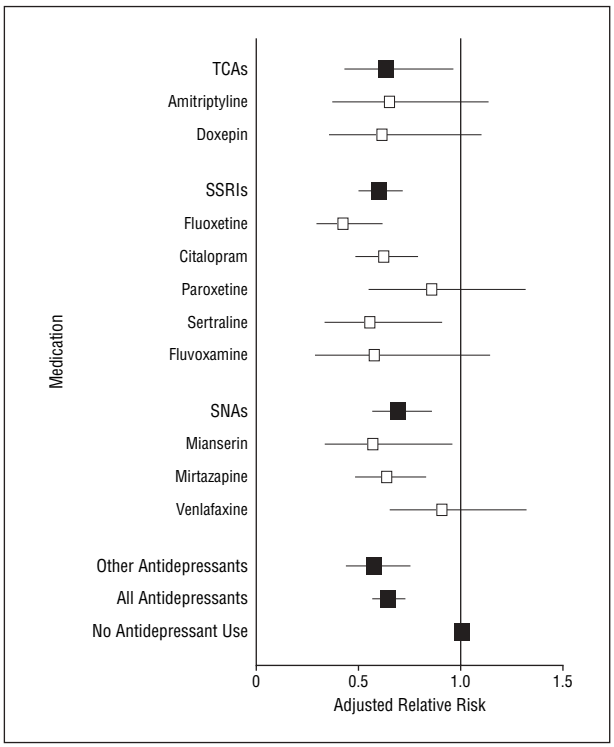

Figure 4. Relative risk and 95% confidence interval of total mortality obtained by using medication as a time-dependent variable. The relative risks were adjusted as explained in the legend to Figure 1. Abbreviations and complete drug names are also given in the legend to Figure 1.

stopped using medication, and those who were using medication. This analysis is analogous to that used in the Million Women Study[23] and an article[28] demonstrating that lithium use was associated with a decreased risk of suicide. While the lithium study by Kessing et al[28] looked at the correlation between the number of purchased lithium prescriptions and the incidence of suicide (eg, with the possibility that a patient could have purchased 10 prescriptions, then stopped using medication and committed suicide a year later), the method used in the present study (and in the Million Women Study[23]) was more accurate and precise, because it was able to detect whether a patient was using an antidepressant medication when the incident (suicide, attempted suicide, or death) happened. In the analysis of current vs past users, we observed that while antidepressant use was associated with an increased risk of a severe suicide attempt, it was also associated with a markedly decreased risk of completed suicide and overall mortality. While residual confounding may have contributed to the observed increased risk of attempted suicide (in the case that patients using medication would be more severely ill and more suicidal), it is extremely unlikely that, at the same time, this residual bias could have contributed to decreased risk of completed suicide and mortality.

A recent report by the United Kingdom's Committee on Safety of Medicines[29] stated that paroxetine is contraindicated for patients younger than 18 years, and a Food and Drug Administration[30] statement in September 2004 concluded that the product specifications for fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxine, mirtazapine, and nefazodone must indicate a warning for increased risk of suicide in pediatric patients. The conclusions of these reports are based on meta-analyses of published and unpublished RCTs. However, a meta-analysis based on the Committee on Safety of Medicines database[12] and on the Food and Drug Administration database[27] revealed that only the use of venlafaxine was associated with a significantly increased risk of (nonfatal) suicidal behavior, and that evidence was inconclusive concerning other antidepressants. Our analysis on subjects aged 10 to 19 years revealed that SSRI use is associated with an increased risk of suicide attempts, but not with a significantly increased risk of suicides among

Table 6. Data for Total Mortality Obtained by Using Medication as a Time-Dependent Variable*

Medication	No. of Person-Years	No. of Deaths	Incidence per 1000 Person-Years	RR (95% CI)		*P* Value
				Crude	Adjusted	
TCAs	923	26	28.2	0.94 (0.64-1.38)	0.63 (0.42-0.96)	.03
Amitriptyline	469	14	29.9	0.99 (0.59-1.68)	0.65 (0.37-1.13)	.13
Doxepin hydrochloride	454	12	26.4	0.88 (0.50-1.55)	0.61 (0.35-1.09)	.09
SSRIs	6946	145	20.9	0.66 (0.56-0.79)	0.59 (0.49-0.71)	<.001
Fluoxetine	2081	29	13.9	0.45 (0.31-0.65)	0.42 (0.29-0.62)	<.001
Citalopram hydrobromide	2752	70	25.4	0.84 (0.66-1.07)	0.62 (0.48-0.79)	<.001
Paroxetine hydrochloride	845	22	26.0	0.86 (0.57-1.32)	0.85 (0.55-1.31)	.46
Sertraline	850	16	18.8	0.62 (0.38-1.02)	0.55 (0.33-0.91)	.02
Fluvoxamine maleate	418	8	19.1	0.63 (0.32-1.27)	0.57 (0.28-1.14)	.11
SNAs	3736	116	31.0	1.03 (0.86-1.25)	0.69 (0.56-0.85)	<.001
Mianserin hydrochloride	600	15	25.0	0.83 (0.50-1.38)	0.56 (0.33-0.95)	.03
Mirtazapine	2113	66	31.2	1.04 (0.81-1.33)	0.63 (0.48-0.82)	<.001
Venlafaxine hydrochloride	1022	35	34.2	1.14 (0.82-1.59)	0.91 (0.64-1.31)	.62
Other antidepressants	4146	106	25.6	0.84 (0.69-1.02)	0.57 (0.43-0.75)	<.001
All antidepressants	15 751	393	25.0	0.77 (0.69-0.87)	0.64 (0.56-0.73)	<.001
No antidepressant use	36 836	1190	32.3	1.00	1.00	NA

Abbreviations: See Table 3.
*The RRs were adjusted as explained in the second footnote to Table 3.

Table 7. Data for Suicides, Suicide Attempts, and Mortality Among Patients Who Have Not Used Any Antidepressant Medication vs Patients Who Have Used Antidepressant Medication During Follow-up*

Variable*	No. of Patients	Person-Years	Incidence	RR (95% CI)		*P* Value
				Overall	Adjusted	
Suicide						
Never use	272	26 553	10.2	1.00	1.00	NA
Ever use	330	26 034	12.7	1.24 (1.05-1.45)	1.27 (1.05-1.54)	.02
Current use	198	15 751	12.6	1.23 (1.02-1.47)	1.10 (0.89-1.36)	.38
No current use	132	10 283	12.8	1.25 (1.02-1.54)	1.62 (1.27-2.07)	<.001
Suicide attempt						
Never use	2912	26 553	109.7	1.00	1.00	NA
Ever use	4224	26 034	162.3	1.48 (1.41-1.55)	1.70 (1.60-1.80)	<.001
Current use	3224	15 751	204.7	1.87 (1.78-1.96)	1.86 (1.74-1.99)	<.001
No current use	1000	10 283	97.2	0.89 (0.83-0.95)	1.34 (1.22-1.48)	<.001
Mortality						
Never use	810	26 553	30.5	1.00	1.00	NA
Ever use	773	26 034	29.7	0.97 (0.88-1.07)	0.97 (0.87-1.09)	.64
Current use	393	15 751	25.0	0.82 (0.73-0.92)	0.73 (0.64-0.84)	<.001
No current use	380	10 283	37.0	1.21 (1.07-1.37)	1.42 (1.24-1.64)	<.001

Abbreviations: See Table 3.
*Never use indicates patients who have not used any antidepressant medication; and ever use, patients who have used antidepressant medication. The incidence and RR among ever users during current antidepressant use and during no current use is also shown (compared with never users). The *P* values for the difference between current vs no current use were as follows: .002 (suicide), <.001 (attempted suicide), and <.001 (mortality).

adolescents. However, paroxetine use was associated with more than 5-fold higher mortality. All 4 deaths were violent or unintentional (although only 1 was classified as suicide), which suggests that the decision to forbid paroxetine use among adolescents based on increased risk of nonfatal suicidal behavior[29] may have been well-grounded. In the total population, we observed an increased risk of suicide during venlafaxine treatment (RR, 1.61; 95% CI, 1.01-2.57; *P*=.04). While no such trend was observed for any other antidepressant (*P*>.60 for increased risk), it is possible that venlafaxine may be associated with a higher risk of suicide than other antidepressants, which agrees with the results by Committee on Safety of Medicines and Food and Drug Administration database studies[12,27] on nonfatal suicidal behavior. However, caution should be used in interpreting these findings for specific antidepressant drugs with *P*>.001 because of the number of comparisons made. Our results for increased risk of suicide attempts during SSRI and TCA use among the suicidal patient population in a real-life setting are well in line with those observed from a meta-analysis on randomized trials among selected patient populations,[13] and those by Jick et al[14] and Martinez et al[31] indicating no significant differences be-

tween these medications. In our adolescent population, SSRI use was associated with somewhat higher risk of attempted suicide than use of other antidepressants. Also, Valuck et al[32] observed an increased risk of suicide attempts during SSRI treatment among adolescents (hazard ratio, 1.59; 95% CI, 0.89-2.82), but because of lower statistical power, their finding did not reach statistical significance. Our results from the entire cohort on the increased risk of attempted suicide and the decreased risk of completed suicide (being statistically significant for fluoxetine) during antidepressant use are in line with the results reported by Gunnell et al,[33] whose odds ratios were 1.57 for nonfatal self-harm and 0.85 for completed suicide; however, these effects did not reach statistical significance because of the relatively small number of events (16 suicides and 172 episodes of nonfatal self-harm). In Finland, it has been estimated that about half of all suicide attempts are treated in the hospital,[34] but those who are treated in the hospital are also the most severe cases. Our results on suicidal behavior from a cohort of suicidal patients may not be representative of the whole patient population with depression, but the effect of SSRIs on cardiovascular- and cerebrovascular-related mortality might apply to all patients receiving antidepressant medication.

No substantial differences were observed in the risk of death or suicide between TCAs, SSRIs, or SNAs. The differences, if any, suggest that SSRI and, especially, fluoxetine use might be associated with a more favorable outcome than the use of TCAs or SNAs (with the exception of paroxetine use among adolescents). Our results on mortality from an unselected cohort of suicidal patients agree with those of a recent study[35] on a patient population with ischemic heart disease, suggesting that antidepressant treatment may decrease cardiovascular-related mortality. Both studies observed a reduction of 30% to 40% in total mortality among patients using SSRIs vs no antidepressant use. Possible mechanisms underlying decreased cardiovascular-related mortality may be associated with improvement in heart rate variability[36,37] or platelet function.[38,39] The advent of new types of drugs has resulted in increased use of medication among depressed patients, for example, in Finland, about 5% of the total population is using antidepressant medication.[40] Our results suggest that antidepressant treatment may contribute to a substantial decrease in mortality among this patient population.

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