Risks of Suicide and Poisoning Among Elderly Patients Prescribed Selective Serotonin Reuptake Inhibitors: A Retrospective Cohort Study

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Background: Treatment with selective serotonin reuptake inhibitors (SSRIs) has been associated with increased suicide risk. Risks of suicide death and of poisoning were compared during periods of SSRI treatment versus periods without any antidepressant treatment among elderly patients.

Method: In this retrospective cohort study, records from the Quebec Health Care Fund and Vital Statistics databases were obtained for patients 65 years and older who had filled a prescription for an SSRI between January 1998 and December 2004. Patients were followed from the filling date of the first SSRI prescription during the study period until death, the end of the first period extending for at least 365 days with no antidepressant supply, or December 31, 2004, whichever occurred first.

Results: The cohort included 128,229 patients (mean age = 75.4 years), 70% of whom were women. Numbers of suicide deaths (crude rate/100,000 patient-years) were 37 (23) during SSRI use, 16 (51) during other antidepressant use, 5 (54) during use of both an SSRI and another antidepressant, and 29 (29) during no antidepressant use. The adjusted risk of suicide death (Cox regression model with time-dependent exposure) was not higher during SSRI use versus nonuse (hazard ratio [95% CI]): any SSRI = 0.64 (0.38 to 1.07), paroxetine = 0.71 (0.37 to 1.35), citalopram = 1.16 (0.59 to 2.25), and sertraline = 0.38 (0.16 to 0.93). The adjusted hazard ratio (95% CI) of poisoning was higher during SSRI use versus nonuse (1.16 [1.07 to 1.25]) and varied between SSRI agents from 0.93 (0.74 to 1.16) for fluoxetine to 1.45 (1.23 to 1.71) for fluvoxamine.

Conclusion: Among elderly patients dispensed SSRIs, the risk of suicide death was not higher during periods of SSRI use compared to when antidepressants were not being used.

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The association between depression and an increased risk for suicide is well established.[1,2] Most patients who commit suicide are untreated for depression at the time of death.[3–5] Although results are conflicting,[6–11] there is some evidence suggesting that the selective serotonin reuptake inhibitors (SSRIs), a widely used class of antidepressant medications, may increase the risk of suicidal behavior and/or suicidal death.[8,12] Regulatory agencies in many countries have issued public health advisories addressing the possible association between the use of all antidepressants and suicidality.[13–15] Nonetheless, SSRIs continue to be widely used in Canada.[16] This is likely attributable to the effectiveness of these medications in relieving symptoms of depression and restoring the ability to conduct daily activities, and continued uncertainty about their association with suicidality. Indeed, while some studies have detected an association between SSRI use and suicidal behavior,[8,9] most have failed to detect such an association with suicide death.[6,7,9,11,17] A few studies have suggested that the risks of suicidal behavior and/or death are increased during the first month of SSRI use compared to subsequent months,[4,10] while others have not detected such an increase.[11] An observational study conducted among suicidal subjects found that while all studied antidepressants increased the risk of suicidal

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behavior, some SSRIs significantly decreased the risk of suicide death.[17]

The association between SSRI use and suicide death remains unclear. Collectively, SSRI clinical trials excluded patients at high risk for suicide and had short follow-up periods, and therefore, the number of suicide deaths in these studies was too low to allow any conclusive assessment. Some observational studies have included larger numbers of patients and compared risks of suicide between antidepressant users but have not compared these risks between times when patients were using antidepressants versus times when patients were not using these medications.[4,10] The only observational study that looked at this issue considered only previous suicide attempters.[17]

We sought to assess the risk of suicide death and "poisoning" by medications or any chemical agent as an indicator of a possible suicide attempt among users of SSRIs during periods of use of any SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) compared to periods of no antidepressant use, among elderly patients 65 years and older in Quebec, Canada.

METHOD

Study Design and Data Source

We conducted a population-based retrospective cohort study using Quebec Health Care Fund administrative databases. We obtained demographic, physician billing, and prescription drug records of all patients 65 years and older who filled at least 1 prescription for an SSRI between January 1998 and December 2004. Mortality data were obtained from the province Vital Statistics database for the same time period.

In Quebec, all persons aged 65 years and older are eligible for coverage for their prescription drugs under the Provincial Health Care Fund administered by the Régie de l'Assurance Maladie du Québec. Coverage for physician services and hospitalizations is universal. The Institut de la Statistique du Québec Vital Statistics database contains information on the date and cause of death coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) codes (before 2000) or *10th Revision* (ICD-10) codes (since 2000). Mortality data are collected from hospitals, doctors, coroners, and social services. Suicide is recorded as the cause of death on the basis of the coroner's report.[18] The Régie de l'Assurance Maladie du Québec and Institut de la Statistique du Québec databases are linkable through a unique patient identifier. Permission to link the data was obtained from the Government of Quebec ethics committee, the Commission d'Accès à l'Information.

Follow-Up

Each patient's index date was defined as the date of the first filled prescription for an SSRI during the time period assessed. The primary outcome of interest was suicide death. Patients were followed until death, the end of the first period extending for at least 365 consecutive days with no antidepressant supply, or the end of the study period (December 31, 2004), whichever occurred first.

Exposures to SSRI

For each patient, the follow-up period was divided into periods of exposure to SSRI, exposure to other antidepressants, exposure to both SSRI and another antidepressant, and nonexposure to any antidepressant. This categorization was based on dispensation dates and number of supplied days as recorded in the database. Periods of exposure to other antidepressants were defined as those days for which patients had been dispensed a supply of antidepressant other than SSRI, including the tricyclic antidepressants (TCAs) amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine and the non–selective serotonin reuptake inhibitors (non-SSRIs) bupropion, nefazodone, trazodone, mirtazapine, and venlafaxine. Monoamine oxidase inhibitors (MAOIs) were also included among the other antidepressants, but since these medications are very rarely prescribed, we will not report their results separately. Periods of exposure to both an SSRI and another antidepressant were defined as those days for which a patient had been dispensed both an SSRI and another antidepressant.

Patient Baseline Characteristics

The following baseline characteristics were assessed on the basis of the data of the year prior to the index date: demographic variables (age; sex; urban vs. rural region of residence; and income stratified as receiving maximal or near maximal income supplement, receiving partial supplement, and not receiving any supplement as defined by the Régie de l'Assurance Maladie du Québec drug plan); psychotropic medications (barbiturates, benzodiazepines, lithium carbonate, and antipsychotic medications); mental health disorders (depression, anxiety, schizophrenia, bipolar disorder, alcohol and drug abuse, and use of naltrexone); conditions that may be associated with depression (poisoning, amputation, trauma, burns); concurrent chronic diseases that may be associated with depression (treatment of alcohol or drug addiction, cancer, heart disease, paralysis, renal insufficiency, and liver disease); specialty of the physician who prescribed the medication (psychiatrist, general practitioner or other specialist); and whether patient visited a psychiatrist in the prior year.

Statistical Analyses

Assessing SSRI utilization. The proportions of patients receiving citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline at the index date and the proportion

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of those receiving a combination of any 1 of these agents with either a TCA or a non-SSRI were assessed for each of these SSRIs separately. The daily dose received at the index date and the number of days supplied, as well as the proportions of patients who switched or added another antidepressant during follow-up, were determined. The total number of prescriptions dispensed during follow-up and the total number of days supplied were assessed. For each prescription, we calculated the daily dose supplied and then classified this dose as "low" or "regular." Low doses were defined as follows: paroxetine, less than 20 mg/day; citalopram, less than 20 mg/day; sertraline, less than 50 mg/day; fluvoxamine, less than 50 mg/day; and fluoxetine, less than 20 mg/day,[19] and proportions of prescriptions from each dose category were calculated. Persistence of use of antidepressant medications was assessed by determining the number of days between the index date and the first treatment interruption or cessation during follow-up. Patients were considered to have interrupted or stopped their treatment if they had a 15-day period without any available antidepressant, as inferred from dispensation dates and number of days supplied. Persistence on antidepressant use was examined using Kaplan-Meier curves.

Assessing patient baseline characteristics. Means and standard deviations (SDs), medians and interquartile ranges, or proportions were used, as appropriate, to report patient characteristics at the index date according to the SSRI used. Suicidal attempts are not reliably recorded as such in the database; however, poisoning by medications has been reported as a means of deliberate self-harm frequently used by the elderly.[20] We assessed poisoning in the previous year as a marker for attempted suicide prior to the index date.

Assessing suicide death occurrence. Unadjusted rates per 100,000 patient-years of suicide death were reported for each exposure category by dividing the total number of suicide deaths occurring in a given category by the total number of "exposure years" within the category in question and then multiplying this proportion by 100,000. The hazard rates of suicide death were compared between the exposure categories using multivariable Cox regression models with time-dependent exposure.[21]

Assessing poisoning occurrence. Similar analyses were conducted to assess the crude and adjusted rates of poisoning during the follow-up period. For these analyses, follow-up was terminated at the date of the first poisoning event following the index date for those who had such events.

Subgroup analyses. Two subgroup analyses were conducted: (1) Cox regression models with time-dependent exposure were constructed as described previously but including only those patients without dispensation for antidepressant medication in the 180 days prior to the index date. (2) Similarly, models were also constructed in the subgroup of patients with a physician billing code specific for depression or anxiety in the year prior to the index date. All analyses were performed using SAS version 9.1 for UNIX (SAS Institute Inc., Cary, N.C.).

RESULTS

Patient Characteristics

The study included 128,229 elderly patients (mean age = 75.4 years), 70% of whom were women (data not shown). Of study patients, 46,269 (36%) received paroxetine (58% of them received it for low doses)[19]; 30,959 (24%) received citalopram (44% for low doses); 33,495 (26%) received sertraline (58% for low doses); 10,968 (9%) received fluvoxamine (25% for low doses); and 6538 (5%) received fluoxetine (44% for low doses) (Tables 1 and 2). Of these patients, 1974 (2%) received one of the SSRI agents in combination with a non-SSRI and 1732 (1%) received a combination of an SSRI with a TCA (data not shown).

Patient characteristics at the index date are displayed in Table 1. Patients in the paroxetine and fluoxetine groups were slightly younger than those in the citalopram, sertraline, or fluvoxamine groups, and more patients in the paroxetine and sertraline groups were residing in rural areas compared to patients in the other groups (Table 1). Although the large majority of patients in all groups were using benzodiazepines in the prior year, the proportion seemed higher in the paroxetine group. The proportions of patients who had psychiatrist encounters in the previous year were low in all groups and ranged from 10% in the paroxetine group to 14% in the sertraline group. Very few patients (2%) in the citalopram group used SSRIs in the prior year compared to patients in the other groups in which the proportions ranged from 17% in the paroxetine group to 53% in the fluoxetine group. The proportions of patients who had a diagnosis of poisoning, who were dispensed lithium, and who had comorbidities in the prior year did not seem to differ between the groups (Table 1).

SSRI Utilization in the Follow-Up

The numbers of SSRI prescriptions dispensed during the follow-up period examined were 1,039,570 (36%) for paroxetine (367,025 [35%] for low doses); 616,076 (21%) for citalopram (144,541 [23%] for low doses); 794,521 (28%) for sertraline (259,838 [33%] for low doses); 264,503 (9%) for fluvoxamine (31,780 [12%] for low doses); and 166,906 (6%) for fluoxetine (54,629 [33%] for low doses) (Table 2). The total numbers of dispensed prescriptions for the cohort during follow-up were 2,676,017 for SSRIs only; 205,559 for SSRIs in combination with another antidepressant; and 607,385 for other antidepressants (Table 3). Of the 205,559 prescriptions that were for both an SSRI and another antidepressant, 91,665 were for SSRIs with a TCA; 113,664 for SSRIs

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Table 1. Baseline Characteristics of Patients Aged 65 and Older Who Filled a Prescription for an SSRI by SSRI Type

	SSRI Used at the Index Date				
Characteristic	Paroxetine (N = 46,269)	Citalopram (N = 30,959)	Sertraline (N = 33,495)	Fluvoxamine (N = 10,968)	Fluoxetine (N = 6,538)
Age, mean ± SD	74.4 ± 7.1	76.0 ± 7.1	76.2 ± 7.0	76.5 ± 7.0	73.5 ± 6.6
Female, %	70.6	69.6	69.4	71.0	69.0
Residing in a rural area, %	21.5	17.1	22.3	18.8	16.8
Income, %					
Low (maximal supplement)	7.3	6.5	7.5	8.0	8.7
Medium (partial supplement)	43.6	44.6	46.1	44.3	37.3
High (no supplement)	49.2	48.9	46.5	47.8	53.9
Medications prescribed, %					
In the prior year					
Lithium carbonate	1.0	1.2	1.4	1.6	2.3
Antipsychotics	5.5	8.6	7.4	8.3	5.4
Barbiturates	0.4	0.6	0.5	0.5	0.5
Benzodiazepines	76.4	69.7	71.7	74.2	69.9
SSRI	16.9	2.2	21.2	35.7	52.9
Non-SSRI	7.1	11.5	6.2	5.8	6.2
TCA	12.4	11.5	11.3	12.4	11.4
In the prior 6 months					
SSRI	15.5	2.1	19.4	33.0	48.8
Non-SSRI, TCA, or MAOI	18.4	17.2	16.4	13.8	13.3
Mental disorders, %	42.5	48.7	45.4	45.1	43.9
Depression	27.9	31.3	33.4	33.5	32.7
Anxiety	32.5	24.9	24.3	24.7	22.7
Bipolar disorders	3.7	1.5	4.4	0.9	0.8
Schizophrenia	0.6	0.8	0.7	0.9	0.9
Alcohol or drug abuse	1.2	1.6	1.3	1.5	1.1
Naltrexone use	0.02	0.01	0.01	0	0.03
Visited a psychiatrist in the prior year, %	10.3	14.0	11.5	13.8	13.1
Comorbidities, %					
Cancer	15.8	17.7	15.4	14.4	15.0
Heart failure	12.5	14.5	15.8	13.7	11.9
Rheumatoid arthritis	1.8	1.9	1.9	1.8	2.0
Cerebrovascular disease	4.1	5.9	6.5	5.6	3.3
Renal failure	1.8	3.4	2.7	2.1	1.9
Amputation	0.1	0.2	0.1	0.2	0.1
Burns	0.4	0.4	0.5	0.4	0.5
Trauma	0.8	0.9	0.9	0.8	0.7
Poisoning in the prior year, %	1.2	1.3	1.1	1.2	1.0

Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 2. SSRI Prescriptions at Index Date and During Follow-Up and Unadjusted Rates of Suicide Death and Poisoning Among Patients Aged 65 and Older

Variable	Paroxetine	Citalopram	Sertraline	Fluvoxamine	Fluoxetine
SSRI use at index date					
No. of prescriptions	46,269	30,959	33,495	10,968	6,538
No. of low-dose prescriptions (%)[a]	26,940 (58)	13,543 (44)	19,517 (58)	2,748 (25)	2,856 (44)
SSRI use during follow-up					
No. of prescriptions	1,039,570	616,076	794,521	264,503	166,906
No. of low-dose prescriptions (%)[a]	367,025 (35)	144,541 (23)	259,838 (33)	31,780 (12)	54,629 (33)
Total drug exposure duration, y	63,648	31,586	45,968	15,661	11,063
Low-dose drug exposure duration, y (%)[a]	22,208 (35)	7,096 (22)	14,370 (31)	1,794 (11)	3,485 (32)
Suicide death during follow-up					
No. of suicide deaths	16	16	7	1	2
No. of suicide deaths during low-dose drug exposure (%)[a]	4 (25)	1 (6)	3 (43)	0 (0)	0 (0)
Rate per 100,000 patient-years	25.1	50.7	15.2	6.4	18.1
Poisoning during follow-up					
No. of patients with poisoning	608	350	369	183	88
No. of patients with poisoning during low-dose drug exposure (%)[a]	187 (31)	66 (19)	103 (28)	21 (11)	23 (26)
Total drug exposure duration censored at first date of poisoning, y	62,510	30,995	45,297	15,388	10,896
Rate per 100,000 patient-years	973	1,129	814	1,189	808

[a]Low doses defined as follows: paroxetine, < 20 mg/day; citalopram, < 20 mg/day; sertraline, < 50 mg/day; fluvoxamine, < 50 mg/day; fluoxetine, < 20 mg/day.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

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Table 3. Prescriptions of Antidepressants and Unadjusted Rates of Suicide Death Among Patients Aged 65 and Older

Variable	SSRI	Other Antidepressant	SSRI and Other Antidepressant	Not Exposed
No. of prescriptions	2,676,017	607,385	205,559	649,550
Total drug exposure duration, y	158,566	31,381	9,244	99,685
No. of suicide deaths	37	16	5	29
Rate per 100,000 patient-years	23	51	54	29
No. of patients with poisoning	1,481	359	117	1,534
Total drug exposure duration censored at first date of poisoning, y	156,130	30,297	8,956	257,417
Rate per 100,000 patient-years	949	1,185	1,306	596

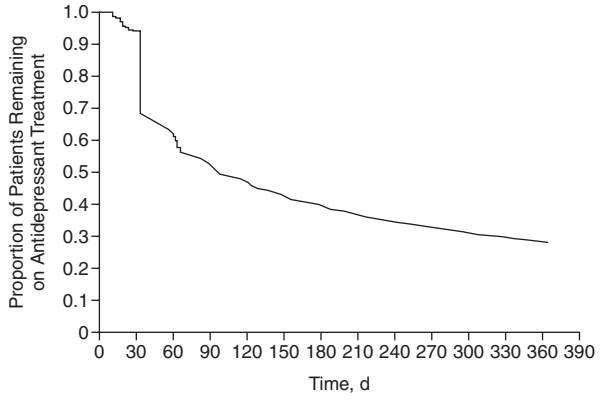
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 4. Antidepressant Utilization and Prescribing Physician in Follow-Up

	Vital Status at the End of the Study		
Variable	Alive (N = 106,054)	Died by Suicide (N = 87)	Died by Another Cause (N = 22,088)
No. of prescriptions (%) written by a:			
Psychiatrist	259,840 (9)	585 (34)	37,610 (7)
General practitioner	2,523,663 (86)	1,124 (65)	471,901 (86)
Other specialist	157,156 (5)	13 (1)	37,069 (7)
Days on any antidepressant, median (interquartile range)	279 (60–922)	244 (48–680)	274 (69–754)
Days on SSRI, median (interquartile range)	200 (45–710)	146 (30–491)	217 (57–640)
Days of follow-up, median (interquartile range)	1,176 (661–1,865)	339 (97–810)	413 (160–951)
Patients who switched from SSRI to other antidepressants, N (%)	15,547 (15)	19 (22)	3,150 (14)

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 1. Kaplan-Meier Curve to Show the Crude Rates of Treatment Interruption or Cessation Over Time During the First Year of Follow-Up Among all Patients



with a non-SSRI; and the remaining 230 were for an SSRI with an MAOI (data not shown). A total of 18,716 patients (15%) received an antidepressant other than an SSRI during follow-up (Table 4). The Kaplan-Meier curves revealed that only 39% of patients had not stopped antidepressant treatment for 15 days or more by 180 days following index date (Figure 1).

Suicide Death

Thirty-seven suicide deaths (23/100,000 patient-years) occurred during SSRI exposure; 16 (51/100,000 patient-years) occurred during exposure to other antidepressants; 5 (54/100,000 patient-years) occurred during exposure to both an SSRI and another antidepressant, and 29 (29/100,000 patient-years) occurred during nonexposure to any antidepressant treatment (Table 3). Among the 37 suicide deaths that occurred during SSRI treatment, 15 (25/100,000 patient-years) occurred during paroxetine use; 14 (48/100,000 patient-years) occurred during citalopram use; 6 (14/100,000 patient-years) occurred during sertraline use; 1 (7/100,000 patient-years) occurred during fluvoxamine use, and 1 (10/100,000 patient-years) occurred during fluoxetine use (data not shown). Table 2 displays the suicide death rates by SSRI agent whether it was used alone or in combination with another antidepressant. Rates displayed in Table 2 are similar to those listed above. Unadjusted time to suicide was not different between periods on or off treatment (Figure 2) as determined by comparing the first period on and first period off treatment for each patient.

The time-dependent Cox regression model (Table 5) suggested that women are at a much lower risk of suicide death than men (hazard ratio [HR] [95% confidence interval] = 0.14 [0.09 to 0.22]). Both prior use of benzodiazepines (2.13 [1.15 to 3.93]) and prior use of antipsychotic medications (2.18 [1.21 to 3.92]) were associated with increased risks of suicide death. Patients were not at increased risk of suicide death during periods of SSRI treatment compared to periods without treatment. The HR (95% CI) of suicide death during exposure to SSRI versus nonexposure to any antidepressant was 0.64 (0.38 to

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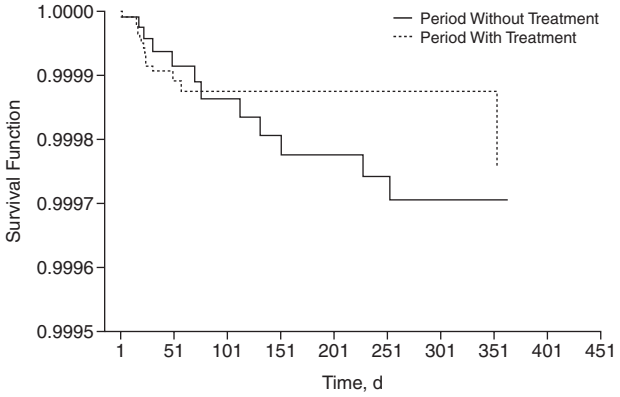
Figure 2. Kaplan-Meier Curves Displaying Time to Suicidal Death During Periods[a] of Treatment With Antidepressant and Periods Without Treatment



[a]Only the first period from each exposure category was considered.

Figure 3. Kaplan-Meier Curve to Show the Crude Rates of Treatment Interruption or Cessation Over Time During the First Year of Follow-Up Among Patients With No Antidepressant Treatment in the Prior 180 Days

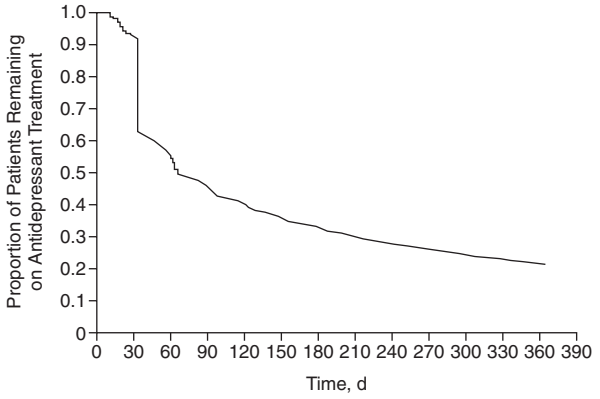


Table 5. Adjusted Hazard Ratio of Suicide Death During Times of Exposure to SSRI[a]

Variable	Hazard Ratio (95% CI)
Age (1-year increase)	0.99 (0.96 to 1.02)
Female	0.14 (0.09 to 0.22)
Medications prescribed in the previous year	
Antipsychotic medications	2.18 (1.21 to 3.92)
Benzodiazepines	2.13 (1.15 to 3.93)
Poisoning in the prior year	5.46 (2.34 to 12.72)
Visits to a psychiatrist in the previous year	1.46 (0.85 to 2.49)
No use of any antidepressant	1 (REF)
SSRI	0.64 (0.38 to 1.07)
Other antidepressant	1.80 (0.96 to 3.39)
Both SSRI and another antidepressant	1.41 (0.53 to 3.70)
SSRI low dose[b]	0.41 (0.17 to 0.96)
SSRI regular dose[b]	0.72 (0.42 to 1.23)
Use of any antidepressant vs no use[c]	0.84 (0.52 to 1.34)
Paroxetine[d]	0.71 (0.37 to 1.35)
Citalopram[d]	1.16 (0.59 to 2.25)
Sertraline[d]	0.38 (0.16 to 0.93)

[a]Cox regression models with time-dependent exposure.
[b]A separate model was constructed separating SSRI prescriptions into those for low doses and those for regular doses.
[c]A separate model was constructed combining SSRI, other antidepressant, and both SSRI and another antidepressant in 1 category.
[d]A separate model was constructed with SSRI separated into 5 categories according to the agent prescribed. We do not report the results of fluoxetine and fluvoxamine because only 1 event occurred in each of these categories and the results are therefore not robust.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

1.07), with the risk being lower during exposure to lower doses of SSRI (0.41 [0.17 to 0.96]). Patients who switched to other antidepressants during follow-up and those who used both an SSRI and another antidepressant in combination appeared to be at increased risk of suicide death. The risk of suicide death during antidepressant treatment overall was not higher than during times without treatment (HR [95% CI] = 0.84 [0.52 to 1.34]). The risk of suicide death was also examined in a similar model separating exposure periods by the SSRI agent used (Table 5).

Subgroup Analyses

A total of 90,794 patients (71% of cohort) had not received any antidepressant medication during the 180 days prior to the index date ("new" patients). Among them, 56 patients (64% of all suicidal deaths) died by suicide during follow up and 14,596 (66% of all deaths from other causes) died from other causes. The baseline characteristics of the new patients did not differ from those of the cohort overall. Kaplan-Meier curves revealed that this subgroup, however, was less persistent on antidepressant treatment with only 60% who were persistent at 6 weeks and 32% at 6 months (Figure 3). Cox regression model results for this subgroup did not differ from the results obtained for the complete cohort (SSRI vs. nonexposure, HR [95% CI] = 0.72 [0.39 to 1.34]; other antidepressants vs. nonexposure, HR [95% CI] = 1.65 [0.65 to 4.22]; and both SSRI and another antidepressant vs. nonexposure, HR [95% CI] = 2.01 [0.46 to 8.75]).

Analyses restricted to those with prior physician billings for depression and/or anxiety (62,496 patients, 49% of cohort) resulted in estimates similar to those obtained for the complete cohort. In this subgroup, 53 patients died by suicide during follow-up and 8823 died from other causes. Baseline characteristics of this subgroup did not appear different from the complete cohort. The results of the Cox regression model for this subgroup were generally similar to the model that included the complete cohort (SSRI vs. nonexposure, HR [95% CI] = 0.53 [0.27 to 1.06]; other antidepressants vs. nonexposure, HR [95% CI] = 2.45 [1.19 to 5.03]; both SSRI

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Table 6. Adjusted Hazard Ratio of Poisoning Events During Times of Exposure to SSRI[a]

Variable	Hazard Ratio (95% CI)
Age (1-year increase)	0.96 (0.95 to 0.96)
Female	0.84 (0.78 to 0.91)
Rural vs urban place of residence	0.92 (0.84 to 1.00)
Receiving maximal financial support vs none	1.12 (0.98 to 1.27)
Receiving partial financial support vs none	1.12 (1.04 to 1.20)
Medications prescribed in the previous year	
Antipsychotic medications	0.99 (0.87 to 1.12)
Benzodiazepines	1.34 (1.23 to 1.45)
Barbiturates	1.79 (1.27 to 2.52)
Lithium	2.05 (1.73 to 2.43)
SSRI	1.12 (1.04 to 1.21)
Poisoning in the prior year	4.96 (4.33 to 5.69)
Alcohol or drug abuse	2.19 (1.86 to 2.58)
Visits to a psychiatrist in the previous year	1.27 (1.16 to 1.40)
No use of any antidepressant	1 (REF)
SSRI	1.16 (1.07 to 1.25)
Other antidepressants	1.67 (1.49 to 1.88)
Both SSRI and another antidepressant	1.45 (1.20 to 1.76)
Paroxetine[b]	1.18 (1.06 to 1.30)
Citalopram[b]	1.23 (1.08 to 1.40)
Sertraline[b]	1.05 (0.93 to 1.18)
Fluvoxamine[b]	1.45 (1.23 to 1.71)
Fluoxetine[b]	0.93 (0.74 to 1.16)

[a]Cox regression models with time-dependent exposure.
[b]A separate model was constructed with SSRI separated into 5 categories according to the agent prescribed.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

and another antidepressant vs. nonexposure, HR [95% CI] = 0.85 [0.19 to 3.77]).

Poisoning During Follow-Up

The cohort incurred 1481 poisoning occurrences (9.5/1000 patient-years) during SSRI exposure; 359 (11.9/1000 patient-years) during exposure to other antidepressants; 117 (13.1/1000 patient-years) during exposure to both an SSRI and another antidepressant; and 1534 (6.0/1000 patient-years) during nonexposure to any antidepressant treatment (Table 3). Among the 1481 poisoning events that occurred during SSRI treatment, 575 (9.7/1000 patient-years) were during exposure to paroxetine; 303 (10.6/1000 patient-years) during exposure to citalopram; 359 (11.9/1000 patient-years) during exposure to sertraline; 169 (11.5/1000 patient-years) during exposure to fluvoxamine; and 81 (7.9/1000 patient-years) during exposure to fluoxetine (data not shown). Table 2 displays the crude rates of poisoning by SSRI agent whether it was used alone or in combination with another antidepressant. Rates displayed in Table 2 are similar to those listed above. Of all poisoning events, 36.4% were by nonspecified medications (ICD-9 code 977.x), 31.5% by drug abuse for nonaddicts (ICD-9 code 305.x), 9.4% by nonmedicinal substances (ICD-9 code 989.x), 4.1% by cardiovascular medications (ICD-9 code 972.x), 3.9% by gas (ICD-9 code 987.x), 2.7% by alcoholic substances (ICD-9 code 980.x), and 1.3% by psychotropic agents (ICD-9 code 969.x). The remaining events were by various medications including antiallergic, analgesic, sedative, anticonvulsant, and antimicrobial agents.

The time-dependent Cox regression model (Table 6) revealed that patients were at higher risk for poisoning during periods of SSRI treatment compared to periods without treatment: SSRI versus nonexposure to any antidepressants, HR (95% CI) = 1.16 (1.07 to 1.25). Patients who used other antidepressants during follow-up and those who used both an SSRI and another antidepressant were also at higher risk of poisoning compared to nonusers. The risks of poisoning were different for individual SSRI agents, ranging from HR (95% CI) = 0.93 (0.74 to 1.16) for fluoxetine to 1.45 (1.23 to 1.71) for fluvoxamine.

DISCUSSION

Our findings indicate that among the elderly, use of SSRIs is not associated with increased suicidal risk. There was no difference in time to suicide between periods on and off active treatment. In our study, periods off treatment were truncated at 1 year. Although risk of depression recurrence in association with time since remission has not been clearly identified in the literature, it is possible that it is higher in the second year after remission than it is in the first year. If this were true, it would imply that the hazard ratio during time on treatment compared to nontruncated time off treatment is lower than the one reported in our study.

Antidepressant treatment may have been inadequate in our study patients with a majority of them interrupting their treatment soon after initiation. Practice guidelines recommend the use of antidepressants for moderate to severe major depressive disorders to be continued for a period of 16 to 40 weeks following the acute phase to prevent recurrence of depression.[22,23] Other published studies have also reported suboptimal treatments of depression and large departures from guideline recommendation for the pharmacologic treatment of depression in terms of duration of use and starting dose.[19] Reasons for stopping treatment are not registered on a database. Further studies are required to compare the risks of suicide between periods on active treatment and periods off treatment among patients who discontinue treatment on their own and those who have been in remission from depression.

Our results also suggest that patients who switched from SSRIs to another antidepressant had a higher risk of suicide death. Reasons for switching from one antidepressant to another are not available in the database; however, the higher rate of suicide death among those who switched may be an indication of either a lack of effectiveness of SSRI in these patients or a higher risk of suicide secondary to SSRI discontinuation.[24,25] The risk of

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suicide death seemed higher among patients using higher versus lower doses of SSRI suggesting perhaps that those patients had more severe conditions.

Our results are consistent with those of another study which found that, among patients previously hospitalized for attempted suicide, current use of any antidepressant was associated with a decreased risk of suicide death compared with nonuse.[17] The possibility of a lower rate of suicide death during periods of use versus nonuse of SSRI observed in our study was also consistent with results of other studies that found that the majority of patients who commit suicide are untreated for depression at the time of death.[3,4,26–28]

Also consistent with results of other studies, use of benzodiazepine was associated with an increased risk for suicide death in our study.[29] Nonetheless, our study does not definitely indicate a causal association between the use of these medications and the occurrence of suicide as some of the benzodiazepines may have been prescribed also to treat depression.[30] A higher proportion of benzodiazepine users compared to nonusers (defined by prior year use) had a diagnosis of anxiety (31% vs. 17%). When both benzodiazepine use and anxiety were included in a Cox regression model, anxiety was not statistically significant and its removal did not substantially impact the association between benzodiazepine use and suicide occurrence.

As expected, women were at a lower risk of suicide death compared to men while prior use of antipsychotic and prior poisoning were independent risk factors for suicide death.[17,31]

One observational study found increased risk of suicide death among elderly patients using SSRI versus those using other antidepressants during the first month following initiation of treatment but not during subsequent months.[4] Such comparison was not possible in our study because all patients were using SSRI at cohort entry. Another published observational study conducted among patients with depression found no difference in risk of suicide death occurring among adults in the first month following antidepressant treatment initiation and those occurring in subsequent months.[11]

Previous studies have suggested an association between SSRI use and suicidal behavior in adults.[8,9] Our data did not include information on suicidal behavior other than poisoning, and therefore we could not specifically examine such an association. Nonetheless, we considered poisoning during follow-up as a marker of suicide attempts. The rate of poisoning occurrences during periods of SSRI use was higher than during periods without any antidepressants, although some of the poisoning events that we considered may have been accidental. We observed no increase in risk of poisoning with either fluoxetine or sertraline use while some increase was observed during times of paroxetine, citalopram, and fluvoxamine use. The finding that poisoning risk was higher during treatment with some SSRIs (even though suicide death was not) may reflect a decrease in aggression and impulsivity with SSRI leading to the use of less violent methods that are not as likely to result in death. Further studies are needed to clarify this issue.

Strengths of our study include the use of administrative databases that were collected independently of the study objectives and therefore are not prone to observation bias; the opportunity to examine the risk of suicide death associated with antidepressant use in a real-world setting; a large sample size; a long follow-up period; and valid data on suicide, based on coroners' reports.[32]

Limitations of the study also pertain to the use of administrative databases where the indication for which a medication is prescribed and the actual drug consumption are not known. Also, information on severity of depression, untreated alcohol or drug abuse, or family history of suicide was not available; it is unknown if these factors were associated with the choice of the SSRI agent.

In conclusion, our findings indicate that in an elderly population of individuals with some history of SSRI use between 1998 and 2004, the risk of suicide death was lower—not higher—during periods of treatment with SSRI. Therefore, treating depressive symptomatology in elderly patients with SSRIs does not likely place these patients at increased risk for suicide death.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan, Zonalon, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), naltrexone (Vivitrol, ReVia, and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), protriptyline (Vivactil), sertraline (Zoloft and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

REFERENCES

1. Isacsson G, Bergman U, Rich CL. Epidemiological data suggest antidepressants reduce suicide risk among depressives. J Affect Disord 1996;41:1–8
2. Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 2004;4:37
3. Oquendo MA, Malone KM, Ellis SP, et al. Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 1999;156:190–194
4. Juurlink DN, Mamdani MM, Kopp A, et al. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. Am J Psychiatry 2006;163:813–821
5. Leon AC, Marzuk PM, Tardiff K, et al. Antidepressants and youth suicide in New York City, 1999–2002. J Am Acad Child Adolesc Psychiatry 2006;45:1054–1058
6. Isacsson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. Acta Psychiatr Scand 2005;111:286–290
7. Khan A, Khan S, Kolts R, et al. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 2003;160:790–792
8. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005;330:396
9. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors

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(SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 2005;330:385
10. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004;292:338–343
11. Simon GE, Savarino J, Operskalski B, et al. Suicide risk during antidepressant treatment. Am J Psychiatry 2006;163:41–47
12. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990;147: 207–210
13. Center for Drug Evaluation and Research. Worsening depression and suicidality in patients being treated with antidepressant medications [US Food and Drug Administration (FDA) Web site]. March 22, 2004. Available at http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm. Accessed Sept 7, 2005
14. Committee on Safety of Medicines. Medicines and Healthcare products Regulatory Agency, United Kingdom. Use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents with major depressive disorder (MDD)-only fluoxetine (Prozac) shown to have a favorable balance of risks and benefits for the treatment of MDD in the under 18s. United Kingdom, 2003. Available at http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_Page&ssDocName=CON019494&ssSourceNodeId=242&ssTargetNodeId=221. Accessed Sept 7, 2005
15. Health Canada. Health Canada advises Canadians of stronger warnings for SSRIs and other newer anti-depressants. Canada; 2004. Available at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2004/2004_31_e.html. Accessibility verified Sept 21, 2007
16. Canada Rx Report 2005. [Announcement posted on the World Wide Web]. Available at: http://www.imshealthcanada.com/vgn/images/portal/cit_40000873/51/30/78610823FINAL_Canada_RX_Report_english.pdf. Accessibility verified Oct 23, 2007
17. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry 2006;63:1358–1367
18. Public Health Agency of Canada. Inventory of Injury Data Sources and Surveillance Activities. Centre for Surveillance Coordination. Ottawa, Ontario, Canada: Public Health Agency of Canada; 2005
19. Moride Y, Galbaud du Fort G, Monette J, et al. Suboptimal duration of antidepressant treatments in the older ambulatory population of Quebec: association with selected physician characteristics. J Am Geriatr Soc 2002;50:1365–1371
20. Hawton K, Harriss L. Deliberate self-harm in people aged 60 years and over: characteristics and outcome of a 20-year cohort. Int J Geriatr Psychiatry 2006;21:572–581
21. Ake CF, Carpenter AL. Extending the use of PROC PHREG in survival analysis. 2003. Available at http://www.caloxy.com/papers/51-ExtendingPHREG.pdf. Accessibility verified Oct 16, 2007
22. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
23. Reynolds CF 3rd, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 1999;281:39–45
24. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996;16:356–362
25. Michelson D, Fava M, Amsterdam J, et al. Interruption of selective serotonin reuptake inhibitor treatment: double-blind, placebo-controlled trial. Br J Psychiatry 2000;176:363–368
26. Isacsson G, Boethius G, Bergman U. Low level of antidepressant prescription for people who later commit suicide: 15 years of experience from a population-based drug database in Sweden. Acta Psychiatr Scand 1992;85:444–448
27. Isacsson G, Holmgren P, Druid H, et al. The utilization of antidepressants—a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992–1994. Acta Psychiatr Scand 1997;96:94–100
28. Callahan CM, Hendrie HC, Nienaber NA, et al. Suicidal ideation among older primary care patients. J Am Geriatr Soc 1996;44:1205–1209
29. Carlsten A, Waern M, Holmgren P, et al. The role of benzodiazepines in elderly suicides. Scand J Public Health 2003;31:224–228
30. Laws D, Ashford JJ, Anstee JA. A multicentre double-blind comparative trial of fluvoxamine versus lorazepam in mixed anxiety and depression treated in general practice. Acta Psychiatr Scand 1990;81:185–189
31. Rubino A, Roskell N, Tennis P, et al. Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study. BMJ 2007;334:242
32. Institut national de santé publique du Québec. L'épidémiologie du suicide au Québec: que savons-nous de la situation récente? Quebec, Canada, 2004. Available at http://www.inspq.qc.ca/pdf/publications/281-EpidemiologieSuicide.pdf. Accessed Feb 24, 2006

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