Article

The Risk of Suicide With Selective Serotonin Reuptake Inhibitors in the Elderly

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Objective: The authors explored the relationship between the initiation of therapy with selective serotonin reuptake inhibitor (SSRI) antidepressants and completed suicide in older patients.

Method: The authors linked population-based coroner's records with patient-level prescription data, physician billing claims, and hospitalization data for more than 1.2 million Ontario residents 66 years of age and older from 1992 to 2000. For each suicide case, four closely matched comparison subjects were selected using propensity score methods. The authors determined the odds ratio for suicide with SSRIs versus other antidepressant treatment, calculated at discrete monthly intervals from the start of treatment.

Results: Of 1,329 suicide cases, 1,138 (86%) were each fully matched to four comparison subjects using propensity scores. During the first month of therapy, SSRI antidepressants were associated with a nearly fivefold higher risk of completed suicide than other antidepressants (adjusted odds ratio: 4.8, 95% confidence interval=1.9–12.2). The risk was independent of a recent diagnosis of depression or the receipt of psychiatric care, and suicides of a violent nature were distinctly more common during SSRI therapy. Numerous sensitivity analyses revealed consistent results. No disproportionate suicide risk was seen during the second and subsequent months of treatment with SSRI antidepressants, and the absolute risk of suicide with all antidepressants was low.

Conclusions: Initiation of SSRI therapy is associated with an increased risk of suicide during the first month of therapy compared with other antidepressants. The absolute risk is low, suggesting that an idiosyncratic response to these agents may provoke suicide in a vulnerable subgroup of patients.

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Depression is common, affecting about one in five people during their lifetime (1–3). Severe depression is also a major risk factor for suicide, and up to 15% of those hospitalized for depression eventually commit suicide (4). Most patients who commit suicide suffer from a psychiatric illness, with advancing age, male gender, and medical illness among important predisposing factors (4, 5). As the cause of death for approximately 1 million people worldwide each year, suicide can be a devastating event with a complex etiology, and a better understanding of contributing factors is essential to suicide prevention (6–8).

Selective serotonin reuptake inhibitors (SSRIs) have become increasingly popular for the treatment of depression (9). These drugs are well tolerated by most patients, are safer in overdose than traditional antidepressants, and their availability has encouraged antidepressant prescribing in primary care (9, 10). Several anecdotal reports describe the emergence of intense suicidality during the initial period of SSRI therapy (11–16), but it is difficult to separate the role of depression from a possible adverse effect of treatment.

The potential association between SSRI antidepressants and suicide has garnered considerable media attention (17), prompting multiple editorials (18–21), litigation against the pharmaceutical industry (22), allegations of corporate malfeasance (23, 24), and national public health advisories (25). Industry-sponsored studies, single case reports, meta-analyses, and practice-based epidemiologic studies have yielded variable findings regarding the association between SSRI antidepressants and suicide (26–37). Moreover, the exclusion of actively suicidal patients from clinical trials of antidepressants renders pooled analyses underpowered to detect differences in mortality, as illustrated by the recent findings of the U.S. Food and Drug Administration (25, 32, 38).

Recent attention has focused on the possible risks of antidepressant treatment in children, yet most cases of SSRI-induced suicidality have been reported in adults (14, 15, 39). No studies have addressed the risk in older patients, despite the high frequency with which antidepressants are used in this population (9, 40). In this study, we linked population-based prescription records and coroner's data to explore the association between the initiation of antidepressant therapy and subsequent risk of suicide in a population of more than 1.2 million elderly patients.

TABLE 1. Elements of the Propensity Score

Variable	Elements
Demographic characteristics	Age (born within 14 days)
	Gender
	Estimated residential income quintile
	Residence in a long-term care facility
	Rural versus urban principal residence
Medical disorders	Acute myocardial infarction
	Alcohol abuse
	Atherosclerotic disease
	Breast cancer
	Chronic lung disease
	Dementia
	Diabetes mellitus
	Dyslipidemia
	Gastrointestinal hemorrhage
	Glaucoma
	Gout
	Heart failure
	Hypothyroidism
	Injury other than poisoning
	Lung cancer
	Osteoarthritis
	Other malignancy
	Other coronary heart disease
	Pain requiring high-potency opiates
	Pain requiring mid-potency opiates
	Parkinson's disease
	Peptic ulcer disease and related conditions
	Pneumonia
	Poisoning or drug toxicity
	Prostate cancer
	Rheumatoid arthritis
	Seizure disorder
	Sepsis
	Stroke
	Urinary incontinence
Psychiatric disorders	Affective disorder
	Anxiety or sleep disorders
	Bipolar disorder
	Psychoses, agitation, and related disorders
	All other mental disorders
Other	Admission to a psychiatric facility during previous year
	Care by a psychiatrist in previous year
	Days in hospital during previous year
	Suicide attempt in previous 3 years

Method

Setting

We conducted a population-based study in Ontario. Ontario is Canada's largest province, with a population of 11,100,876 at the midpoint of the study period, which included 1,264,686 who were 66 years of age or older. All Ontario residents 65 years and older had universal access to health insurance for prescription drug coverage, physicians' services, and hospital care. The study was approved by the Chief Coroner for Ontario and the research ethics board of Sunnybrook and Women's College Health Sciences Centre.

Subjects

Using records from the Office of the Chief Coroner for Ontario, we identified consecutive cases of suicide among Ontario residents aged 66 years and older that occurred over a 9-year period (Jan. 1, 1992, to Dec. 31, 2000). We did not examine the first year of eligibility for prescription drug benefits (age 65) to avoid incomplete medication records, and we excluded patients younger than 65 because prescription records were not available for analysis. The date of suicide served as the index date for all analyses.

Propensity score methods were used to select comparison patients from the general population (41, 42). This is an advanced matching technique that involves modeling a large amount of information on each subject to minimize differences between suicide and comparison groups. This included demographic data as well as clinical information regarding specific medical and psychiatric conditions, collectively identified from hospital admission records, physician diagnosis claims, and outpatient prescription claims. A complete list of the various elements of the propensity score is shown in Table 1.

A structured, iterative process similar to that described by Rosenbaum and Rubin (43) was used to construct a propensity score for each individual that predicted suicide outcome by balancing all characteristics shown in Table 1 between the suicide cases and comparison subjects. To account for changing patterns of antidepressant use in Ontario over the study period (9), propensity scores were calculated for all possible comparison patients for each case at every index date. Once the final propensity score model was developed and scores calculated for all potential comparison subjects, we identified all eligible comparison patients for each case using calipers of 0.2 standard deviations of the propensity score. From these we randomly selected four comparison subjects for each suicide case. Suicide cases whose propensity scores were too high to permit a match to four comparison subjects were retained for descriptive purposes but excluded from the matched analyses.

Exposure to Antidepressants

We examined prescription records of suicide cases and comparison subjects through the Ontario Drug Benefit program database. The Ontario Drug Benefit program collects detailed records of prescriptions dispensed to all elderly residents of Ontario, contains little (<1%) missing data, and is regularly used to analyze medication use in the community (44–47). SSRI antidepressants included fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram. Other antidepressants included secondary amine cyclic antidepressants (desipramine, nortriptyline, protriptyline, maprotiline, and amoxapine), tertiary amine cyclic antidepressants (amitriptyline, imipramine, doxepin, trimipramine, and clomipramine), and miscellaneous antidepressants (venlafaxine, trazodone, bupropion, and nefazodone). We did not examine monoamine oxidase inhibitors given their infrequent use, and we did not study mirtazapine because it was not an insured benefit during most of the study period.

In all main analyses, new use of an antidepressant was defined as no previous prescription for a drug from the same class in the previous 6 months. In a secondary analysis, we defined new use as no prescription for any other antidepressant in the preceding 6 months.

Statistical Analysis

Databases were linked in an anonymous fashion using an encrypted version of each patient's health card number. The primary analysis used conditional logistic regression to estimate the odds ratio and 95% confidence interval (CI) for suicide associated with new use of an antidepressant at discrete monthly intervals from the start of treatment.

Multivariable analysis adjusted for rural place of residence (imputed from home postal code) (48), estimated residential income quintile, previous suicide attempt, the number of prescription medications dispensed in the previous year (49), and any evidence (from prescription records, physician diagnosis codes, or hospital discharge records during the preceding year) of alcohol abuse, malignancy, anxiety or sleep disorder, bipolar disorder, de-

TABLE 2. Demographic and Clinical Characteristics of Elderly Suicide Cases and Matched Comparison Subjects

Characteristic	Suicide Cases (N=1,138)		Comparison Subjects (N=4,552)	
	Mean	SD	Mean	SD
Age (years)	74.9	6.7	74.9	6.7
Total days in the hospital during preceding year	6.1	15.0	5.6	17.0
Number of drugs dispensed in preceding year	10	8	10	8
	N	%	N	%
Male	882	78	3528	78
Lowest residential income quintile[a]	290	25	1062	23
Highest residential income quintile	200	18	729	16
Urban place of residence	3636	80	906	80
Long-term care facility	19	2	112	2
Use of health services in preceding year				
Any psychiatrist visit	152	13	590	13
Admission to psychiatric unit	32	3	68	1
Prevalence of selected illnesses in preceding year				
Affective disorder	361	32	910	20
Alcohol abuse	47	4	92	2
Anxiety or sleep disorders	668	59	2799	61
Bipolar disorder	50	4	147	3
Cancer (any)	94	8	370	8
Chronic lung disease	242	21	969	21
Coronary artery disease	235	21	1052	23
Dementia	48	4	268	6
Diabetes mellitus	188	17	739	16
Dyslipidemia	77	7	249	5
Heart failure	178	15	833	18
Injury other than poisoning (regardless of intent)	306	27	1207	27
Pain requiring nonsteroidal anti-inflammatory drug	320	28	1330	29
Pain requiring high-potency opiate[b]	44	4	141	3
Parkinson's disease	28	2	139	3
Peptic ulcer disease and related conditions	274	24	1172	26
Pneumonia	92	8	378	8
Poisoning or drug toxicity (regardless of intent)	60	5	263	6
Psychotic disorders and related conditions	118	10	432	9
Seizure	31	3	125	3
Stroke	97	9	455	10
Suicide attempt in preceding 3 years	38	3.3	22	0.5

[a] Imputed from residential postal code and expressed in 1996 Canadian dollars.
[b] Includes morphine, hydromorphone, and transdermal fentanyl.

pression or other mood disorder, agitation or psychosis, poisoning or other injury, provision of care by a psychiatrist, or admission to a psychiatric facility. All tests of significance used a two-tailed p value of 0.05 for statistical significance and were conducted using SAS version 8.2 (SAS Institute, Cary, N.C.)

Results

Overview

During the study period, we identified 1,354 cases of suicide among individuals 66 years or older. Of these, 25 (2%) were excluded because of an invalid health card number, erroneous identifying data, or principal residence outside Ontario. Of the remaining 1,329 cases, the propensity scores of 191 (14%) were too high to permit propensity-based matching with four comparison subjects. Therefore, the matched analyses included 1,138 suicide cases and 4,552 comparison subjects with comparable demographic characteristics and antecedent patterns of illness (Table 2). The majority of patients who died of suicide were men living in an urban setting, and few had seen a psychiatrist in the year before death. The most common mechanisms of suicide were death by firearm (N=370), hanging (N=318), and self-poisoning (N=285).

Use of Antidepressants

Of the 1,329 suicide cases, 907 (68%) had received no antidepressant therapy in the 6 months before death. The risk of suicide during the first month of treatment with SSRI antidepressants was about fivefold higher than that with other antidepressants (Table 3). In contrast, no differential risk of suicide was evident during the second and subsequent months of SSRI therapy. The temporal relationship between initiation of antidepressant therapy and risk of suicide for SSRI and other antidepressants is depicted in Figure 1.

Antidepressant Subgroups

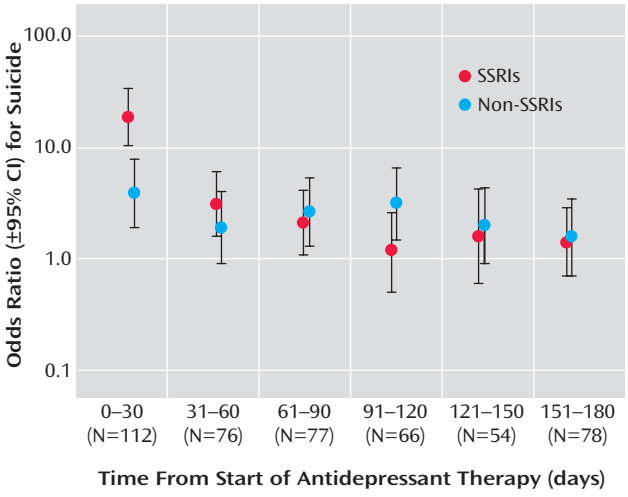
Some antidepressants are used for illnesses other than depression. This is particularly true for tertiary amine cyclic antidepressants such as amitriptyline and doxepin (often prescribed for conditions such as migraine, pruritus, and neuropathic pain) and for clomipramine

TABLE 3. Likelihood by Month of Suicide Among Elderly Ontario Residents After Initiation of Treatment With SSRI Antidepressants Versus Other Antidepressants

	Suicide Cases Initiating Therapy During Interval (N=1,138)		Comparison Subjects Initiating Therapy During Interval (N=4,552)		Analysis[a]	
Interval Prior to Suicide	SSRI	Non-SSRI	SSRI	Non-SSRI	Odds Ratio	95% CI
0 to 30 days	62	17	16	17	4.8	1.9 to 12.2
31 to 60 days	17	11	24	24	1.7	0.6 to 4.6
61 to 90 days	16	14	26	21	0.8	0.3 to 2.1
91 to 120 days	8	15	26	17	0.4	0.1 to 1.1
121 to 150 days	7	10	17	20	0.8	0.2 to 2.8
151 to 180 days	11	10	31	26	0.8	0.3 to 2.5

[a] Comparison of suicide likelihood with SSRIs relative to other antidepressants, adjusted for rural place of residence, residential income quintile, suicide attempt in the preceding 3 years, prescription-based comorbidity index (45), and any of the following in the preceding year: receipt of treatment from a psychiatrist, alcohol abuse, malignancy, anxiety or sleep disorder, bipolar disorder, depression or other mood disorder, agitation or psychosis, poisoning or other injury, or admission to a psychiatric facility.

FIGURE 1. Month-by-Month Analysis of Suicide Risk Among Elderly Ontario Residents After Initiation of Treatment With SSRI Antidepressants Versus Other Antidepressants[a]



[a] During the first month of treatment, the risk of suicide with SSRI antidepressants is approximately 5-fold higher than that with other antidepressants (p=0.0009), but no difference in risk is seen with continued therapy.

(often used for obsessional disorders). Our findings did not change significantly when we excluded all tertiary amine cyclic antidepressants from the group of non-SSRI antidepressants.

Several antidepressants have distinguishing characteristics from others in the same class. We found consistent results when we categorized venlafaxine (which blocks both serotonin and norepinephrine reuptake at higher doses) (50) as an SSRI antidepressant, despite evidence that venlafaxine may be prescribed to patients with a greater burden of risk factors for suicide (51). Similarly, our findings persisted when we excluded amoxapine and maprotiline (which are structurally dissimilar from other secondary amine cyclic antidepressants) from the analysis, and when we excluded clomipramine (which selectively interferes with serotonin transport and is often used for obsessive disorders) from the group of tertiary amine cyclic antidepressants.

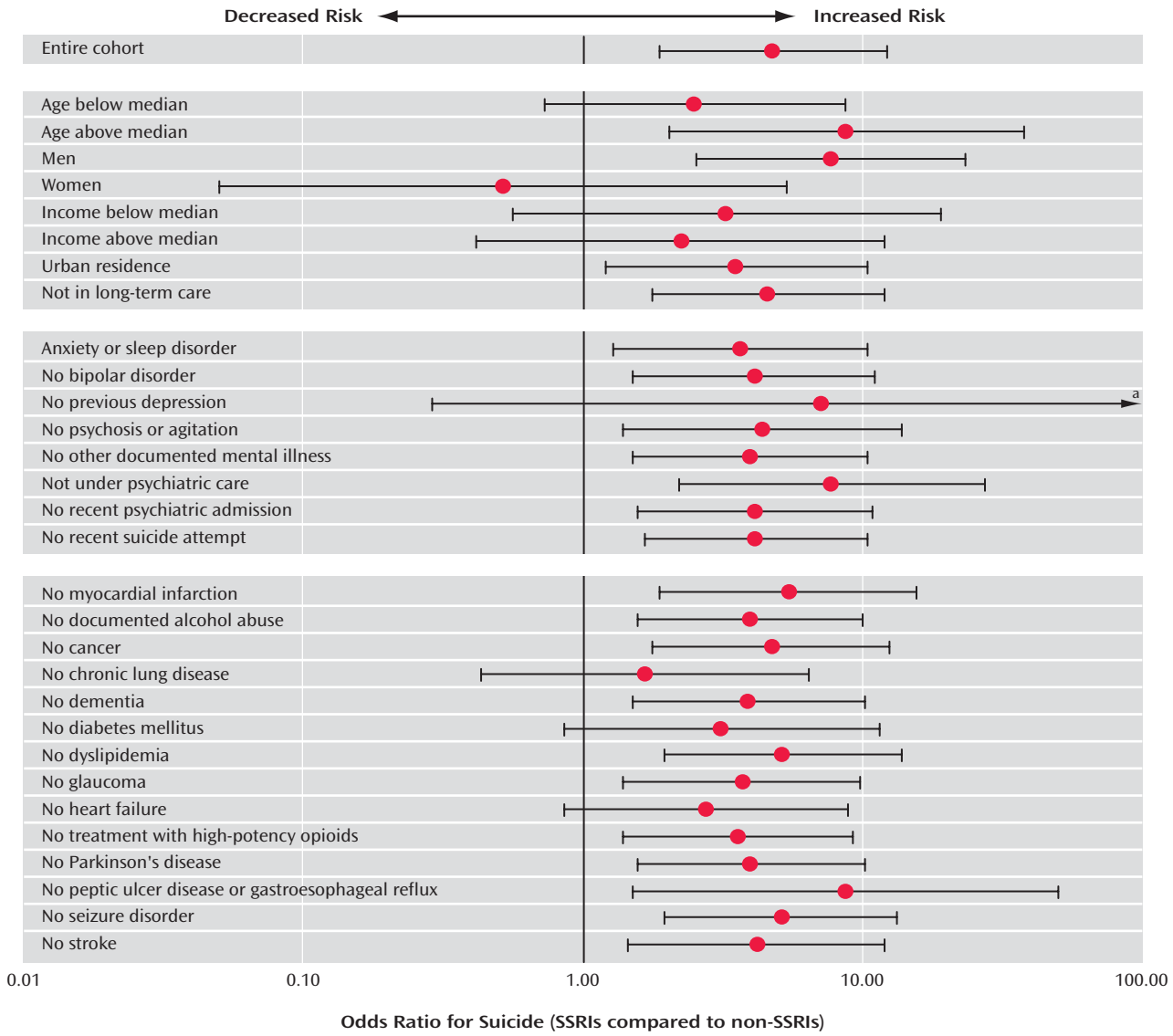
Additional Analyses

Our original findings persisted when we defined new use of antidepressants as no use of any other antidepressant in the preceding 6 months, and also when we replicated our analysis without the propensity score-based matching process by studying all 1,329 cases and 5,315 randomly selected community-dwelling controls matched only on age, gender, and residential income quintile. Some previous studies of the association between antidepressants and suicidal behavior have been confined to patients receiving treatment (31, 32, 52), and we therefore also conducted a nested case-control study of patients treated with antidepressants within 6 months of the index date. These findings also mirrored our original analysis. (An appendix presenting these additional analyses accompanies the online version of this article.) Finally, we found consistent results in a series of analyses stratified by demographic characteristics, mental health history, and patterns of medical illness (Figure 2). The only exception was that the first month of treatment with SSRI antidepressants was not associated with a disproportionate increase in suicide among women.

Spectrum of Suicide

We examined the association between antidepressant use and method of suicide, since some reports have linked SSRI antidepressants with especially violent suicidal ideation (15, 39). Relative to other antidepressants, SSRIs were more strongly associated with suicides of a violent nature (hanging, gunshot, jumping, stabbing, vehicle collision, blunt trauma, explosion, electrocution, and self-immolation) than other antidepressants (Figure 3). A tendency toward violent suicide was apparent only during early therapy with SSRIs, whereas nonviolent suicide was equally common among patients treated with SSRIs and other antidepressants.

FIGURE 2. Suicide Risk Among Elderly Ontario Residents After Initiation of Treatment With SSRI Antidepressants Versus Other Antidepressants, by Subgroups



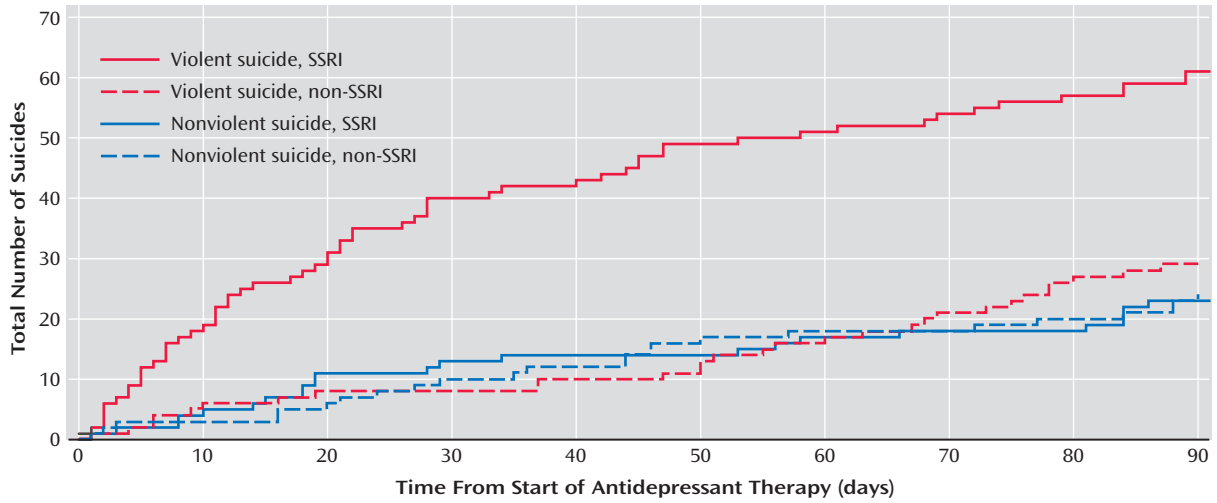
[a] Extends to 170.3.

Absolute Risk of Suicide

We estimated the absolute risk of suicide during the first month of treatment with SSRI antidepressants by dividing the total number of suicides in such patients (N=73 of 1,329 total cases) by the total number of patients who received an SSRI antidepressant during the study period (N=244,749). The same calculation was performed for other antidepressants. Using this approach, we found that the absolute risk of suicide during the first month of treatment was low in both groups (approximately 1 in 3,353 SSRI-treated patients and about 1 in 16,037 patients receiving other antidepressants). Because many suicides during the first month of treatment likely result from depression itself rather than an adverse effect of treatment, the actual risk of suicide due to antidepressant therapy is probably far lower.

To place the absolute risk of suicide in context, we found that 907 of 1,329 suicide cases (68%) received no antidepressant in the 6 months before suicide, yet many were likely depressed (53, 54). Although no studies have proven that antidepressants prevent suicide, recent evidence suggests that treating depression reduces suicidal ideation in older patients (55). If treatment with SSRI antidepressants reduces the risk of suicide by as little as 2% in patients with major depression, we speculate that the number of suicide deaths that might be prevented through increased use of SSRI antidepressants among older patients with major depression would exceed the number of deaths attributable to these drugs.

FIGURE 3. Spectrum of Suicide Among Elderly Ontario Residents After Initiation of Treatment With SSRI Antidepressants Versus Other Antidepressants[a]



[a] Violent suicides were distinctly more common among those who recently initiated treatment with SSRI antidepressants (p=0.0016 by Kruskal-Wallis test of median interarrival time).

Discussion

Previous research on SSRI antidepressants and suicide has been limited by an absence of suitable controls, small study group sizes, use of surrogate endpoints, inefficient study designs, and a lack of population-based data (15, 26, 31, 32, 38, 52, 56–59). Using 9 years of comprehensive coroner's records and prescription data in a population of more than 1 million older patients, we found a substantial increase in the relative risk of suicide following the initiation of SSRI treatment. The differential risk compared with other antidepressants was confined to the initial month of therapy, after which time no heightened risk was evident. It is interesting that we found SSRI antidepressants to be not associated with an increased suicide risk among women; however, as with all post-hoc analyses, this observation may be due to chance and should be interpreted cautiously.

Although case/control studies cannot generally yield estimates of excess risk, the population-based nature of our data indicates that the absolute risk of suicide during initial treatment with SSRI antidepressants is very low. In contrast, more than two-thirds of cases committed suicide while not receiving an antidepressant, highlighting the undertreatment of depression in older patients (60, 61).

Several mechanisms may underlie the association between SSRI antidepressants and suicide (18, 19). During initial therapy, the risk of suicide may increase as some aspects of depression resolve (e.g., psychomotor retardation), thereby energizing the patient to suicide (62). Patients may also develop akathisia-like symptoms during treatment with SSRI antidepressants, which may increase the risk of suicide (4, 14, 63–65). In addition, emerging evidence suggests that genetic differences in drug metabolism or serotonin receptor polymorphisms influence the safety and tolerability of these drugs (66, 66–69). Our findings mirror the clinical observation that the vast majority of patients treated with SSRI antidepressants do not attempt suicide, but that in rare instances these drugs appear to incite suicidal ideation during the first weeks of therapy (39, 70, 71). We speculate that treatment-emergent agitation or dysphoria can provoke suicidal ideation in some patients (72). Like other rare adverse drug events, this idiosyncratic response may have a pharmacogenetic basis (73–76), and future research may provide a means of identifying such individuals before commencing treatment (77, 78).

An alternative explanation for our findings might be that physicians preferentially prescribe SSRI antidepressants to patients at higher risk for suicide because these drugs are safer in overdose. However, this is unlikely to explain our findings for several reasons. Physicians frequently cannot identify patients at increased risk of suicide, particularly among the elderly (79, 80). Moreover, we selected comparison patients matched to cases on important characteristics (Table 1), many of which are independently associated with suicide (54, 81, 82). In addition, we found consistent results regardless of a previous history of depression or psychiatric care, and in a separate nested case/control analysis restricted to patients receiving antidepressant therapy. Notably, no heightened risk of suicide was evident beyond the first month of treatment with SSRIs compared with other antidepressants. Had depression (rather than drug treatment) explained our findings, a more persistent risk should have been identified with SSRI therapy, since depressive symptoms rarely abate completely during the first month of therapy. Finally, the distinctly violent pattern of suicides during early SSRI therapy is consistent with previous reports and argues strongly

against selection bias (15, 39), which would have yielded an increase in both violent and nonviolent suicide among patients treated with SSRI antidepressants.

Some limitations of our research merit emphasis. We used administrative data and had no direct measure of antidepressant doses or adherence, and the applicability of our findings to younger patients is not known. These limitations are particularly important given recent warnings regarding antidepressant use in adolescents (21, 83). We could not directly measure important risk factors such as bereavement and social isolation. Although administrative data are an imperfect means of identifying certain medical problems such as malignancy and alcoholism, differential detection of these conditions with SSRIs versus other antidepressant treatment is not likely to explain our findings. Although we used a population-based registry to identify suicides, some cases of nonviolent suicide in older patients may have been misattributed to natural causes (84). Finally, we cannot exclude the possibility that SSRI antidepressants merely reduce the risk of suicide less effectively than other treatments.

Our study does not address the benefits of SSRI antidepressants and cannot establish the number of suicides prevented by treatment (85–87). The findings should not serve to anathematize SSRIs as a class, since they represent an important therapeutic option for patients with depression (85). Patients responding well to SSRI antidepressants should not discontinue therapy, and individuals with depression must not be deterred from seeking treatment based upon our findings (55). Indeed, in patients with major depression, the hazards of undertreatment almost certainly outweigh the risks of therapy, which our study suggests are low and transient. Further research is needed to explore the basis of our findings, including the possible role of genetic variability in drug response (66, 68). In the interim, our findings reaffirm the need for clinicians to reserve SSRI antidepressants for patients with established indications, monitor them closely after commencing treatment, and inform patients and their families of the possible emergence of suicidality during the first month of therapy.

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