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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Selective serotonin re-uptake inhibitors and the risk of violent suicide: a nationwide postmortem study

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Abstract

Purpose We endeavored to investigate whether previous findings of an association between antemortem exposure to selective serotonin re-uptake inhibitors (SSRI) and method of suicide could be replicated.

Methods Using the Swedish National Board of Forensic Medicine's toxicology database and the Swedish National Board of Health and Welfare's national registries of causes of death and prescriptions, 10,002 incidents of suicide were retrieved. Risks of violent suicide conferred by SSRIs, expressed as odds ratios (ORs) with 95% confidence intervals (CIs), were estimated using logistic regression. In accordance with previous work, suicide by violent means—cases—were defined as death attributable to causes designated by ICD-10 codes X70-X83 and Y20-Y33; and suicide by non-violent means—controls—by codes X60-X69 and Y10-Y19.

Results Our results imply that SSRI exposure confers a risk of violent suicide for shorter treatment durations; and that antemortem exposure to other substances (including illegal drugs) confounds estimates of risk. After adjustment for age, sex, and other substances, SSRIs treatment not exceeding 28 days conferred an almost fourfold risk of violent suicide (OR 3.6 [95% CI 1.9–6.8]), a finding partly in line with a recent Swedish study that employed a case-crossover design.

Conclusions Although risks associated with shorter treatment duration may reflect latencies to onset of therapeutic effect, it is unclear how latencies would influence the choice of suicide method, unless conditions for which SSRIs are prescribed are themselves associated with violent suicide. Finally, in the total dataset, SSRIs were not associated with an increased risk of violent suicide; however, by adjusting for other substances, we avoided the spurious conclusion that the effect of medications in this regard is protective.

Keywords Completed suicide · Violence · Postmortem · Toxicology · Selective serotonin re-uptake inhibitors · Dispensed prescription

Introduction

The degree to which use of selective serotonin re-uptake inhibitors (SSRIs) may confer an elevated risk of suicidality and criminal violence has been a topic of recurrent discussion [1, 2]. Levels of activity in monoamine systems in the brain are believed to play a major role in the course of affective disorders [3]. Apart from the extensive body of research regarding

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serotonin's role in depression, low serotonergic activity has also been associated with risk-taking behavior and aggressiveness [4, 5]. The latter behaviors have been further conceptualized as part of an atypical depressive syndrome, particularly in the male population [6, 7]. In addition, there is plausible support for the notion that the degree of aggression or violence in a suicidal act affects the likelihood of fatal outcome [8, 9].

At the same time, there exist conflicting results from previous studies on SSRIs and their possible association with violent suicidal behavior, which has become a source of unease and uncertainty for both patients and prescribers. Anecdotal legal reports aside, larger cohort studies have linked SSRIs to violent suicides in subgroups stratified by age, sex, and the presence of substance-use disorder [10–13]; yet, these results have been contradicted by findings from studies based on nationwide prescription and forensic-toxicological data [14, 15]. Still, however, no previous studies have addressed whether the concomitant use of other substances (including other medications and illegal drugs) may confound estimates of the risk of violent suicidal death during treatment with SSRIs. Moreover, although several studies have attempted to account for confounding by indication through the use of propensity-score matching [16–18], there is little consensus regarding the manner in which propensity should be defined and quantified [19, 20]. Thus, conclusions concerning possible associations between SSRIs, on the one hand, and violent suicidality and aggression, on the other, remain speculative.

In the present case-control study, using toxicological results from forensic autopsies performed in Sweden during the years 2005 to 2012, we made use of the following novel design in order to investigate a potential association between SSRIs and the risk of violent suicide, in subgroups of subjects exhibiting two ultimate phenotypes—violent suicide (cases) and non-violent suicide (controls)—we compared antemortem exposure to SSRIs, thus accounting for a common penultimate phenotype, the subjects' shared propensity to commit suicide.

Methods

Study population

The Swedish judicial system attempts, by way of autopsies performed at the country's designated forensic units, to clarify causes of fatality in all instances of unnatural or unwitnessed death. The Swedish National Board of Forensic Medicine's department of forensic toxicology holds a distinctive global position, in that it performs sensitive toxicological analysis in nearly all incidents of unnatural death; analysis is capable of detecting most legal and illegal substances available either by prescription or on the "black market," as well as selected metabolites [21, 22]. Toxicological analysis is performed on femoral blood, urine, and vitreous humor extracted at autopsy from the remains of the deceased; results—forensic-toxicological findings and determined causes of death—are then registered in the National Board of Forensic Medicine's database, Toxbase, and the National Board of Health and Welfare's national registry of causes of death, respectively. The National Board of Health and Welfare has since July 1, 2005, also coordinated the Swedish National Prescription Registry, which covers individual-level information on all dispensed prescriptions in the country. For the present study, we retrieved complete records for all registered instances of completed suicide from the years 2005 to 2012 ($n = 10{,}002$) and linked them to data in the Swedish National Prescription Registry.

Outcome measures

Causes of death were assigned codes categorizing external causes of morbidity and mortality in the ninth and tenth revisions of the International Classification of Diseases and Related Health Problems (ICD-9 and ICD-10); for the analysis, ICD-9 codes were translated to their ICD-10 counterparts. In accordance with previous work, suicide by violent means—cases—were defined as death attributable to causes designated by the ICD-10 codes X70-X83 and Y20-Y33 (which include death by drowning or submersion) [14, 23–25]; and suicide by non-violent means—controls—by the ICD-10 codes X60-X69 and Y10-Y19.

With regard to the ICD-10 codes X83 ("Intentional self-harm by other specified means") the cause of death was adjudged to be violent or non-violent depending on specific registered circumstances. Incidents adjudged to be suicide for which methods were unreported (ICD-10 codes X84 and Y34; $n = 434$) were excluded, as were incidents with missing data regarding age or sex ($n = 15$). Of the 9553 incidents included in the study, 7515 were events of certain suicide and 2038 of uncertain suicide (for the complete list of specified suicide methods, see Supplementary Table 1).

Identification of exposure

SSRI treatment was defined as forensic-toxicological detection of any active substance (or its metabolite) contained in a medication assigned an Anatomic Therapeutic Chemical Classification System code of N06AB (fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine); whereas, the presence of "other substances" was defined as detection of any substance other than SSRIs (including other medications and illegal drugs). Durations of SSRI treatment, measured in days from the date of the first dispensed prescription to the date of death, were categorized as never; between 0 and 28 days; between 29 and 56 days; and more than 56 days.

Statistical analysis

Risks of violent suicide conferred by SSRI treatment were estimated using logistic regression, by comparing exposure to treatment in cases and controls, and expressed as odds ratios (ORs) with 95% confident intervals (CIs); analyses were performed separately for males and females and stratified by age (after categorization of subjects as either younger than 30 years of age; between 30 and 49 years of age; between 50 and 69 years of age; and 70 years of age or older). To study the effect of individual SSRIs, SSRI-treated subjects were categorized by SSRI (citalopram, sertraline, and other SSRIs grouped together) and duration of SSRI treatment; when appropriate, adjustments were made for sex, age, SSRI, and categories of other substances (entered into regression models as one dichotomous covariate for each category). Incidents of both certain and uncertain suicide were included in the main analyses; yet, sensitivity analyses restricted to incidents of certain suicide were also performed. All analyses were performed in both R version 3.1.3 and Statistical Analysis System version 9.4; risk estimates for which 95% CIs did not overlap unity were considered statistically significant.

Ethics

Our investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The research ethics committee in Stockholm, Sweden, approved the current research (reference number 2013/1411–31/5).

Results

From a total of 10,002 forensically investigated incidents of completed suicide, complete records regarding age, sex, cause of death, and postmortem toxicological findings were available for 9553 subjects. Among males, suicides committed using violent methods were more common than suicides committed using non-violent methods ($n = 4585$ [67.4%] vs. $n = 2217$ [32.6%]); whereas, among females, suicides committed using violent methods were less common than suicides committed using non-violent methods ($n = 1251$ [45.5%] vs. 1500 [54.5%]). Mean and median ages were similar regardless of suicide method or exposure to SSRI treatment (Table 1); however, stratification by age-group revealed that suicides by violent methods were more common in all age-groups, yet most strikingly so among the oldest subjects (Table 4). The mean number of categories of other detected substances (including other medications and illegal drugs) was greater in subjects who had committed suicide using non-violent methods (Table 1).

In the model adjusted for age, sex, and categories of other substances (including other medications and illegal drugs), there were no associations between violent suicide and detection in postmortem blood of citalopram/escitalopram, sertraline and other SSRIs, even after stratification by sex (Table 2), nor in a sensitivity analysis restricted to instances of certain suicide (Supplementary Table 2).

In a model stratified by sex and categorized by duration of SSRI treatment (as number of days), an increased risk of committing violent suicide was found for the shortest duration of SSRI treatment (0 to 28 days; OR 3.6 [95% CI 1.9–6.8]), among both males (OR 3.6 [95% CI 1.6–8.1]) and females (OR 3.9 [95% CI 1.3–11.9]); the risk was attenuated by the length of use, in both sexes (Table 3). A sensitivity analysis restricted to instances of certain suicide yielded similar risk estimates (Supplementary Table 3). The increased risk of committing violent suicide associated with SSRI treatment was attenuated by the duration of treatment in all age categories, yet most prominent among subjects aged above 50 years (Table 4). Additional analyses, after stratification by sex and positivity upon forensic-toxicological analysis for the most commonly occurring categories of other substances (including other medications and illegal drugs), yielded similar results (Supplementary Table 4).

Discussion

This nationwide postmortem study included information on nearly all forensically investigated incidents of completed suicide in Sweden during the years 2005 to 2012. Our work addresses a question previously addressed in an earlier Swedish dataset from 1992 to 2004; yet, it employs a novel design—entailing group-level matching for suicidal propensity, as well as individual-level adjustment for postmortem detection of other substances (including other medications and illegal drugs) and duration of treatment—to investigate the potential association between violent methods of suicidal death and antemortem exposure to SSRIs.

The earlier findings by Fazel and co-workers, which suggested that SSRIs have a protective influence upon the risk of committing violent suicide, could, in our study, not be replicated [14]; however, our findings are similar to those of Björkenstam and co-workers in their case-crossover study regarding the risk of completed suicide upon initiation of SSRI treatment, which made use of data from virtually the same time period (2007–2010) [26]. Our results indicate that SSRI exposure confers a risk of using a violent suicide method for shorter treatment durations, regardless of age-group; however, the association is particularly prominent among subjects aged 70 years or older, which is in line with previous findings from Ontario, Canada, on SSRI use and suicide risk in the elderly [11].

Our results imply that antemortem exposure to other substances (including other medications and illegal drugs)

Table 1 Characteristics, including sex, age, and results of forensic-toxicological analysis, for subjects characterized by type of suicide method and presence or absence of treatment with selective serotonin re-uptake inhibitors (SSRIs; defined as presence or absence in postmortem blood of fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine, or their metabolites)

Characteristics	Violent suicide SSRI+	SSRI–	Non-violent suicide SSRI+	SSRI-
Total (*n*)	925	4911	865	2852
Men (*n*, %)	618 (67)	3967 (81)	409 (47)	1808 (63)
Women (*n*, %)	307 (33)	944 (19)	456 (53)	1044 (37)
Mean age in years (SD)	55.7 (19.5)	51.3 (19.8)	50.4 (15.6)	49.4 (16.5)
Median age in years	57	52	51	50
Ethanol, other alcohols (*n*, %)	249 (27)	1725 (35)	364 (42)	1231 (43)
Non-opioid analgetics (*n*, %)	117 (13)	474 (10)	215 (25)	582 (20)
Other antidepressants (*n*, %)	220 (24)	644 (13)	203 (23)	657 (23)
Organic solvents (*n*, %)	28 (3)	126 (3)	66 (8)	229 (8)
Psychostimulants (*n*, %)	32 (3)	164 (3)	44 (5)	226 (8)
GABAergic drugs (*n*, %)	303 (33)	879 (18)	558 (65)	1563 (55)
Mood stabilizers (*n*, %)	52 (6)	147 (3)	62 (7)	174 (6)
Antipsychotics (*n*, %)	71 (8)	178 (4)	126 (15)	271 (10)
Non-GABAergic sedatives (*n*, %)	194 (21)	419 (9)	414 (48)	867 (30)
Opioid analgetics (*n*, %)	68 (7)	333 (7)	349 (40)	1291 (45)
Organic gases (*n*, %)	8 (1)	63 (1)	44 (5)	324 (11)
Illegal drugs (*n*, %)	19 (2)	157 (3)	43 (5)	214 (8)
Other (*n*, %)	30 (3)	146 (3)	67 (8)	196 (7)
Mean number of substance categories (SD)	1.5 (1.3)	1.1 (1.1)	3.0 (1.4)	2.7 (1.3)

confounds estimates of risk: before adjustment for such other substances, SSRI treatment appeared to exert a protective influence with regard to the risk of violent suicide (OR = 0.62 [95% CI 0.56–0.69]; Table 1, data not explicitly shown), a finding that would have been in accordance with those of Fazel and co-workers [14]. However, our findings show that the presence of other substances (including other medications and illegal drugs) in postmortem blood is an important negative confounder when the potential association between SSRIs and violent suicide is under investigation. In the present study, other substances were positively correlated with the exposure under investigation, SSRIs, and negatively correlated with the outcome under investigation, suicide by violent means; thus, by failing to adjust for other substances, we would have spuriously estimated the general effect of SSRIs on the risk of violent suicide to be protective. In reality, in certain subgroups such as subjects with shorter durations of treatment, SSRIs, on the contrary, appeared to predispose to suicide by violent means. Indeed, other substances (including other medications and illegal drugs) have not previously been taken into consideration as a confounding variable in studies exploring the potential association between SSRIs and the risk of violent suicide, which presumably explains why previous studies have yielded inconsistent results.

Possible causes underlying other substances' positive associations with both SSRI exposure and non-violent suicide might include the following: SSRIs are often prescribed together with other medications that may represent a lethal means of self-harm; and other substances may exert a negative influence on violent behavior. Antidepressants are the most commonly co-prescribed drugs in multi-class polypharmacy for psychiatric disorders, which furthermore have high co-morbidity rates with both somatic illness and substance misuse [27–30]. In this context, apart from intentional self-poisoning being the predominant non-violent suicide method, the biological effects of other substances may also have diminished subjects' impulsivity and aggressiveness, ultimately influencing the choice of suicide method.

The time course of response to SSRIs in major depression has been shown to differ depending on a number of factors, including age. The elderly exhibit a lower rate of response to antidepressants, including SSRIs, up till the sixth week of treatment [31]. It could thus be argued that the increased risks associated with shorter treatment durations (especially among people above the age of 70) in the present study merely reflect latencies to onset of therapeutic effect. At the same time, it is unclear how such latencies would influence the choice of suicide method, unless the conditions for which SSRIs are commonly prescribed

Table 2 Odds ratios (ORs) with 95% confidence intervals (CIs) for suicide by violent methods among subjects positive upon forensic-toxicological analysis for selective serotonin re-uptake inhibitors (SSRIs) in postmortem blood, compared with subjects negative for SSRIs upon postmortem screening, before and after stratification by sex

	SSRI	Violent suicide: non-violent suicide	OR (95% CI)[1]	OR (95% CI)[2]
Total	None	4911:2852	1 (reference)	1 (reference)
	Citalopram[3]	570:479	0.7 (0.6–0.8)	0.8 (0.7–1.0)
	Sertraline	237:217	0.7 (0.6–0.9)	1.0 (0.8–1.2)
	Other SSRIs	118:169	0.5 (0.4–0.7)	0.9 (0.6–1.2)
Males	None	3967:1808	1 (reference)	1 (reference)
	Citalopram[3]	389:241	0.7 (0.6–0.8)	0.8 (0.7–1.0)
	Sertraline	163:111	0.7 (0.5–0.9)	0.9 (0.6–1.2)
	Other SSRIs	66:57	0.5 (0.4–0.8)	1.1 (0.7–1.7)
Females	None	944:1044	1 (reference)	1 (reference)
	Citalopram[3]	181:238	0.8 (0.7–1.0)	0.8 (0.7–1.1)
	Sertraline	74:106	0.8 (0.6–1.0)	1.1 (0.8–1.6)
	Other SSRIs	52:112	0.5 (0.4–0.7)	0.7 (0.5–1.1)

[1] Adjusted for age (and, before stratification, sex)

[2] Adjusted for age and categories of other substances (including other medications and illegal drugs) (as well as, before stratification, sex)

[3] The enantiomer of citalopram—escitalopram—is detected as citalopram

are themselves specifically associated with suicide by violent means—particularly in the absence of treatment response.

Limitations and strengths

One important limitation in our study was the lack of consistent outpatient clinical data, which precluded investigation of a possible tendency to violent suicidal behavior prior to the prescription of antidepressants. Such residual confounding by indication is difficult to adjust for but could be addressed in future research by means of propensity-score matching; however, an effort in this vein would be to perform a limited study incorporating data regarding historical psychiatric factors—including diagnoses, previous violent behavior and its consequences, prescription records, and suicide-risk assessments—as well as other relevant data from in- and outpatient care. A second important limitation is that, in an observational study, the possibility of the existence of unknown confounding factors will always remain.

Given these limitations, forensic-toxicological detection of pharmacological substances post mortem is the closest possible proxy for actual ongoing pharmacotherapy and its conceivable

Table 3 Odds ratios (ORs) with 95% confidence intervals (CIs) for suicide by violent methods among subjects positive upon forensic-toxicological analysis for selective serotonin re-uptake inhibitors (SSRIs) in postmortem blood, compared with subjects negative for SSRIs upon postmortem screening, by duration of treatment, before and after stratification by sex

	Days since first SSRI prescription	Violent suicide:non-violent suicide	OR (95% CI)[1]	OR (95% CI)[2]
Total	Never	4912:2852	1 (reference)	1 (reference)
	0–28	109:17	3.6 (2.2–6.1)	3.6 (1.9–6.8)
	29–56	55:24	1.5 (0.9–2.4)	1.7 (0.9–3.1)
	> 56	585:655	0.6 (0.5–0.7)	0.8 (0.7–0.9)
Males	Never	3967:1808	1 (reference)	1 (reference)
	0–28	87:10	3.6 (1.8–6.9)	3.6 (1.6–8.1)
	29–56	38:13	1.3 (0.7–2.4)	1.5 (0.6–3.4)
	>56	376:299	0.6 (0.5–0.7)	0.8 (0.6–1.0)
Females	Never	945:1044	1 (reference)	1 (reference)
	0–28	22:7	3.6 (1.5–8.5)	3.9 (1.3–11.9)
	29–56	17:11	1.8 (0.8–3.8)	2.0 (0.8–4.8)
	>56	209:356	0.7 (0.5–0.8)	0.8 (0.6–1.0)

[1] Adjusted for age (and, before stratification, sex)

[2] Adjusted for age and categories of other substances (including other medications and illegal drugs) (as well as, before stratification, sex)

Table 4 Odds ratios (ORs) with 95% confidence intervals (CIs) for suicide by violent methods among subjects positive upon forensic-toxicological analysis for selective serotonin re-uptake inhibitors (SSRIs) in postmortem blood, by duration of treatment, before and after stratification by age

Age in years	Days since first SSRI prescription	Violent suicide: non-violent suicide	OR (95% CI)[1]	OR (95% CI)[2]
Total	Never	4911:2852	1 (reference)	1 (reference)
	0–56	164:41	2.4 (1.7–3.4)	2.5 (1.6–3.8)
	> 56	585:655	0.6 (0.5–0.7)	0.8 (0.7–0.9)
< 30	Never	861:418	1 (reference)	1 (reference)
	0–56	14:6	1.4 (0.5–3.7)	2.3 (0.7–7.8)
	> 56	88:81	0.6 (0.4–0.8)	0.9 (0.5–1.4)
30–49	Never	1357:996	1 (reference)	1 (reference)
	0–56	26:14	1.5 (0.8–3.0)	1.7 (0.7–4.1)
	> 56	137:220	0.5 (0.4–0.7)	0.7 (0.5–1.0)
50–69	Never	1748:1119	1 (reference)	1 (reference)
	0–56	75:16	3.0 (1.7–5.2)	2.5 (1.3–4.7)
	> 56	210:290	0.6 (0.5–0.7)	0.7 (0.5–0.8)
70 or over	Never	946:319	1 (reference)	1 (reference)
	0–56	49:5	4.0 (1.5–10.4)	3.6 (1.2–11.1)
	> 56	150:64	1.1 (0.8–1.5)	1.3 (0.8–2.0)

[1] Adjusted for age (and, before stratification, sex)

[2] Adjusted for age and categories of other substances (including other medications and illegal drugs) (as well as, before stratification, sex)

biological impact on the suicidal process. The strengths of our study derive from its unique dataset, which comprises reliable forensic-toxicological findings from a virtually complete national record of incidents of certain completed suicide and individual-level information on all dispensed prescriptions.

Clinical implications

The dataset of the current study consists only of people who have committed suicide; given the lack information about previous attempts, psychiatric comorbidity and other factors, our results have limited immediate clinical implications. However, based on our findings, it cannot be excluded that SSRIs, in particular in users who attempt suicide within the first months of treatment, might increase the risk of choosing a violent method, resulting in a greater risk of fatal outcome than if a non-violent method had been chosen [32, 33]. SSRIs as a class of medication do, nonetheless, represent an important therapeutic option for mood and anxiety disorders; moreover, there is evidence that suicide rates worldwide have decreased following the introduction of SSRIs [34, 35]. Ongoing treatment should not be discontinued, nor initiation of treatment delayed, based on the outcomes of this study, since the hazards of undertreatment outweigh the risks of therapy. Clinicians must closely monitor patients prescribed any kind of antidepressant until recovery and must also inform patients and relatives of possible side effects, including the risk of persisting or emergent suicidal ideation.

Conclusions

Our study failed to replicate the findings of an earlier study that reported a protective effect of SSRIs in postmortem blood upon the risk of committing violent suicide. We have shown that other substances (including other medications and illegal drugs) as a group are an important confounding variable when the influence of SSRIs on the choice of suicide method is under investigation. Thus, our study emphasizes the need to include data regarding other substances when analyzing SSRIs or other psychotropic substances in the context of adverse effects such as suicidal ideation, self-harm, or aggression. Finally, we have shown that the duration of treatment is inversely correlated with the risk of committing violent suicide, a finding partly in line with a recent Swedish study that employed a case-crossover design.

Contributors JF, TM, and AH contributed to the study concept and design; all authors contributed to data acquisition and collection; JF, TM, GI, and AH contributed to data analysis and interpretation; JF, TM, and AH drafted the manuscript; all authors contributed to revision of the manuscript and read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In this

registry-based postmortem study, all personal information was anonymized, rendering unnecessary the need for formal consent or ethical approval. The study was nonetheless reviewed and approved by the Regional Ethical Review Board in Stockholm (2013/1411-31/5).

Data-sharing statement The data that support the findings of this study are available from the Swedish National Board of Forensic Medicine's department of forensic toxicology (Rättsmedicinalverket - Rättskemi); and the National Board of Health and Welfare (Socialstyrelsen), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Rättsmedicinalverket and Socialstyrelsen.

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