European Neuropsychopharmacology (2020) 36, 1–9

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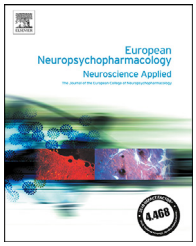

Associations between selective serotonin reuptake inhibitors and violent crime in adolescents, young, and older adults – a Swedish register-based study

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Received 12 August 2019; received in revised form 13 March 2020; accepted 30 March 2020

KEYWORDS
Selective serotonin reuptake inhibitors;
Crime;
Aggression;
Cohort studies

Abstract
This study identified individuals ever dispensed a selective serotonin reuptake inhibitor (SSRI) aged 15–60 years during 2006–2013, using Swedish national registers. The outcome was violent crime conviction. The main statistical analyses assessed risks of violent crime during periods on compared to off SSRI treatment within individuals. Further analyses investigated risk over time in relation to treatment initiation and discontinuation. The study identified 785,337 individuals (64.2% female), experiencing 32,203 violent crimes in 5,707,293 person-years. Between-individual analyses found statistically significantly elevated Hazard Ratios (HRs) overall (HR = 1.10), and in 15–24 and 25–34 year-olds (HR = 1.19 and 1.16), but non-significant HRs in 35–44 and 45–60-year-olds (HR = 1.02 and 1.04). In within-individual analyses, where 2.6% of SSRI users were informative, hazards were elevated overall (HR = 1.26, 95% CI = 1.19, 1.34), and across age groups (HR of 1.35 [95% CI = 1.19, 1.54] in 25–34-year-olds to 1.15 [95%

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https://doi.org/10.1016/j.euroneuro.2020.03.024

CI = 0.99, 1.33] in 35–44-year-olds). In the overall cohort, the within-individual HRs were significantly elevated throughout treatment (HRs of 1.24 to 1.35) and for up to 12 weeks post-discontinuation (HRs of 1.37 and 1.20). While questions on causality remain, these results indicate that there may be an increased risk of violent crime during SSRI treatment in a small group of individuals. It may persist throughout medicated periods, across age groups, and after treatment discontinuation. Further confirmation is needed from studies with different designs, and clinical focus should be on high-risk individuals, as a majority of SSRI-users (around 97% in our cohort) will not commit violent crimes.

1. Introduction

Mood disorders are leading contributors to disease burden globally (Vos et al., 2016) and, if left untreated, lead to substantial morbidity and mortality (Rapaport et al., 2005; Rihmer, 2007; Stewart et al., 2003). Antidepressant medications are a major part of the treatment of these disorders – and selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed type in a number of countries (Abbing-Karahagopian et al., 2014; Mars et al., 2017; Mojtabai and Olfson, 2014), where their use has been increasing across age groups over the last two decades (Abbing-Karahagopian et al., 2014; Lagerberg et al., 2019; Pratt et al., 2011). For example, in the US, the population prevalence of antidepressant use increased from 6.5% in 1999–2000 to 10.4% in 2009–2010, with almost two-thirds of those prescribed antidepressants being treated with SSRIs in 1999–2010 (Mojtabai and Olfson, 2014).

Despite their increasing prevalence, there is apprehension about the unintended outcomes of SSRIs – with one area of concern being aggression and violence (Sharma et al., 2016). There is some evidence that SSRIs are associated with an elevated risk of these outcomes in young people (Hemminki et al., 2017), though the evidence is less clear for adults. A pharmacosurveillance study using the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) finds that SSRIs are consistently associated with violent events in an adult-majority population (Moore et al., 2010). Meanwhile, a systematic review of randomized controlled trials (RCTs) finds an almost three-fold increased odds of serious aggression outcomes in child and adolescent antidepressant users versus controls, and a slightly elevated, though non-significant, effect estimate in adults (Sharma et al., 2016). Similarly, a previous register-based study from Sweden (with follow-up ending in 2009) finds a 43% increased hazard of violent crime during periods on versus periods off SSRI medication in those aged 15–24 years, and slightly elevated but non-significant effect estimates in older age groups (Molero et al., 2015). It remains unclear whether there is an elevated risk in middle-aged and older adults, due to the relatively small number of events in these age groups in previous RCTs and cohort studies, and the lack of age-specific subgroup analyses in pharmacosurveillance studies. As middle-aged and older adults make up the majority of SSRI users (Abbing-Karahagopian et al., 2014), it is important to understand the risk of severe violence in these populations.

In addition to age-related effects, there is uncertainty about how the risk of violence varies with time after initiating and discontinuing treatment with SSRIs. Periods of elevated risk of suicide within a short time after starting and stopping antidepressant treatment have been documented (Coupland et al., 2015). To our knowledge, there have been no such investigations in relation to violence. Providing evidence on critical periods of risk is important to prevent an outcome that carries high costs to victims, perpetrators, and society (Dolan et al., 2005; McCollister et al., 2010).

In this nationwide cohort study, we therefore investigate the association between SSRI medication and violent crime in the largest sample to date. In addition, we assess how risks might vary by age and time after treatment initiation and discontinuation. We are testing the null hypothesis that there is no association between SSRI treatment and violent crime overall and in analyses stratified by age category.

2. Experimental procedures

2.1. Data sources

Information from several Swedish national registers was linked, based on unique personal identification numbers (Ludvigsson et al., 2009). We extracted prescription information from the Swedish Prescribed Drug Register, which includes all dispensed pharmaceuticals in Sweden since July 2005 (Wettermark et al., 2007); violent crime information from the National Crime Register, which covers crime convictions since 1973 (Chang et al., 2015); patient hospital stays from the National Patient Register (Ludvigsson et al., 2011); demographic information from the Total Population Register (Ludvigsson et al., 2016); incarceration data from the Prison Register; and emigration data from the Migration Register (Ludvigsson et al., 2016). Information on psychiatric discharge diagnoses was available from the National Patient Register. The register includes information on inpatient care since 1973 and specialist (non-general practitioner) outpatient care since 2001 (Ludvigsson et al., 2011). All diagnoses are coded in accordance with the Swedish ICD-10 system during the study period (Ludvigsson et al., 2011). Diagnosis data from this register have moderate to excellent validity for conditions including schizophrenia, bipolar disorder, and depression (Ekholm et al., 2005; Fazel et al., 2015; Sellgren et al., 2011). The study was approved by the Regional Ethics Committee, Stockholm, Sweden (reference number 2013/862–31/5). The requirement for informed con-

sent was waived, as the study was register-based and the included individuals were not identifiable.

2.2. Study population

The cohort included all individuals in Sweden who had dispensed SSRI medication aged 15–60 years between January 1st 2006 until December 31st 2013. Follow-up began on January 1st 2006 or at attainment of age 15, whichever occurred last. Individuals were censored on December 31st 2013, at death, first emigration, or attainment of age 60, whichever occurred first. Follow-up did not stop at a violent crime event, meaning each individual could experience several events during follow-up. Periods of follow-up where individuals were in prison or hospital were excluded to account for actual time at risk.

2.3. Measures

2.3.1. Exposure

Treatment periods with SSRI medication (ATC code: N06AB) were defined by the assumption that two dispensed prescriptions falling within 120 days (4 months) of each other belonged to the same treatment period. This span was chosen as oral medications are not likely to be dispensed for more than 90 days at a time in Swedish psychiatric care (the Swedish "90-day rule") (Fazel et al., 2014) – a number to which we added an additional 30 days to allow for non-adherence. At the last dispensed prescription in a treatment period, we defined the end of treatment by adding the average number of days between dispensed prescriptions for the drug to the date of dispensation.

2.3.2. Outcomes

The main outcome was conviction of a violent crime – including homicide, manslaughter, unlawful threats, harassment, robbery, arson, assault, assault on official, kidnapping, stalking, coercion, and sexual offences (Fazel et al., 2015; Molero et al., 2015). We only included crimes where the date of perpetration was known (Molero et al., 2015). We used arrest for a violent crime as an alternative outcome ("suspicion" of a violent crime) in sensitivity analyses, using data from the Register of People Suspected of Offences.

2.3.3. Covariates

We included the following time-fixed covariates: sex, family income in quartiles (<20th percentile in the population, 20th-80th percentile, >80th percentile; categorical), highest attained education between parents and the index individual (completed primary, secondary, or tertiary education; categorical), county of residence (categorical), birth country (Nordic/extra-Nordic; binary), and history of violent crime (binary) (all measured at start of follow-up), as well as lifetime psychiatric diagnoses (see Table 4 for ICD10-codes). We also included the following time-varying covariates: age (in one-year bands; continuous), recent violent crime (any violent crime occurring within the last one month of follow-up), use of benzodiazepines (ATC-code: N05BA), non-SSRI antidepressants (N06A, excluding N06AB), and any other psychotropic medications (all binary covariates). Other psychotropic medications included: Antipsychotics (N05A); Anxiolytics (N05B, excluding N05BA); Hypnotics, and Sedatives (N05C); ADHD medication (N06B); Drugs used in Addictive Disorders (N07B); Opioids (N02A); Anti-Epileptics (N03A); and Anti-Dementia Drugs (N06D). Periods treated with other psychotropic medications were defined in the same way as those for SSRI treatment, but 30 days were added to the date of dispensation at the last dispensed prescription to define treatment end.

2.4. Statistical analyses

The analyses were carried out overall and as stratified by age. The age groupings were 15–24-year-olds, 25–34-year-olds, 35–44-year-olds, and 45–60-year-olds.

First, we calculated absolute rates of violent crime per 1000 person-years during on- and off-treatment periods across age categories, without accounting for any covariates. We then conducted between-individual analyses using Cox Proportional Hazards models to assess the hazard of a violent crime conviction during periods on relative to off SSRI treatment across individuals with adjustment for time-fixed covariates at start of follow-up, lifetime diagnoses, and time-varying covariates during follow-up. Confidence intervals were calculated using robust sandwich covariance to account for the correlation of person-time within individuals (Lee et al., 1992). We carried out additional between-individual analyses stratified by conviction of a previous violent crime. Because between-individual estimates were susceptible to individual differences in selection into treatment, we then conducted within-individual analyses using stratified Cox Proportional Hazards models to compare the rate of violent crime during periods on versus periods off SSRI treatment within the same individual. This allowed us to control for all time-invariant confounders, including genetic make-up and family background (Molero et al., 2015). In the within-individual analysis, only individuals who switch SSRI treatment status and experience at least one event during follow-up contribute directly to the effect estimates (Allison, 1996). All within-individual models were adjusted for the time-varying covariates age, recent violent crime, as well as use of benzodiazepines, non-SSRI antidepressants, and other psychotropic medication.

We carried out additional within-individual analyses to assess whether HRs of violent crime convictions varied by period after treatment initiation/discontinuation (see Figure 1). On-treatment periods were divided into 0–28 days, 29–84 days, and >84 days after treatment initiation (Coupland et al., 2015). Off-treatment periods were divided into 0–28 days, 29–84, and >84 days after the latest treatment period discontinuation. The reference category was the time before any treatment with SSRI medication. The cut-offs were chosen a priori, based on a previous study of the time-varying risk of antidepressant use and suicidality (Coupland et al., 2015), and on the Swedish "90-day rule" (Fazel et al., 2014).

We also examined the within-individual association between SSRI and violent crime in specific diagnostic groups, including individuals with lifetime diagnoses of: Attention Deficit Hyperactivity Disorder (ADHD), Alcohol use disorder, Anxiety Disorder, Autism spectrum disorder, Bipolar Disorder, Conduct disorder, Depression, Personality Disorder, accidental poisoning by alcohol, accidental poisoning by drugs and noxious substances excluding alcohol, Schizophrenia Spectrum Disorder, and Substance Use Disorder excluding alcohol. See Table 4 for the ICD-10 codes for each of these disorders.

Finally, we carried out sensitivity analyses to investigate the robustness of our within-individual results with different exposure and outcome definitions. First, within-individual HRs were estimated using the assumption that patients take one SSRI pill per day. This involved an estimation of the treatment duration from the number of pills included in each dispensed prescription. Second, we assessed the association between SSRI medication and suspected violent crime outcomes. All sensitivity analyses were age-stratified.

Statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.6.1.

3. Results

We identified 785,337 individuals who dispensed SSRIs aged 15–60 during 2006–2013 – see supplementary figure S1 for a flowchart of inclusion in the cohort. Violent crime con-

Figure. 1 Division of treatment periods in relation to initiation and discontinuation.

Table 1 Cohort characteristics.

	Overall cohort ($N = 785,337$)	Males ($N = 281,135$)	Females ($N = 504,202$)
Age at start of follow-up			
15-24 years (%)	201,447 (25.7%)	72,363 (25.7%)	129,084 (25.6%)
25-34 years (%)	171,251 (21.8%)	61,480 (21.9%)	109,771 (21.8%)
35-44 years (%)	193,034 (24.6%)	68,292 (24.3%)	124,742 (24.7%)
45-60 years (%)	219,605 (28.0%)	79,000 (28.1%)	140,605 (27.9%)
No. with event (%)	20,821 (2.7%)	16,008 (5.7%)	4813 (1.0%)
No. with treatment switching (%)	777,304 (99.0%)	278,286 (99.0%)	499,018 (99.0%)
Follow-up length (mean, years)	7.3	7.2	7.3

victions occurred among 2.7% ($N = 20,821$) of the cohort, amounting to 32,203 crimes overall. Around 99% ($N = 777,304$) of cohort members changed their SSRI treatment status over the follow-up (Table 1). The mean follow-up time was 7.3 years. These characteristics were similar across males ($N = 281,135$) and females ($N = 504,202$), though males had a higher proportion of individuals convicted of a violent crime than females (5.7% versus 1.0%).

Absolute rates of violent crime, with no covariates taken into account, were lower in treated versus non-treated periods across all age categories apart from the youngest. When hazards were compared during periods on and off treatment between individuals, adjusting for all measured confounders, SSRI treatment was associated with a modest increased risk of violent crime conviction overall (1.10; 95% CI = 1.06, 1.13) (Table 2). When this analysis was stratified on previous violent crime, the elevated risk for violent crime convictions seemed to be confined to the individuals with previous criminality (HR = 1.13, 95% CI = 1.09, 1.18) as compared to those without such a history (HR = 1.07, 95% CI = 1.02, 1.12; Table S1) When studying age effects in the between-individual setting, SSRI treatment was associated with statistically significantly elevated hazards for violent crime among those aged 15-24 and 25-34 years (HRs of 1.19 and 1.16, respectively). In the oldest two age categories, there was a null effect of treatment (Table 2).

As receiving medication may be influenced by differences in confounding factors across individuals (for example, receipt of medication at any point during follow-up may be influenced by socioeconomic status, which may in turn be associated with crime propensity), a within-individual analysis that controls for all time-invariant confounding is a potentially more informative test of the association between SSRI treatment and violent crime. There were 20,735 individuals (2.6% of the cohort) who contributed to our within-individual analysis by virtue of experiencing both SSRI treatment switching and at least one event. These individuals tended to be younger (46% were aged 15-24 years, compared to 26% in the overall cohort), and had a higher representation of males (77% of the informative individuals, versus 36% in the overall cohort). When the hazard of violent crime was compared between periods on and off medication within individuals, there was a statistically significantly increased hazard during treatment in the whole cohort (HR = 1.26, 95% CI = 1.19, 1.34), and across most age categories - from 1.35 (95% CI = 1.19, 1.54) in the 25-34-year-olds, to 1.25 (1.08, 1.45) in the 45-60-year-olds. The 35-44-year-olds saw a statistically non-significant result of 1.15 (95% CI = 0.99, 1.33), though the majority of the confidence interval fell above one (Table 2). Sex-stratified analyses showed similar patterns of results to the overall cohort, though females only had statistically significantly elevated on-treatment hazards in the youngest age category, and also had lower numbers of crimes across ages (Table S2). Treatment with benzodiazepines was associated with a statistically significantly elevated hazard of violent crime (HR=1.32, 95% CI = 1.20, 1.45), while treatment with non-SSRI antidepressants was associated with a modest and non-significantly elevated hazard (HR = 1.09, 95% CI = 1.00, 1.19, $p = 0.055$). Treatment with other psychotropic drugs as a group was not associated with violent crime (HR = 0.97, 95% CI = 0.91, 1.02; Table S3).

When considering risks after treatment initiation and discontinuation (Table 3), the overall cohort saw increased hazards throughout all treatment periods compared to periods before treatment; with HRs of 1.28 (95% CI = 1.13, 1.45), 1.35 (95% CI = 1.22, 1.49) and 1.24 (95% CI = 1.14, 1.35) during the first 28 days, 29-84 days, and >84 days after treatment initiation, respectively. Post-discontinuation, hazards remained elevated in the first 84 days, with HRs of 1.37 (95% CI = 1.21, 1.55) and 1.20 (95% CI = 1.08, 1.33) in the first 28 days and 29-84 days after treatment discontinuation, respectively. In the period more than 84 days after treatment discontinuation, the HR estimate for the overall cohort was non-significant (0.94 [95% CI = 0.88, 1.01]). This pattern was largely consistent across age groups.

There was no substantial difference in HRs across diagnosis groups (Table 4). For depression and anxiety, the groups with the highest representation among SSRI users, the HRs were 1.28 (95% CI = 1.18, 1.39) and 1.24 (95% CI = 1.16, 1.34), respectively.

Table 2 Between- and within-individual associations between SSRI treatment and violent crime, by sex and age.

Age	No. individuals[a]	Treated periods		Non-treated periods		Effect estimates	
		No. events	Rate (per 1000 person-years)[b]	No. events	Rate (per 1000 person-years)[b]	Between-individual Hazard Ratio (95% CI)[c]	Within-Individual Hazard Ratio (95% CI)[d]
Overall	785,337	6306	4.64	25,897	5.96	1.10 (1.06, 1.13)	1.26 (1.19, 1.34)
15–24 years	201,447	1972	13.37	10,580	12.89	1.19 (1.13, 1.26)	1.28 (1.17, 1.41)
25–34 years	290,531	1547	6.10	6255	6.22	1.16 (1.10, 1.24)	1.35 (1.19, 1.54)
35–44 years	330,612	1431	3.89	4954	4.44	1.02 (0.96, 1.09)	1.15 (0.99, 1.33)
45–60 years	374,306	1356	2.30	4108	2.92	1.04 (0.97, 1.12)	1.25 (1.08, 1.45)

[a] Individuals may contribute to more than one age category during follow-up.
[b] Not adjusted for any covariates.
[c] Adjusted for time-varying covariates: age, recent violent crime, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications; non-time-varying covariates: sex, family income, highest attained educational attainment between the index person and its parents, county of residence, birth country, lifetime diagnoses, and history of violent crime before study entry.
[d] Adjusted for time-varying covariates: age, recent violent crime, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications.

Table 3 Within-individual hazard ratios of violent crime over period after treatment initiation and discontinuation.

		Reference Before ever-treatment	From treatment initiation			From treatment discontinuation		
			0–28 days	29–84 days	>84 days	0–28 days	29–84 days	>84 days
Overall	**No. events**	13,229	847	1483	3976	922	1400	10,346
	HR (95% CI)[a]	1.00	1.28 (1.13, 1.45)	1.35 (1.22, 1.49)	1.24 (1.14, 1.35)	1.37 (1.21, 1.55)	1.20 (1.08, 1.33)	0.94 (0.88, 1.01)
15-24	**No. events**	6825	330	538	1104	315	470	2970
	HR (95% CI)[a]	1.00	1.25 (1.02, 1.53)	1.37 (1.16, 1.62)	1.13 (0.98, 1.30)	1.42 (1.16, 1.74)	1.01 (0.85, 1.19)	0.86 (0.76, 0.96)
25-34	**No. events**	2715	201	368	978	204	363	2973
	HR (95% CI)[a]	1.00	1.35 (1.02, 1.80)	1.55 (1.23, 1.95)	1.47 (1.21, 1.79)	1.37 (1.02, 1.82)	1.42 (1.13, 1.79)	1.03 (0.87, 1.22)
35-44	**No. events**	2147	164	307	960	209	312	2286
	HR (95% CI)[a]	1.00	1.02 (0.74, 1.40)	1.18 (0.91, 1.53)	1.11 (0.89, 1.39)	1.26 (0.92, 1.72)	1.03 (0.80, 1.32)	0.90 (0.74, 1.09)
45-60	**No. events**	1542	152	270	934	194	255	2117
	HR (95% CI)[a]	1.00	1.29 (0.91, 1.82)	1.08 (0.82, 1.43)	1.26 (1.00, 1.58)	1.15 (0.82, 1.55)	1.15 (0.87, 1.53)	0.87 (0.71, 1.08)

[a] Adjusted for time-varying covariates: age, recent violent crime, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications.

Table 4 Within-individual hazard ratios of violent crime when including only individuals with each type of psychiatric diagnosis in turn.

Included diagnosis	No. individuals	No. events	Hazard Ratio (95% CI)
ADHD	37,139	7874	1.21 (1.09, 1.35)
Alcohol use disorder	64,384	12,939	1.27 (1.16, 1.38)
Anxiety disorder	252,005	18,359	1.24 (1.16, 1.34)
Autism spectrum disorder	17,104	1940	1.16 (0.95, 1.41)
Bipolar disorder	31,147	2385	1.09 (0.89, 1.33)
Conduct disorder	2957	1487	1.29 (1.03, 1.60)
Depression	226,161	14,040	1.28 (1.18, 1.39)
Personality disorders	37,557	5574	1.24 (1.09, 1.40)
Poisoning by alcohol	697	171	1.65 (0.74, 3.69)
Poisoning by drugs and noxious substances	49,497	7576	1.22 (1.09, 1.36)
Schizophrenia	22,525	3509	1.21 (1.03, 1.43)
Substance use disorder	51,203	13,255	1.19 (1.09, 1.30)

[a]ICD-10 codes: Attention Deficit Hyperactivity Disorder (ADHD; F90), Alcohol use disorder (F10), Anxiety Disorder (F4), Autism spectrum disorder (F84), Bipolar Disorder (F30-F31), Conduct disorder (F91), Depression (F32-F39), Personality Disorder (F60-F61), Poisoning by alcohol, accidental (X45), Poisoning by drugs and noxious substances excl. alcohol, accidental (X40-X44; X46-X49; T36-T50), Schizophrenia Spectrum Disorder (F2), Substance Use Disorder excl. alcohol (F11-F19).

Table S4 gives the results of sensitivity analyses with different exposure and outcome definitions. The one-pill-per-day treatment period method gave similar HR estimates to those presented in the main analysis for all age categories. The analysis using suspected violent crime as an alternative outcome also gave a similar pattern of HRs over the age strata, though all HRs were slightly lower.

4. Discussion

In this nationwide cohort study, SSRI treatment was associated with an increased hazard of violent crime across age categories, in a cohort of SSRI users where 2.7% went on to commit violent crimes. The hazard was possibly elevated throughout on-treatment periods, and for up to 12 weeks after treatment discontinuation, though more research is necessary to confirm these findings. Young men and those with a history of violent crime seem to contribute most to the observed associations.

Key to interpreting our findings is the acknowledgement that any pharmacoepidemiological study is likely to be subject to confounding by indication. Mood disorders, the main indication for SSRI treatment, are associated with violent crime – for example, a Swedish study found a 3-fold increased odds of violent crime among depressed individuals compared to population controls (Fazel et al., 2015). There is prior evidence that SSRIs may not fully treat the psychiatric disorders they are prescribed for (Insel and Wang, 2009), suggesting that onset, or worsening, of the underlying disorder that led to the indication for treatment could be driving the associations in our study. We did not have information on the indications for antidepressant prescriptions, nor on diagnoses made in primary care, where the majority of adult mood disorders are treated in the Swedish setting. While our within-individual analyses account for all time-invariant confounding by indication – and have consistently higher effect estimates than our between-individual analyses – we were unable to fully account for time-varying confounding by indication in our study.

However, there are biologically plausible explanations for the elevated rate of violent crime that we observe during SSRI treatment. Notably, several studies suggest that SSRI treatment can lead to behavioural activation in children and adolescents (Luft et al., 2018; Reinblatt et al., 2009). Such behavioural activation, combined with an incomplete remission from the underlying disorder, could lead to higher risk for aggression outcomes. SSRIs have been found to have limited efficacy in treating depression among the young (Cipriani et al., 2016) as compared to adults (Cipriani et al., 2018). A potential causal effect of SSRIs on aggression is supported by a meta-analysis of RCTs (Sharma et al., 2016), which finds significantly elevated odds of aggression outcomes in SSRI/SNRI arms relative to placebo among young users, but non-significantly elevated odds among adults. However, it is unclear how such evidence, relating to aggression outcomes in a selected population of individuals eligible for RCTs, relate to the more severe and rare outcome of violent crime conviction, which is even less frequent among adults than younger persons (Loeber and Farrington, 2014). Population-based register studies provide the possibility to study rare outcomes over long follow-up time in non-selected populations, although they allow for less certainty regarding causality. A prior Swedish register-based study (Molero et al., 2015) finds significantly elevated hazards of violent crime in adolescents and young adults during SSRI treatment periods, but non-significantly elevated hazards among adults. Our study, drawing on a larger sample size and follow-up time, finds significantly increased hazards during treatment periods across age categories. While we cannot fully parse out the extent to which our results are causal, they suggest the need for further research on the risk of serious aggression outcomes across age categories and on potential causal pathways.

To our knowledge, this is the first study investigating the time-varying association, in relation to treatment start and end, between SSRI use and violent crime. Our finding of an elevated risk after treatment discontinuation supports prior findings that SSRI treatment termination is accompanied by irritability and aggression, possibly lasting for months, in some patients (Fava et al., 2015; Horowitz and Taylor, 2019; Iacobucci, 2019; NICE, 2009). Recently updated clinical guidelines from the UK National Institute of Health and Clinical Excellence (NICE) have highlighted the need to inform patients about withdrawal risks (Iacobucci, 2019; NICE, 2009). Still, it is also possible that the elevated hazard of violent crime that we observe for up to 12 weeks after treatment discontinuation is due to some individuals remaining symptomatic of the underlying disease that indicated them for SSRI treatment, or to misclassification of the SSRI treatment periods. Moreover, most prior evidence of long-term discontinuation effects derive from non-blinded studies – further evidence from controlled trials is called for to help illuminate issues of causality in this area.

It should also be reiterated that the outcome of interest is very rare, occurring in only about 2.7% of individuals in an average of 7.3 years of follow-up. This means that small differences in absolute hazards may lead to larger differences in relative ones. Given that a vast majority of individuals taking SSRIs will not commit violent crimes, our results should also not be used as reason to withhold SSRI treatment from patients who may benefit from it, especially as causality remains unclear. Further research on how our results relate to more common aggression-related outcomes is called for. Notably, only individuals with an outcome and treatment switching were informative in the within-individual setting, amounting to about 2.6% of our cohort. These individuals tended to be younger, and a majority were male. When the between-individual analyses were stratified on previous violent criminality, the increased hazards seemed to be confined to those who had already committed a violent crime. This is congruent with results from another study from Sweden, where depressed men with co-occurring substance abuse, self-harm, and a history of violent crime had a 16.3% violent crime risk between 2001 and 2009, compared with 3.7% in the overall population of depressed men, and 0.5% in that of depressed women (Fazel et al., 2015). The main clinical attention should therefore be directed towards those with the greatest susceptibility to violent crime based on key risk factors. In our study, rates of convictions were elevated during on-treatment periods across diagnostic subgroups, meaning that diagnosis data was not enough to identify individuals that would require more intensive clinical follow-up. Still, there might be more complex clusters of risk factors that influence the relationship between SSRI use and violent crime, and many of the psychiatric disorders considered in our study are highly comorbid (Kessler et al., 1994; Merikangas et al., 1996). Prediction models could be developed to help identify high-risk groups defined by combinations of several different risk factors.

Our results suggest that clinicians be aware of the risk of violent crime related to SSRI medication, and that they inform high-risk individuals about possible precursors to violence – such as hostility, aggressiveness, and irritability – so that patients may seek medical advice if they experience these during or after SSRI treatment, regardless of whether the symptoms arise from side effects of SSRIs or from a lack of remission from the underlying disorder being treated. In general, the finding of an increased risk of violent crime during SSRI treatment across treatment periods and ages is of public health interest, as an increasing proportion of antidepressant users experience long-term treatment (Mojtabai and Olfson, 2014; Noordam et al., 2015), and as middle-aged and older adults make up a larger proportion of antidepressant users than the young (Abbing-Karahagopian et al., 2014).

Finally, we must recognize several limitations of our study. First, confounding by indication is likely to be affecting our results, as discussed previously. Additionally, it is possible that a range of time-varying factors related to accessing psychiatric healthcare services and dispensing medication explain our results. However, the differences in associations between different types of psychotropic medications and violent crime suggest that aforementioned types of unmeasured time-varying factors could not fully explain the observed associations, as we would otherwise expect similar effect estimates across medication types. Second, we are not able to determine whether the purchased medications were consumed, meaning all estimates should be regarded as intention-to-treat (Molero et al., 2015). This may underestimate the risks of treatment (Hernán and Hernández-Díaz, 2012). Third, our treatment period definition may induce some misclassification regarding the length of antidepressant exposure. However, sensitivity analyses with an alternative treatment period definition did not substantially affect our results. Fourth, our results derive from Sweden, and do not necessarily generalize to other contexts. Still, levels of antidepressant use in Sweden are comparable to those in other Western settings. For example, around 11% of the population were prescribed SSRIs during 2006–2009 in Sweden, which is similar to the prevalence of antidepressant use in the US over 2005–2008 (Molero et al., 2015; Pratt et al., 2011). Finally, it is worth repeating that the observational nature of our study means we cannot infer causality from our results. The observed associations should be further investigated with studies of different samples or designs to triangulate our findings.

In conclusion, this nationally representative study found that there may be an increased hazard of violent crime during SSRI medication in a small group of patients; that it may exist across age groups and throughout treatment periods; and that it possibly persists for up to twelve weeks after treatment discontinuation. While further research is called for to illuminate questions of causality and risk prediction, our results suggest the need for clinical awareness of the risk for severe violence during and possibly after SSRI treatment across age groups, and provision of information to high-risk individuals. However, a large majority of SSRI-users will not experience the outcome of violent crime, and our results should be understood in this context.

Author disclosures

Role of the funding source:
This work was supported by the Swedish Research Council (2018-02213), the Horizon 2020 ACTION project, the Stockholm County Council, and the Thurings Foundation. YM is

funded by Karolinska Institutet Funds (2016fobi50581). SF is funded by the Wellcome Trust (#202836/Z/16/Z).

The sponsors had no role in the design, conduct, or write-up of the study; or in the decision to submit the manuscript for publication.

Contributors

TL conducted the analyses, with support from ZC and MAF. TL wrote the manuscript, with detailed input from all co-authors. All authors contributed to the design of, and hypotheses tested in, the study, and have approved the final manuscript.

Conflict of Interest

All authors declare no financial relationships with commercial interests.

Acknowledgments

We thank the reviewers for their thoughtful comments, which helped us improve the paper substantially.

Ethics

The study was approved by the Regional Ethics Committee, Stockholm, Sweden (Reference NO 2013/862-31/5). The requirement for informed consent was waived, as the study was register-based and the included individuals were not identifiable.

Data sharing

We cannot share the data due to privacy considerations, but the code is available upon request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2020.03.024.

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