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Association of selective serotonin re-uptake inhibitor (SSRI) treatment with acute substance misuse outcomes

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ABSTRACT

Background and aims Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed medications for patients with anxiety/depression. These patients often have problems with substance use, but it remains unclear whether the risk of substance misuse is influenced by SSRI treatment. We aimed to determine whether SSRI treatment is associated with a decreased risk of acute substance misuse-related outcomes. **Design** Cohort study following individuals through Swedish nation-wide registers between July 2005 and December 2013 and comparing the risk of substance misuse outcomes during periods on- versus off-treatment within the same individual. **Setting** Swedish general population. **Participants** Individuals with a newly dispensed prescription of SSRIs between July 2006 and December 2013 and an ICD-10 diagnosis of anxiety/depressive disorder before the first treatment initiation. The cohort included 146 114 individuals (60.7% women). **Measurements** Substance misuse outcomes included ICD-10 diagnoses of acute intoxications (F10.0–F19.0), accidental poisonings by alcohol or drugs (X41–X42, X45–X46) and substance-related criminal offenses. **Findings** The absolute rate of substance misuse increased sharply before the onset of SSRI treatment and decreased after treatment initiation. Stratified Cox regression models showed an elevated risk [hazard ratio (HR) = 1.70, 95% confidence interval (CI) = 1.62–1.78] of substance misuse outcomes during a 1-month period preceding treatment initiation, compared with the reference period of more than 1 month before treatment start. The on-treatment estimates (1–30 days, HR = 1.29, 95% CI = 1.23–1.37; 31–120 days, HR = 1.30, 95% CI = 1.24–1.35; and > 120 days, HR = 1.24, 95% CI = 1.18–1.30 after treatment initiation] were consistently lower than the 1-month pre-treatment estimate, but still elevated compared with the reference period. **Conclusions** For people with anxiety/depression, the risk of substance misuse appears to be particularly elevated immediately before initiating selective serotonin reuptake inhibitor (SSRI) treatment, which may reflect the emergence or worsening of substance use problems concurrently with anxiety/depression. SSRI treatment appears to be associated with a lower risk of substance misuse compared with the 1-month period preceding treatment initiation, but causality remains uncertain.

Keywords Anxiety, depression, longitudinal, register-based, SSRI, substance use.

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INTRODUCTION

Selective serotonin re-uptake inhibitors (SSRIs) are widely prescribed medications for patients with anxiety and depression [1,2]. These patients often have co-occurring problems with substance use [3–8], but it remains unclear whether the risk of substance misuse is influenced by SSRI treatment. Randomized controlled trials (RCTs) suggest that SSRIs used as monotherapy [9] or in combination with naltrexone [10] may reduce alcohol consumption and relapse in patients with depression and alcohol use disorder, but the results have not been replicated in larger samples [11]. Meta-analyses of all available RCTs have found no significant effect in reducing substance use [12–17]. However, conclusions from the meta-analyses are constrained by methodological problems in the RCTs,

such as low statistical power, short follow-ups, high dropout rates and excessive placebo response in the control groups [12,16,17].

Pharmacoepidemiological studies provide an alternative for examining SSRI treatment effects. Observational studies cannot confirm causality, but using health record data allows for investigating non-selected, large samples of patients with long-term follow-up, often not feasible in RCTs [18]. Further, the use of within-individual designs comparing medicated and non-medicated periods, treating each patient as his or her own control, increases validity compared to traditional observational studies by eliminating confounding by factors which remain constant over time within the individual [19]. However, a within-individual design can lead to misleading results if potential dynamic treatment-initiation processes are not accounted for. For instance, Quinn *et al.* found an increased risk of substance misuse events during SSRI treatment in patients with attention-deficit/hyperactivity disorder [20]. The authors speculated that the increased risk on-treatment was unlikely to represent true adverse effects, but rather reflected a time-varying effect of confounding by indication. The period shortly preceding SSRI treatment initiation might have been associated with a particularly high risk for substance-related problems, which would not have completely resolved once treatment was initiated, producing a spurious positive association. Dynamic treatment-initiation processes have been reported for other outcomes, such as suicide attempts [21,22]. To the best of our knowledge, there are no prior epidemiological studies investigating this particular topic in patients with anxiety/depression.

We utilized Swedish nation-wide registers and a within-individual design to estimate the association of SSRI treatment with acute substance misuse-related outcomes in patients with an anxiety or depressive disorder. Specifically, we investigated the risk of acute intoxications, accidental poisonings and substance-related criminal offenses in periods before and after SSRI treatment initiation. Further, we studied whether SSRI treatment was associated with a decreased risk of substance misuse compared to off-treatment in patients with and without comorbid substance use disorder, and examined the role of naltrexone treatment on the risk of substance misuse outcomes.

METHODS

Study population

The primary cohort included all individuals in Sweden, aged 15 years or older, with a prescription of SSRIs in the Swedish Prescribed Drug Register [23] between 1 July 2006 and 31 December 2013, and an International Classification of Diseases, 10th revision (ICD-10) diagnosis of anxiety (F40–F41) or depressive (F32–F39, excluding F34.0) disorder in the National Patient Register [24] between 1997 and the first treatment initiation. In sensitivity analyses, we studied an alternative cohort including those with SSRI medication but no diagnoses of anxiety or depression (see below). All individuals had at least 1 year with no record of dispensed SSRI prescriptions before their first treatment initiation. Supporting information, Figure S1 illustrates inclusion and exclusion criteria for the cohort and subsamples. We utilized several Swedish nation-wide registers, interlinked via the unique personal identity number [25]. Demographic characteristics, deaths and emigrations were obtained from the Total Population Register, the Cause of Death Register and the Migration Register, respectively [26]. The cohort was followed-up from 1 year before the first treatment initiation (with data available from 1 July 2005 onwards) until the end of 2013. The use of register-linkage was approved by the Regional Ethics Committee of Karolinska Institutet in Sweden. Informed consent requirement was waived because the data have been anonymized.

Measures

Exposures

The main exposure was dispensed prescriptions of SSRI medication. Treatment status (i.e. on- versus off-treatment) was used as a time-varying exposure, where treatment initiation and discontinuation could occur several times during the follow-up. Oral psychiatric medications are typically not dispensed for more than 90 days at a time in Sweden [27]. Therefore, we defined on-treatment periods by assuming two dispensed prescriptions falling within 120 days of each other belonged to the same treatment period. We added 30 days to the 90 days to account for potential treatment non-adherence [28]. For the last dispensed prescription in a treatment period, we defined the end of treatment by adding the median number of days between prescriptions to the date of dispensation. Time-periods of 120 days or more without dispensed prescriptions were considered off-treatment.

Outcomes

Acute substance misuse outcomes included ICD-10 codes for acute intoxications (F10.0–F19.0, excluding F17.0) and accidental poisonings by alcohol and drugs (X41, X42, X45, X46), which were retrieved from the National Patient Register (NPR). The NPR has coverage of ICD-10 diagnoses from inpatient/outpatient specialist services since 1997/2001, respectively, but excludes primary care and private practice diagnoses. For inpatient diagnoses, we used the date of admission. We also included alcohol- and drug-related criminal offenses from the Crime Register and the Register of People Suspected of Offenses. They

included convictions for driving under the influence of alcohol/drugs and being suspected by the police for use or possession of illicit drugs, which had a known date of perpetration. Substance misuse was measured as a recurring outcome: an individual could experience the outcome more than once during the follow-up, and time-at-risk was reset to 0 after each event. Diagnoses and criminal offenses occurring on the same date were only counted once.

Covariates

We adjusted the models for several time-varying covariates. Age was included as a continuous variable. We selected the covariates a priori, in accordance with previous studies [28]. Polypharmacy was adjusted for by including binary variables indicating concurrent use of benzodiazepines, non-SSRI antidepressants and other psychotropic medications. The drugs and ATC codes are shown in Supporting information, Table S1. On-treatment periods were defined in the same manner as the SSRI medication periods, except for the end of the last prescription, which was estimated by adding 30 days to the date of dispensation.

We also retrieved diagnoses of substance use disorders (F10–F19, excluding F17 and acute intoxications) registered during the follow-up, and dispensed prescriptions of naltrexone between 2005 and 2013, which were used to identify clinically relevant subgroups.

Analyses

To describe dynamic changes in the risk of acute substance misuse outcomes, we first calculated the absolute rate of events (per 1000 person-years) monthly for 12 months before and after the first SSRI treatment initiation. Individuals were censored at switching from on- to off-treatment, emigration, death or at 12 months after the first treatment initiation, whichever occurred first.

Next, we estimated the association between SSRI treatment and substance misuse with stratified Cox proportional-hazards regression models where each individual enters as a separate stratum, and the rate of substance misuse outcomes is compared during periods on- versus off-treatment. Because the design uses an individual as his/her own control, it eliminates confounding by all factors which remain constant over time (e.g. genetic factors) [29]. Cluster-robust standard errors were used to account for the non-independence of observations within individuals. We further divided the on- and off-treatment periods in relation to treatment initiation to study potential time-varying effects. Off-treatment periods were divided into periods of more than 30 days before treatment start and 0–30 days before treatment start. On-treatment periods were divided into 1–30, 31–120 and more than 120 days after treatment initiation. The period more than 30 days before treatment start was used as the reference category (Supporting information, Fig. S2). Individuals were censored on 31 December 2013, death or first emigration, whichever occurred first. Time-periods in prison or in inpatient care were excluded. We considered an estimate to show a statistically significantly elevated/decreased risk if the 95% confidence interval (CI) did not include 1. When comparing separate estimates with each other, a difference was inferred if there was no overlap in the CIs.

Further, we estimated the associations restricted to individuals with and without a diagnosis of comorbid substance use disorder registered during the follow-up (excluding acute intoxications, which were included in the outcome). The models were estimated separately for alcohol and drug use disorders.

Finally, as previous studies have indicated SSRIs to be effective in reducing substance misuse only when used together with naltrexone [10], we examined whether the associations were similar in individuals with least one dispensed prescription for naltrexone at any time from 2005 to 2013 compared to those without. Analyses were restricted to patients with a comorbid alcohol use disorder (F10.1–F10.9). Because the number of patients with a naltrexone prescription was insufficient to formally test an interaction between time-varying SSRI and naltrexone treatment periods, these analyses should be considered descriptive.

Sensitivity analyses

We investigated the robustness of the results with different exposure, outcome and cohort definitions.

First, we estimated the association using an alternative method for defining on-treatment periods, where treatment duration was based on the number of dispensed SSRI pills. The Prescribed Drug Register includes the size of tablet package (i.e. number of tablets per package) and the number of packages an individual purchased. The duration of treatment period was calculated from the total number of tablets, assuming that the daily dosage was consumed once per day. Citalopram and Sertraline are the most frequently prescribed antidepressants in Sweden [30], and the European Medicines Agency recommends that both be administered as a single daily dose.

In the second sensitivity analysis, substance-related diagnoses and criminal offenses were analyzed separately. Because the criminal justice system is independent from health-care services, separating the outcomes can help to clarify the extent to which the relationship between SSRI treatment and substance misuse reflects surveillance biases, such as SSRI treatment being initiated due to the patient coming into contact with health care because of an acute intoxication or poisoning.

Thirdly, we estimated the association of SSRI treatment with alcohol-related (intoxication/poisoning) and drug-related (intoxication/poisoning, suspicions of use/possession of drugs) outcomes separately to test the robustness of the substance use disorder subgroup analyses.

Finally, using an alternative cohort, we investigated whether our results generalize to individuals receiving SSRIs but not having an anxiety or depressive disorder diagnosis from specialist services, aiming to capture patients treated in primary care or private clinics not covered by the NPR. We included all individuals aged 15 years or older, with a new prescription of SSRIs between 1 July 2006 and 31 December 2013 and without a life-time (registered 1997–2013) diagnosis of anxiety or depressive disorder in the NPR.

All analyses were performed in SAS version 9.4 (SAS Institute, Cary NC, USA). The analysis plan was not pre-registered, and the analyses should be considered exploratory.

RESULTS

The primary study cohort with anxiety/depressive disorders included 146 114 individuals (60.7% women). A total of 21 712 (14.9%) cohort members experienced at least one acute substance misuse outcome during the follow-up, with 62 574 events overall. The median length of the follow-up was 4.5 years (Table 1).

During the 12 months preceding the first SSRI treatment period the absolute rate of substance misuse increased steadily, with a markedly sharp increase from 118 to 191 events per 1000 person-years during 1 month before the treatment start (Fig. 1). Substance misuse started to decrease after treatment initiation.

Stratified Cox regression models showed a 70% [hazard ratio (HR) = 1.70, 95% CI = 1.61–1.78] increased risk of substance misuse outcomes during the month preceding SSRI treatment, compared to the period during 1 month before treatment start (Table 2). The on-treatment estimates were consistently lower (> 120 days, HR = 1.24, 95% CI = 1.18–1.30), but still elevated when compared to the reference period. Estimates for other medications are presented in Supporting information, Table S2.

The risk of substance misuse was elevated during the 1-month period before treatment onset in individuals with a diagnosis of comorbid alcohol use disorder and drug use disorders, but also in patients who did not have a substance use disorder diagnosis (Table 3). The 1-month pre-treatment risk was more elevated in people with a comorbid alcohol use disorder (HR = 1.71, 95% CI = 1.60–1.84) than in those with drug use disorders (HR = 1.28, 95% CI = 1.19–1.37). The associations attenuated after SSRI treatment initiation in people with alcohol use disorders (> 120 days, HR = 1.25, 95% CI = 1.16–1.34), but the risk for substance misuse remained similar to the 1-month pre-treatment period in people with drug use disorders (> 120 days, HR = 1.26, 95% CI = 1.18–1.35).

Patients who had a dispensed prescription for naltrexone had a higher overall rate of substance misuse outcomes than those without a naltrexone prescription. However, the risk of events attenuated on-treatment in both groups, compared to the 1-month pre-treatment period (Table 4).

Sensitivity analyses

In the first sensitivity analysis, using an alternative definition for SSRI treatment periods did not change the pattern of associations found in the main analysis (Supporting information, Table S3).

Table 1 Sample characteristics.

	Cohort with anxiety/depression diagnosis (n = 146 114)	*Alternative cohort with SSRI prescription but no anxiety/depression diagnosis (n = 517 913)*
Age at start of follow-up, years (%)		
15–24	44 286 (30.3)	59 285 (11.4)
25–34	26 583 (18.2)	76 622 (14.8)
35–44	22 739 (15.6)	89 913 (17.4)
45–59	26 055 (17.8)	112 678 (21.8)
60 or older	26 451 (18.1)	179 442 (34.6)
Substance misuse outcomes (%)		
Total	21 712 (14.9)	24 729 (4.8)
Poisonings and intoxications	9351 (6.4)	5209 (1.0)
Criminal offenses	15 748 (10.8)	21 131 (4.1)
Median follow-up length in years	4.5	4.3

SSRI = selective serotonin re-uptake inhibitor.

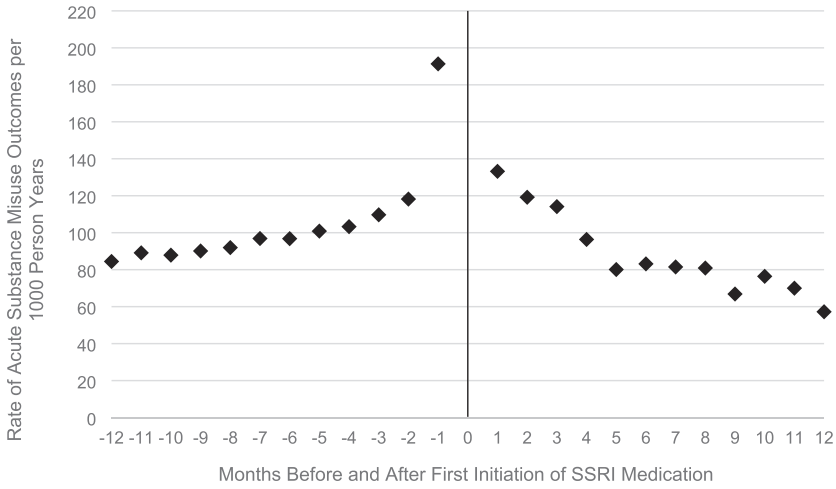

Figure 1 Rate of acute substance misuse outcomes 12 months before and after first initiation of selective serotonin re-uptake inhibitor (SSRI) medication

Table 2 Within-individual association of SSRI treatment with acute substance misuse outcomes in patients with a diagnosis of anxiety or depressive disorder.

	Days before treatment initiation		*Days after treatment initiation*		
	> 30 days	*0–30 days*	*1–30 days*	*31–120 days*	*> 120 days*
Rate[a]	99.02	153.30	113.64	98.24	61.45
HR (95% CI)[b]	Ref.	1.72 (1.64–1.80)	1.35 (1.28–1.43)	1.33 (1.28–1.39)	1.27 (1.12–1.33)
Adj. HR (95% CI)[c]	Ref.	1.70 (1.62–1.78)	1.29 (1.23–1.37)	1.30 (1.24–1.35)	1.24 (1.18–1.30)

Ref. = reference period. [a]Rate of acute substance misuse outcomes per 1000 person-years; reflects the rate accounting for all corresponding time-periods during the follow-up. [b]Adjusted for time-varying age only. [c]Adjusted for time-varying covariates: age, use of non-SSRI antidepressants, benzodiazepines and other psychotropic medications. SSRI = selective serotonin re-uptake inhibitor; HR = hazard ratio; CI = confidence interval.

When substance-related diagnoses and criminal offenses were analyzed separately, the highest risk of both outcomes was observed during the 1-month period before treatment start (diagnoses: HR = 2.61, 95% CI = 2.40–2.83; crimes: HR = 1.33, 95% CI = 1.24–1.41) and the association attenuated in diagnoses once treatment was initiated (> 120 days, HR = 1.20, 95% CI = 1.10–1.30), although remaining elevated compared to the reference period (Supporting information, Table S4). Overall, the estimates were lower for criminal offenses, with confidence intervals for the on-treatment (> 120 days, HR = 1.28, 95% CI = 1.21–1.36) and the 1-month pre-treatment periods overlapping. The pattern of a first increasing and then decreasing trend in the absolute rate of criminal offenses 12 months before and after first treatment initiation was similar to the main analysis (Supporting information, Fig. S3).

Separate analyses for alcohol- and drug-related events showed an elevated risk of both outcomes during the 1-month pre-treatment period (Supporting information, Table S5; alcohol, HR = 2.64, 95% CI = 2.38–2.92; drugs, HR = 1.63, 95% CI = 1.48–1.80). SSRI treatment was associated with a decreased risk of both alcohol- (> 120 days, HR = 1.19, 95% CI = 1.07–1.32) and drug-related (> 120 days, HR = 1.13, 95% CI = 1.03–1.23) outcomes compared to the 1-month pre-treatment estimate, although for drug-related outcomes the CIs became non-overlapping only after the first month on-treatment.

Composition of the alternative cohort was slightly different from the primary cohort: the cohort members were older and had a lower prevalence of substance misuse outcomes (Table 1), but the associations remained consistent with the main results (Supporting information, Table S6).

DISCUSSION

Studying nearly 150 000 individuals with an anxiety/depressive disorder, followed-up in the Swedish nation-wide registers, we found a steadily increasing rate of acute substance misuse-related outcomes over the year leading up to the first SSRI treatment initiation during the follow-up, with a sharp increase 1 month pre-treatment. The underlying cause for the increase is difficult to establish using register-based data. It could reflect self-medication as a

Table 3 Within-individual association of SSRI treatment with acute substance misuse outcomes in patients with and without comorbid substance use disorder diagnosis.

	Days before treatment initiation		*Days after treatment initiation*		
Diagnoses	*> 30 Days*	*0–30 days*	*1–30 days*	*31–120 days*	*> 120 days*
Anxiety/depression without SUD (*n* = 128 016)					
Rate[a]	36.89	72.74	51.19	43.95	28.01
HR (95% CI)[b]	Ref.	2.08 (1.91–2.27)	1.56 (1.41–1.72)	1.50 (1.39–1.61)	1.30 (1.20–1.40)
Adj. HR (95% CI)[c]	Ref.	2.04 (1.87–2.23)	1.41 (1.28–1.56)	1.41 (1.31–1.52)	1.24 (1.15–1.34)
Anxiety/depression with alcohol use disorder (*n* = 11 978)					
Rate[a]	411.07	721.89	476.31	442.11	311.85
HR (95% CI)[b]	Ref.	1.73 (1.61–1.86)	1.27 (1.17–1.38)	1.29 (1.21–1.37)	1.28 (1.19–1.37)
Adj. HR (95% CI)[c]	Ref.	1.71 (1.60–1.84)	1.23 (1.13–1.33)	1.26 (1.19–1.34)	1.25 (1.16–1.34)
Anxiety/depression with drug use disorder (*n* = 9314)					
Rate[a]	671.37	785.73	753.07	668.62	489.41
HR (95% CI)[b]	Ref.	1.29 (1.20–1.38)	1.21 (1.12–1.30)	1.21 (1.14–1.27)	1.29 (1.21–1.38)
Adj. HR (95% CI)[c]	Ref.	1.28 (1.19–1.37)	1.18 (1.09–1.27)	1.18 (1.12–1.25)	1.26 (1.18–1.35)

SSRI = selective serotonin re-uptake inhibitor; SUD = any substance use disorder; HR = hazard ratio; CI = confidence interval. Ref. = reference period. [a]Rate of acute substance misuse outcomes per 1000 person years; reflects the rate accounting for all corresponding time-periods over the follow-up. [b]Adjusted for time-varying age only. [c]Adjusted for time-varying covariates: age, use of non-SSRI antidepressants, benzodiazepines and other psychotropic medications.

Table 4 Within-individual association of SSRI treatment with acute substance misuse outcomes in patients with and without a naltrexone prescription.

	Days before treatment initiation		*Days after treatment initiation*		
	> 30 days	*0–30 days*	*1–30 days*	*31–120 days*	*> 120 days*
With naltrexone prescription (*n* = 2589)					
Rate[a]	522.21	832.21	556.33	556.42	395.67
HR (95% CI)[b]	Ref.	1.66 (1.45–1.90)	1.16 (0.98–1.36)	1.22 (1.10–1.36)	1.26 (1.11–1.43)
Adj. HR (95% CI)[c]	Ref.	1.65 (1.44–1.89)	1.13 (0.96–1.33)	1.20 (1.08–1.34)	1.24 (1.09–1.42)
No naltrexone prescription (*n* = 9389)					
Rate[a]	380.93	688.34	452.23	406.98	285.97
HR (95% CI)[b]	Ref.	1.76 (1.61–1.91)	1.31 (1.19–1.45)	1.32 (1.23–1.43)	1.29 (1.18–1.40)
Adj. HR (95% CI)[c]	Ref.	1.74 (1.59–1.89)	1.27 (1.15–1.39)	1.29 (1.19–1.39)	1.25 (1.15–1.39)

Ref. = reference period. [a]Rate of acute substance misuse outcomes per 1000 person years; reflects the rate accounting for all corresponding time-periods over the follow-up. [b]Adjusted for time-varying age only. [c]Adjusted for time-varying covariates: age, use of non-SSRI antidepressants, benzodiazepines and other psychotropic medications. SSRI = selective serotonin re-uptake inhibitor; HR = hazard ratio; CI = confidence interval.

response to the emergence or worsening of anxiety/depression [31–33]. Increased substance use may also have induced anxiety/depression, although the cohort members had been diagnosed before the first treatment initiation with an anxiety/depressive disorder, where exclusion criteria for diagnosis include symptoms being 'substance-induced'. Nevertheless, there is a risk of diagnostic misclassification because differential diagnosis of substance use disorders and anxiety/depression can be challenging [34]. An alternative explanation for the increase in substance misuse is surveillance bias: SSRI treatment may have been initiated after the patient came into contact with health care because of a prior substance misuse event. As we found a similar pattern for substance-related criminal offenses, which are independent from health care, this suggests that surveillance bias did not solely explain the finding.

After treatment initiation, the absolute rate of substance misuse started to decrease. The on-treatment estimates in stratified Cox regression models were consistently lower than the 1-month pre-treatment estimate, but still elevated when compared to periods over 1 month before treatment. Thus, SSRI treatment seemed to reduce the risk of substance misuse when compared to the particularly high-risk off-treatment period, but it did not fully resolve the elevated risk of substance use problems. This may be due to non-response to SSRIs in some individuals [35], or alternatively to SSRIs not necessarily increasing sustained abstinence, even though they

effectively treat anxiety/depressive symptoms and reduce problematic substance use, as some studies suggest [12].

We also found a decreased risk of acute substance misuse outcomes when on-treatment compared to 1 month pre-treatment among people with a comorbid alcohol use disorder, in line with some RCTs [9,10]. Most RCTs investigated SSRIs as monotherapy [16,17], whereas our study included patients on multiple medications, which is typical in psychiatric specialist services. To preserve the ecological validity of our sample, we did not investigate patients on SSRI only, which future studies (e.g. with access to primary care samples) can address. Pettinati *et al.* found SSRIs to be effective only in combination with naltrexone [10], but our analysis suggests that the risk of substance misuse attenuated on-treatment in those with and without naltrexone prescription. However, we were unable to test the potential interaction effect using time-varying treatment periods, which we encourage future pharmacoepidemiological studies to investigate. In patients with comorbid drug use disorders, the associations did not attenuate on-treatment in a similar fashion as in patients with an alcohol use disorder. Prior RCTs also show no evidence for SSRIs in reducing substance use in drug use disorders [13]. It is important to point out that our sensitivity analysis focusing upon drug-related outcomes, but not restricted to those with a drug use disorder, showed an attenuated risk on-treatment. Patients with drug use disorders had the highest baseline rate of substance misuse, possibly because they use 'riskier' substances, i.e. substances with a higher likelihood of leading to hospitalizations and contacts with the police, more frequently and in higher doses than others. Therefore, the effect of SSRIs on drug-related outcomes may depend upon the severity of the substance use disorder and the frequency of use of high-risk substances.

Limitations

Our study has some important limitations. First, the decreased risk of substance misuse events when on-treatment compared to the 1-month pre-treatment period does not establish a causal effect of SSRI treatment. Instead, unmeasured treatment-related factors, such as counseling, psychosocial treatment or instructions to abstain from using alcohol and other substances during SSRI medication may explain the change in the risk of substance misuse, rather than SSRI treatment itself. There were many clinical confounding factors we were unable to account for. Therefore, our results did not necessarily reflect the pharmacological treatment effect specific to SSRIs, but the combined effect of SSRI and receiving treatment in general.

Secondly, data coverage for diagnoses was incomplete, as common mental health disorders are often treated at primary care [36] and underutilization of substance use disorder treatment in particular is common. Because the NPR captures patients in specialist services, individuals with more severe anxiety/depressive disorders were overrepresented in the primary cohort. We partially addressed this limitation by repeating the analyses in the alternative cohort, where most patients probably received treatment from primary care or other services not covered by the NPR. Because our outcomes involved substance misuse events requiring immediate medical treatment, they are likely to be covered by the NPR. We also included criminal offenses, which do not depend upon treatment-seeking, to expand data coverage.

Thirdly, it is possible that the dispensed medications were not consumed, and therefore all estimates should be regarded as intention-to-treat, which may produce attenuated effect sizes [37]. Because the treatment periods were estimated based on the 90-day rule and median lengths between prescriptions, there is imprecision regarding the periods when individuals were exposed to SSRI medication. The results were comparable when we used an alternative definition for on-treatment periods, although these treatment periods have imprecision for patients whose daily dosage was not consumed once daily (e.g. patients on fluvoxamine). Finally, as we did not have access to the diagnosis for which the SSRI was indicated the sample is clinically heterogeneous, and the anxiety or depressive disorder diagnosis before first treatment initiation does not necessarily capture the specific disorder for which SSRI was prescribed.

CONCLUSIONS

The rate of acute substance misuse outcomes increased during the year preceding the first SSRI treatment initiation, which may reflect the emergence or worsening of pre-existing substance use problems concurrently with anxiety/depression, possibly via self-medication. SSRI treatment appeared to reduce the risk of substance misuse compared to the 1-month period preceding treatment initiation, but whether or not the association is causal remains unclear. This pattern of results was found in patients with comorbid alcohol use disorder, but not with comorbid drug use disorders. Thus, our findings lend support to previous RCTs showing SSRIs to be effective in reducing substance use problems in patients with comorbid depression and alcohol use disorder. Further, the risk of substance misuse remained somewhat elevated even after treatment was initiated, suggesting that clinicians should continue to monitor patients for problematic substance use throughout SSRI treatment.

Declaration of interests

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Author contributions

Suvi Virtanen: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization. **Tyra Lagerberg:** Conceptualization; data curation; formal analysis; methodology. **Lotfi Khemiri:** Conceptualization. **Jaana Suvisaari:** Conceptualization. **Henrik Larsson:** Conceptualization. **Paul Lichtenstein:** Conceptualization; funding acquisition; resources; supervision. **Zheng Chang:** Conceptualization; supervision. **Antti Latvala:** Conceptualization; funding acquisition; resources; supervision.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Inclusion and Exclusion Criteria for the Cohorts and Sub-samples.
Table S1 Drugs and ATC-codes.
Table S2 Within-individual Association of Other Medications with Acute Substance Misuse Outcomes.
Figure S2 Division of Treatment Periods in Relation to Treatment Initiation.
Table S3 Within-individual Association of SSRI Treatment with Acute Substance Misuse Outcomes Using an Alternative Treatment Period Definition (One-pill-per-day).
Table S4 Within-individual Association of SSRI Treatment with Substance Misuse-related Diagnoses and Criminal Offenses.
Figure S3 Rate of Substance-related Offenses 12 Months Before and After First Initiation of SSRI Medication.
Table S5 Within-individual Association of SSRI Treatment with Alcohol- and Drug-related Outcomes.
Table S6 Within-individual Association of SSRI Treatment with Acute Substance Misuse Outcomes in the Alternative Cohort.