Substance use disorders and risk for treatment resistant depression: a population-based, nested case-control study

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ABSTRACT

Background and aims   Treatment-resistant depression (TRD), defined as inadequate treatment response after at least two adequate treatment trials, is common among patients initiating antidepressant treatment. Current or previous substance use disorders (SUD) are common among patients with depression and often lead to worse treatment outcomes. However, in clinical studies, SUD have not been found to increase the risk for TRD. The aim of this study was to investigate the association between SUD and TRD. **Design**   Nested case–control study. **Setting**   Nation-wide governmental health-care registers in Sweden. **Cases and controls**   Data on prescribed drugs and diagnoses from specialized health care were used to establish a prospectively followed cohort of antidepressant initiators with depression ($n = 121\,669$) from 2006 to 2014. Of these, 15 631 patients (13%) were defined as TRD cases, with at least three treatment trials within a single depressive episode. Each case with TRD was matched on socio-demographic data with five controls with depression. **Measurements**   Crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI) estimated the association between TRD and SUD diagnosis and/or treatment in five different time intervals until the time for fulfillment of TRD definition for the case. The analysis was adjusted for clinical and socio-demographic covariates. **Findings**   Having any SUD during, or ≤ 180 days before start of, antidepressant treatment was associated with almost double the risk for TRD [≤ 180 days before: adjusted OR (aOR) = 1.86, CI = 1.70–2.05]. Increased risks for TRD were found ≤ 180 days before treatment start for the subcategories of sedative use (aOR = 2.37; 1.88–2.99), opioids (aOR = 2.02; 1.48–2.75), alcohol (aOR = 1.77; CI = 1.59–1.98) and combined substance use (aOR = 2.31; 1.87–2.99). **Conclusions**   Recent or current substance use disorders is positively associated with treatment resistance among patients initiating treatment for depression.

Keywords   Addiction, alcoholism, antidepressant, depressive disorder, epidemiology, hypnotics and sedatives, opioid-related disorders, treatment-resistant..

INTRODUCTION

Substance use disorders (SUD) are conditions in which the use of one or more psychoactive substances leads to clinically significant distress or functional impairment [1]. SUD are major contributors to disability world-wide, and constitute risk factors for a vast array of adverse mental and physical outcomes, including depressive disorders [2,3].

Among patients with depression the life-time prevalence of SUD is up to 40%, most commonly alcohol use

disorder [4]. Self-reported 12-month prevalence of SUD is 19% [5]. Although the association between SUD and depression is robust in the literature, causality is unclear, as the temporal association appears bidirectional and may show life-time variation [6]. Alcohol, opioid, and in some studies also cannabis use, have been identified as risk factors for depression [7–9]. The role of benzodiazepine and stimulant use is less clear, and may also be influenced by post-SUD anhedonia [2,10,11].

Depression is a leading cause of disability in the world, with potentially disastrous outcomes such as suicide

[12,13]. In clinical studies of sequential antidepressant treatment of depression, designed to emulate real-life treatment conditions, up to 30% of patients do not respond, and up to 50% do not respond adequately after two antidepressant treatment trials [14,15]. As a consequence, the study of patients with treatment resistant depression (TRD) has garnered increasing interest during the last decades. Several methods of defining and staging TRD have been proposed, with failure to achieve an adequate treatment response after two separate, adequate treatment trials being the most common definition [16,17]. The current recommended treatment strategies in TRD include switching within and between classes of antidepressants, combining antidepressants, add-on medication with anti-convulsant or anti-psychotic agents, psychotherapy alone or in combination with pharmacological therapy and neurostimulation [18]. In the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a multi-center randomized treatment study taking patient preference into account (*n* = 4177), no strategy emerged as superior over another; instead, response and remission rates were, rather, dependent on the number of previously failed trials [14].

Identified risk factors for TRD include symptom severity, comorbid anxiety disorders, psychotic symptoms, elevated risk of suicide, a higher number of life-time depressive episodes and longer episode duration [19]. Although, historically, comorbid SUD had been reported to lower the effect of treatment in depression [5,20], the STAR*D trial could not identify an association between SUD at study baseline and subsequent treatment response [21]. A closer analysis of response to step 1 treatment with citalopram did not show a worse response among patients with either alcohol or other substance SUD; however, patients with SUD with combined alcohol and other substances had worse outcomes [22]. In a European multi-center observational study of 702 clinically evaluated patients with depression and < 1 treatment trials, the Group for the Study of Resistant Depression (GSRD) did not identify SUD as a risk factor for TRD [15]. Two systematic reviews on risk factors for TRD failed to identify any association with SUD [23,24]. However, in two recent studies benzodiazepines and opioid analgesics as prescription drugs—not including corresponding SUD—have been suggested to increase the risk for TRD [25,26].

Clinical studies of risk factors for TRD can be hampered by limited patient numbers and follow-up time and by selected patient populations. Observational studies based on administrative health registers may offer an alternative, provided that an acceptable proxy for TRD can be modeled from records of antidepressant treatment and that historical data on SUD are available. In a recent study, our group demonstrated an increased risk for SUD among patients with TRD compared to other depressed patients, among patients both with and without previous SUD [27]. The aim of the present study was to investigate the reverse relationship, i.e. whether SUD increase the risk for TRD, using a register-based definition of TRD in a population-based setting.

METHODS

Source population

The antidepressant initiator cohort used as source population for this nested case–control study was constructed from a combination of data from Swedish health-care registers and has been described in detail elsewhere [27]. The Swedish National Patient Register (NPR) [28] and the Prescribed Drug Register [29] were used to identify all residents in Sweden who were registered in 2006–14 with the ICD-10 diagnostic codes F32–F34 (depressive episodes, recurrent depressive episodes and persistent mood disorders) in specialized health care. Diagnoses in the NPR are registered by clinicians as the main reasons for patients' health-care contacts and procedures. Depression diagnoses are expected to meet the criteria for depression listed in the ICD-10 manual [30]. While specifying the level of severity is possible, according to the ICD-10, the validity of this specifier when registered has not been confirmed and was not taken into account in this study.

Among these patients, those who had a novel dispensed prescription of an antidepressant (ATC code N06A) with a preceding 180-day period with neither dispensed antidepressant prescriptions nor treatment with electroconvulsive therapy (ECT), or repetitive transcranial magnetic stimulation (rTMS), were identified. Patients who, before the first dispensed antidepressant prescription, had been diagnosed with bipolar disorders, psychotic disorders or dementia, or who had dispensed prescriptions of antipsychotics or mood stabilizers, were excluded; however, previous registrations of depression diagnoses were allowed. Linkage between registers was made through the 10-digit personal number assigned to all Swedish residents. This yielded a cohort of 121 669 patients.

Cases and controls

Patients were classified as having TRD if they experienced at least two additional treatment trials within 365 days after the first dispensed antidepressant prescription with antidepressants, augmentation therapy with anti-psychotics or mood stabilizers, ECT or rTMS. An adequate treatment trial was defined as lasting for at least 28 days, in single or multiple dispensings, according to prescribed package sizes in combination with dosage instructions on the prescriptions and/or procedure codes for ECT/rTMS. Treatment gaps had to be a maximum 28 days in order to emulate sequential treatment. Patients who experienced

a gap of ≥ 180 days were eligible for re-entering the depression cohort anew under the same criteria as above if they were registered with a new dispensed prescription, which was then counted as the start of a first treatment trial.

Each patient defined with TRD was matched with up to five controls without TRD from the depression cohort using incidence density sampling [31]; i.e. at the date when a TRD case was identified, controls were drawn from all depression patients eligible at that time-point, including patients who might later be classified as TRD. This sampling procedure prevents selection bias and allows performing a nested case–control study where the person-time contributed is representative of that in the cohort study base. The ratio of cases and controls was chosen weighing statistical power against eligibility of controls for each case [32]. Controls were matched on year of inclusion in the depression cohort and the variables age, sex and county of residence, available in the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) [33].

Definition of SUD

The exposure of SUD was defined as at least one diagnosis or dispensed prescription of medication used in SUD. Definitions of subcategories of SUD and drugs used to identify SUD are given in Table 1. In the Swedish health-care system, mild to moderate depressive and alcohol use disorders are normally initially treated in primary care with pharmacological and/or psychotherapeutic treatment, while treatment-resistant or severe disorders, and all other types of substance use disorders, are treated directly in, or referred to, secondary/specialized care.

Covariates

Highest attained level of education was stratified as <10, 10–13 and > 13 years. Any occurrence of ICD-10 codes for the comorbidities of anxiety disorders (F40–F48) and personality disorders (F60–F61) were identified in the NPR.

Statistical analysis

Crude and adjusted odds ratios (ORs) were calculated using conditional logistic regression models to compare TRD patients with controls regarding comorbid SUD during the treatment period until TRD status/the matching date and before treatment initiation. Results were hierarchically stratified on five time intervals in which SUD might have occurred, from the antidepressant treatment period and backwards in time: (a) from date of the first dispensed antidepressant prescription to fulfillment of TRD definition, i.e. the treatment period; (b) 1–180 days before first dispensed antidepressant prescription, i.e. the lead-in period; (c) 1–365 days before start of period (b) (the lead-in period); (d) 1–5 years before start of the lead-in period;

Table 1 ICD 10- and ATC-codes used to define substance use disorders.

ICD codes	
F10.1–9	Mental and behavioral disorders due to use of alcohol (0.0, acute intoxication, not included)
F11.0–9	Mental and behavioral disorders due to use of opioids
F12.0–9	Mental and behavioral disorders due to use of cannabinoids
F13.0–9	Mental and behavioral disorders due to use of sedatives or hypnotics
F14.0–9	Mental and behavioral disorders due to use of cocaine
F15.0–9	Mental and behavioral disorders due to use of other stimulants, including caffeine
F16.0–9	Mental and behavioral disorders due to use of hallucinogens
F18.0–9	Mental and behavioral disorders due to use of volatile solvents
F19.0–9	Mental and behavioral disorders due to combined drug use and use of other psychoactive substances

ATC codes	
Alcohol use disorder	
N07BB01	Disulfiram
N07BB03	Acamprosate
N07BB04	Naltrexone
N07BB05	Nalmefene
Opioid use disorder	
N07 BC01	Buprenorphine
N07 BC02	Methadone
N07 BC51	Buprenorphine, combinations

ATC = Anatomic Therapeutic Chemical.

and (e) > 5 years before start of the lead-in period. Every exposure, i.e. any SUD or subcategory of SUD, was analyzed separately and an individual could experience more than one exposure. Within each exposure, if the patient had occurrence of SUD in more than one time interval only the most recent interval was counted. The analysis was adjusted for education level, anxiety disorders and personality disorders as covariates. The primary research question and analysis plan were not pre-registered on a publicly available platform, and the results should therefore be considered exploratory. All analyses were performed in SAS® 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The study was performed in accordance with the Declaration of Helsinki and approved by the regional ethical review board in Stockholm (approval no. 2017/1236–31/2). Adult participant consent was not required, as no data could be linked to a specific individual.

RESULTS

Of the 121 669 depression patients in the source population, 15 631 (13%) patients were classified as TRD and subsequently matched with 78 108 controls with depression. Descriptive data for cases and controls are shown in Table 2. Cases were predominantly women (58%), and the mean age was 39.9 years [standard deviation (SD) ± 15.0]. The most common attained education level was 10–12 years (47%), while 24% had a recorded diagnosis of an anxiety disorder and 3% of a personality disorder.

In Table 3, results from crude and adjusted analyses are shown, with and without *post-hoc* stratification by sex, anxiety disorders and personality disorders. The covariates were explored in strata *post hoc* due to unexpected variation between adjusted and unadjusted models in the exposure period of SUD during the 180-day lead-in (Table 3 and Supporting information, Table S1). Patients with personality disorder and SUD in the year before the 180-day lead-in period were found to have a disproportionately elevated risk for TRD [OR = 21, 95% confidence interval (CI) = 1.4–295]. Because the number of patients with comorbid personality disorder was limited ($n = 174$) we decided to exclude them—and their corresponding controls—from the final analysis rather than adjusting, due to the possibly disproportionate effect on risk patterns for the whole study population.

Results from the final model, adjusted for education level and anxiety disorders, are shown in Table 4. Risk patterns were largely unaffected by adjustment. The risk for TRD remained elevated among patients with any SUD during the treatment period (OR = 1.6, 95% CI = 1.4–1.7) and during the 180-day lead-in period (OR = 1.9, 95% CI = 1.7–2.1). However, patients with SUD ≤ 1 year before the lead-in period (OR = 0.5, 95% CI = 0.4–0.7) and with SUD 1–5 years before the lead-in period (OR = 0.8; 0.7–0.9) had a significantly lowered risk for TRD. When stratified by subcategories of SUD, this negative association was seen only among patients with alcohol SUD.

Table 2 Characteristics of cases with treatment resistant depression (TRD) and controls with other major depressive disorder (depression).

	Cases (TRD)		Controls (other depression)		
	n	*%*	*n*	*%*	χ^2
Total number	15 631		78 108		
Age (years)[a]					Matched
18–29	4879	31	24 733	31.7	
30–49	6325	41	31 590	40.4	
50–69	3926	25	19 649	25.2	
> 70	501	3	2136	2.7	
Sex[a]					Matched
Male	6613	42	33 047	42.3	
Female	9018	58	45 061	57.7	
Education level					P = 0.0002
Missing	144	1	863	1.1	
< 10 years	3962	25	18 937	24.2	
10–13 years	7333	47	36 308	46.5	
> 13 years	4192	27	22 000	28.2	
Anxiety disorder[b]	3601	23	13 835	17.7	P = 0.001
Personality disorder[c]	464	3	1998	2.6	P = 0.003

[a]Matching variable; [b]ICD-10 codes F42–F48; [c]ICD-10 codes F60–69.

Table 3 Risk for treatment resistant depression (TRD) among patients with substance use disorders (SUD). Crude and adjusted odds ratios (OR) with 95% confidence intervals comparing cases with TRD versus controls with other major depressive disorder (depression). Stratified by latest time interval for occurrence of SUD in health-care registers.

	Cases (TRD) n (%)	Controls (other depression) n (%)	Crude OR	Adjusted OR[a]	Cases (TRD) n (%)	Controls (other depression) n (%)	Crude OR	Adjusted OR[a]	Effect modification
All patients									
SUD during treatment period	956 (6.1%)	3150 (4.0%)	**1.59 (1.48–1.72)**	**1.54 (1.42–1.66)**					
SUD during the 180-day lead-in period	729 (4.7%)	1846 (2.4%)	**2.05 (1.88–2.24)**	**1.93 (1.76–2.10)**					
SUD ≤ 1 year before the lead-in period	128 (0.8%)	1157 (1.5%)	**0.57 (0.48–0.69)**	**0.54 (0.45–0.65)**					
SUD within 1–5 years before the lead-in period	392 (2.5%)	2507 (3.2%)	**0.81 (0.73–0.90)**	**0.76 (0.68–0.85)**					
SUD > 5 years before the lead-in period	292 (1.9%)	1553 (2.0%)	0.98 (0.86–1.11)	0.95 (0.84–1.08)					
Sex	*Men*				*Women*				*P* = 0.040
SUD during treatment period	587 (8.9%)	1888 (5.7%)	**1.65 (1.50–1.82)**	**1.61 (1.46–1.78)**	369 (4.1%)	1262 (2.8%)	**1.51 (1.34–1.70)**	**1.45 (1.28–1.63)**	
SUD during the 180-day lead-in period	406 (6.1%)	1115 (3.4%)	**1.91 (1.70–2.15)**	**1.80 (1.60–2.03)**	323 (3.6%)	731 (1.6%)	**2.26 (1.98–2.58)**	**2.11 (1.84–2.41)**	
SUD ≤ 1 year before the lead-in period	68 (1.0%)	676 (2.0%)	**0.53 (0.41–0.68)**	**0.50 (0.39–0.65)**	60 (0.7%)	481 (1.1%)	**0.64 (0.49–0.84)**	**0.59 (0.45–0.77)**	
SUD within 1–5 years before the lead-in period	193 (2.9%)	1278 (3.9%)	**0.79 (0.68–0.92)**	**0.75 (0.64–0.88)**	199 (2.2%)	1229 (2.7%)	**0.83 (0.72–0.97)**	**0.77 (0.66–0.90)**	
SUD > 5 years before the lead-in period	131 (2.0%)	705 (2.1%)	0.98 (0.81–1.18)	0.97 (0.80–1.17)	161 (1.8%)	848 (1.9%)	0.97 (0.82–1.16)	0.94 (0.80–1.12)	
Anxiety disorder	*No*				*Yes*				*P* = 0.025
SUD during treatment period	685 (5.7%)	2388 (3.7%)	**1.59 (1.45–1.75)**	**1.57 (1.44–1.73)**	271 (7.5%)	762 (5.5%)	**1.27 (1.01–1.58)**	**1.27 (1.01–1.58)**	
SUD during the 180-day lead-in period	422 (3.5%)	1285 (2.0%)	**1.83 (1.62–2.05)**	**1.81 (1.61–2.03)**	307 (8.5%)	561 (4.1%)	**1.77 (1.41–2.22)**	**1.77 (1.41–2.23)**	
SUD ≤ 1 year before the lead-in period	77 (0.6%)	784 (1.2%)	**0.55 (0.43–0.69)**	**0.54 (0.42–0.68)**	51 (1.4%)	373 (2.7%)	0.69 (0.46–1.03)	0.70 (0.46–1.05)	
SUD within 1–5 years before the lead-in period	241 (2.0%)	1672 (2.6%)	**0.81 (0.71–0.93)**	**0.80 (0.69–0.92)**	151 (4.2%)	835 (6.0%)	**0.73 (0.56–0.94)**	**0.73 (0.56–0.94)**	
SUD > 5 years before the lead-in period	211 (1.8%)	1222 (1.9%)	0.95 (0.82–1.11)	0.94 (0.81–1.10)	81 (2.2%)	331 (2.4%)	0.80 (0.56–1.13)	0.81 (0.57–1.14)	
Personality disorder	*No*				*Yes*				*P* = 0.06
SUD during treatment period	915 (6.0%)	3019 (4.0%)	**1.60 (1.48–1.73)**	**1.55 (1.43–1.67)**	41 (8.8%)	131 (6.6%)	3.01 (0.38–23.6)	5.13 (0.49–53.6)	
SUD during the 180-day lead-in period	666 (4.4%)	1746 (2.3%)	**1.98 (1.80–2.17)**	**1.86 (1.70–2.05)**	63 (13.6%)	100 (5.0%)	**17.3 (1.71–175)**	**20.5 (1.43–295)**	
SUD ≤ 1 year before the lead-in period	119 (0.8%)	1083 (1.4%)	**0.57 (0.47–0.69)**	**0.54 (0.44–0.65)**	9 (1.9%)	74 (3.7%)	0.64 (0.11–3.70)	0.68 (0.10–4.46)	
SUD within 1–5 years before the lead-in period	355 (2.3%)	2282 (3.0%)	**0.81 (0.72–0.91)**	**0.76 (0.68–0.85)**	37 (8.0%)	225 (11.3%)	2.13 (0.39–11.5)	2.94 (0.50–17.4)	
SUD > 5 years before the lead-in period	268 (1.8%)	1477 (1.9%)	0.95 (0.83–1.08)	0.93 (0.81–1.06)	24 (5.2%)	76 (3.8%)	8.27 (0.44–154)	5.27 (0.34–81.4)	

[a]Adjusted for anxiety disorders (ICD-10 codes F40–F41), personality disorders (ICD-10 codes F60–F61) and highest attained education level. The OR reflects the relative risk of TRD associated with having versus not having a history of SUD in the respective time-period. Confidence intervals that do not include 1 are shown in bold type.

Table 4 Risk for treatment resistant depression (TRD) among patients with substance use disorders (SUD). Crude and adjusted odds ratios (OR) with 95% confidence intervals comparing cases with TRD versus controls with other major depressive disorder (MDD). Stratified by latest time interval for occurrence of SUD in health-care registers. Patients with personality disorders are excluded.

	Cases (TRD)	Controls (other depression)	Adjusted OR[a]
Any SUD			
SUD during treatment period	915 (6.0%)	3019 (4.0%)	**1.55 (1.43–1.67)**
SUD during the 180-day lead-in period	666 (4.4%)	1746 (2.3%)	**1.86 (1.70–2.05)**
SUD ≤ 1 year before the lead-in period	119 (0.8%)	1083 (1.4%)	**0.54 (0.44–0.65)**
SUD within 1–5 years before the lead-in period	355 (2.3%)	2282 (3.0%)	**0.76 (0.68–0.85)**
SUD > 5 years before the lead-in period	268 (1.8%)	1477 (1.9%)	0.93 (0.81–1.06)
Alcohol SUD			
SUD during treatment period	587 (3.9%)	2222 (2.9%)	**1.32 (1.20–1.45)**
SUD during the 180-day lead-in period	469 (3.1%)	1278 (1.7%)	**1.77 (1.59–1.98)**
SUD ≤ 1 year before the lead-in period	95 (0.6%)	831 (1.1%)	**0.55 (0.44–0.68)**
SUD within 1–5 years before the lead-in period	277 (1.8%)	1863 (2.4%)	**0.71 (0.63–0.81)**
SUD > 5 years before the lead-in period	207 (1.4%)	1098 (1.4%)	0.94 (0.81–1.09)
Opioid SUD			
SUD during treatment period	57 (0.4%)	210 (0.3%)	1.32 (0.98–1.77)
SUD during the 180-day lead-in period	58 (0.4%)	133 (0.2%)	**2.02 (1.48–2.75)**
SUD ≤ 1 year before the lead-in period	21 (0.1%)	100 (0.1%)	0.99 (0.62–1.59)
SUD within 1–5 years before the lead-in period	39 (0.3%)	169 (0.2%)	1.03 (0.72–1.46)
SUD > 5 years before the lead-in period	21 (0.1%)	106 (0.1%)	1.00 (0.62–1.60)
Cannabinoid SUD			
SUD during treatment period	68 (0.4%)	206 (0.3%)	**1.65 (1.25–2.19)**
SUD during the 180-day lead-in period	29 (0.2%)	107 (0.1%)	1.26 (0.83–1.90)
SUD ≤ 1 year before the lead-in period	12 (0.1%)	84 (0.1%)	0.72 (0.39–1.31)
SUD within 1–5 years before the lead-in period	39 (0.3%)	186 (0.2%)	0.98 (0.69–1.39)
SUD > 5 years before the lead-in period	21 (0.1%)	125 (0.2%)	0.80 (0.50–1.28)
Sedative SUD			
SUD during treatment period	119 (0.8%)	261 (0.3%)	**2.15 (1.72–2.67)**
SUD during the 180-day lead-in period	112 (0.7%)	217 (0.3%)	**2.37 (1.88–2.99)**
SUD ≤ 1 year before the lead-in period	17 (0.1%)	122 (0.2%)	0.64 (0.38–1.07)
SUD within 1–5 years before the lead-in period	63 (0.4%)	323 (0.4%)	0.90 (0.69–1.18)
SUD > 5 years before the lead-in period	68 (0.4%)	320 (0.4%)	1.03 (0.79–1.34)
Combined SUD			
SUD during treatment period	222 (1.5%)	504 (0.7%)	**2.19 (1.86–2.57)**
SUD during the 180-day lead-in period	135 (0.9%)	266 (0.3%)	**2.31 (1.87–2.86)**
SUD ≤ 1 year before the lead-in period	30 (0.2%)	202 (0.3%)	0.69 (0.47–1.01)
SUD within 1–5 years before the lead-in period	89 (0.6%)	428 (0.6%)	0.96 (0.76–1.21)
SUD > 5 years before the lead-in period	63 (0.4%)	360 (0.5%)	0.85 (0.65–1.12)

[a]Adjusted for anxiety disorders and attained education level. The OR reflects the relative risk of TRD associated with having versus not having a history of SUD in the respective time-period. Confidence intervals that do not include 1 are shown in bold type.

Patterns for risk increase were similar for the subcategories of SUD. The largest risk increase for TRD was seen among patients with sedative SUD during the 180-day lead-in period (OR = 2.4, 95% CI = 1.9–3.0) and among those with combined substance SUD (OR = 2.3, 95% CI = 1.9–2.9). The risk for TRD was also elevated among patients with alcohol SUD during both the treatment period and the 180-day lead-in period, while there were also positive associations or trends toward significance among the patients with cannabinoid SUD and those with opioid SUD. In the SUD subcategories of cocaine (*n* = 31), hallucinogen (*n* = 23) and volative solvent SUD (*n* = 10), too few cases were identified for meaningful stratification.

DISCUSSION

In this nested case–control study of antidepressant-treated patients with depression, we found that SUD before start of, or during, treatment increases the risk for subsequent TRD. Findings were similar for alcohol, opioid, cannabinoid, sedative and combined drug SUD. Conversely, risk for TRD was lowered among patients with a history of alcohol SUD more than 180 days before treatment start.

Previous literature

Long-standing perceptions, clinical observations and treatment trials support the negative impact of ongoing or recent SUD on the effect of antidepressant treatment [20,34,35]. However, the findings from the present study differ from the only specific study comparing patients with and without SUD regarding risk for TRD, the European Study of Resistant Depression (ESRD) clinical data set, where no association could be demonstrated [15]. In the ESRD, SUD was assessed through a clinical interview, while in the present study registered diagnoses or dispensed prescriptions for SUD were the exposures. Also, the rates of TRD were much higher in the ESRD than in the present study (52 versus 13%), together suggesting a different study population. Comparing a clinical investigation with observational data is difficult, and both methods have advantages; the former has clinical validity with increased chance for TRD detection and treatment adherence, while the latter eliminates recall bias and is performed in a population-based setting.

For further comparison, a re-examination of the STAR*D trial showed that having alcohol or other SUD at start of antidepressant treatment did not influence the outcome of the first treatment trial in the study [22]. Again, the present study may capture a different study population regarding both the exposure and outcome than the STAR*D by only identifying SUD registered in contacts with health care. Also, in a clinical study setting such as the STAR*D there may be fewer patients lost to clinical follow-up than in a naturalistic setting, and hence more patients who receive subsequent treatment trials.

In other studies, prescription use of benzodiazepines and opioids have recently been suggested to be associated with TRD [25,26]. The present study focuses on clinically established SUD, which differs from having prescription use only, although the latter may certainly be a risk factor for SUD.

Possible mechanisms

The relation between SUD, depression and TRD is likely to be complex and multi-dimensional, as these conditions may not only be directly associated with each other [7–9], but also share underlying socio-demographic and biological risk factors. SUD may inflict various structural and biochemical changes in the brain, especially in the dopamine system, which may induce a depression-like state of anhedonia and affect substrates for antidepressant mechanisms [36,37]. According to the 'self-medication hypothesis', patients with an undiagnosed depression may also be more prone to developing SUD [38]. Underlying genetic factors may increase susceptibility to both SUD and

depression, and may also increase risk for psychopathology in general [39,40].

As possible mediators, different measures of lower socio-economic status (SES) are highly associated with depression [41] but have not, as yet, been identified as risk factors for TRD [24]. Low SES is also a risk factor for SUD but results are not consistent, especially among adolescents [42,43]. It has also been suggested that the comorbidity of depression and SUD contributes to lower SES through forward social selection [44]. Anxiety and personality disorders are known risk factors for depression, TRD and SUD alike [15,45–47]. This is supported in the present study by the substantial risk increase for TRD among patients with comorbid SUD and personality disorders.

The lower risk for TRD among patients with a distal history of alcohol SUD in this study may be attributed to a combination of factors: (1) the diagnosis of alcohol SUD may have been recorded in conjunction with treatment of a previous depression episode, influencing the treatment pattern in the present episode; (2) patients with a history of alcohol SUD may be more prone to dropout and/or adherence failure, hence not being available for the third treatment trial required for fulfillment of TRD criteria in this study; (3) prescribing physicians may be biased in treatment patterns regarding patients with a history of SUD; (4) the temporal hierarchy in the design of this study leads to fewer patients being available for study in the more distal time intervals, decreasing statistical inference; and (5) the distal history of alcohol SUD in the control group may have provided opportunities for treatment or management of alcohol SUD prior to diagnosis of depression in a manner that reduced risk for TRD.

Strengths and weaknesses

The strengths of this study include high-quality nationwide register data and coverage, the identification of a large, population-based cohort and the possibility to adjust for comorbidity and socio-demographic data. The nested case–control design allowed for close matching on cases and controls from the source population of depression patients undergoing treatment. Administrative data have been used increasingly in studies of TRD in health databases from different countries, including Sweden [48–51].

There are also several limitations. The diagnoses from the NPR used in this study have not been clinically validated, although the diagnoses in the NPR generally have acceptable to good clinical validity [28]. Also, our definition of TRD is solely based on administrative diagnostic and dispensed prescription data, and has yet to be verified through clinical data. Depression severity level, side effects, clinical effectiveness of treatment and reasons for treatment discontinuation or loss to follow-up could not be assessed. Also, patients who do not

adhere to a treatment trial for adequate time and dosage in clinical studies are generally not counted in the TRD group, and comparability with clinical studies of TRD is therefore reduced. Most clinical studies of TRD implement a threshold on a recognized severity rating scale of depression for detection of TRD, which was not possible in this study. Furthermore, recurrent depression is a risk factor for TRD [19], and depressive episodes and treatment trials may have occurred before the years of register data available for this study.

The prescription data used in this study cover dispensed medications but actual patient adherence is uncertain, which may be of relevance, especially regarding patients with SUD. Also, patients with SUD are, in general, more prone to non-adherence and loss to follow-up than other patients in psychiatric care [52,53], which may lead to underestimated ORs, as our definition of TRD requires the start of a third sequential treatment trial. Conversely, repeated contacts with health care may lead to a higher detection rate of SUD and possible misclassification bias among patients with TRD during the treatment period.

As the NPR only covers diagnoses from specialized care, any patients who received all treatment trials in primary care were not included. At least regarding SUD, this number should be low, as most SUD care in Sweden is given in the specialized psychiatric care system. The exception is alcohol SUD which, however, was partly identified in this study through prescription data with full coverage also for primary care patients. A limitation of this operationalization of SUD—using both diagnostic and/or prescribed treatment data—is that it may not fully correspond to diagnostic definitions of SUD. Conversely, as both cases and controls had depression of sufficient severity to be treated in specialized care, specificity of the depression diagnosis should be high. Absolute number of patients in three subcategories of SUD were too low for analysis, which could be related to the method of identifying these through registered diagnoses in specialized health care only.

Clinical implications

The results from this study suggest that history of SUD should always be taken and considered at the treatment planning stage when a patient presents with depression. Patients with SUD who develop depression, and similarly depressed patients who develop SUD, may be less prone to seek help than patients without comorbidity, and rates of undetected comorbidities are high when screened for [54]. Prospective, population-based cohorts which include screening for depression and SUD alone and in combination, as well as offering interventions for these patient groups, may be of value. When a SUD is identified, current guidelines state that both conditions should be treated simultaneously, targeting both depression and SUD, preferably using integrative models and with a low threshold for involving social and community services [55,56]. If treatment resistance emerges among patients with depression, measures with proven efficacy in TRD such as add-on medication or ECT/rTMS should generally be considered. However, to our knowledge, no treatment studies on patients with comorbid SUD and TRD exist, and it is yet to be specifically investigated if these measures are also valid for this group of patients [18]. Of special interest is the fact that emerging, potentially effective treatment strategies for TRD such as NMDA receptor agonists and hallucinogens may have a known potential for illicit use, but have also shown potential for treatment of SUD [57–60]. Their role in the treatment of patients with combined TRD and SUD is yet to be determined.

CONCLUSION

Present or recent comorbidity of SUD may be a risk factor for treatment resistance among patients seeking treatment for depression. Future research should aim at identifying effective interventions for this prioritized group of patients.

Declaration of competing interests

Funding

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Supporting Information

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

Table S1 Crude and adjusted odds ratios (OR) with 95% confidence intervals for treatment resistant depression among patients with substance use disorders (SUD), stratified by latest time period for registered SUD and education level. Adjusted for sex, anxiety disorders (ICD-10 codes F40-F41), personality disorders (ICD-10 codes F60-F61), and highest attained education level. Confidence intervals excluding 1 are in bold. AD = Antidepressant prescription.