Treatment-resistant depression as risk factor for substance use disorders—a nation-wide register-based cohort study

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ABSTRACT

Background and aims Treatment-resistant depression (TRD) is common among patients with major depressive disorder (MDD). MDD may increase the risk for developing substance use disorders (SUD). The aim of this study was to investigate the risk for developing SUD among patients with TRD compared with other depressed patients. **Design** Observational cohort study. **Setting** Nation-wide governmental health registers in Sweden. **Participants** All patients aged 18–69 years with an MDD diagnosis in specialized health care who had received at least one antidepressant prescription during 2006–14 were identified. Patients with at least three treatment trials within a single depressive episode were classified with TRD. **Measurements** Patients with TRD were compared with the whole MDD cohort regarding risk for obtaining a SUD diagnosis or medication using survival analyses adjusted for socio-demographics and comorbidities. **Findings** Of 121 669 MDD patients, 13% were classified with TRD. Among the patients without any history of SUD, patients with TRD had a risk increase for any SUD both ≤ 1 and > 1 year after antidepressant initiation [> 1 year hazard ratio (HR) = 1.4; 95% confidence interval (CI) = 1.3–1.5]. Risks were elevated for the subcategories of opioid (HR = 1.9, 95% CI = 1.4–2.5) and sedative SUD (HR = 2.7, 95% CI = 2.2–3.2). Patients with a history of SUD had a risk increase for any SUD ≤ 1 year after start of treatment (HR = 1.2, 95% CI = 1.1–1.4), and both ≤ 1 year and > 1 year for sedative (> 1 year HR = 2.0, 95% CI = 1.3–3.0) and multiple substance SUD (HR = 1.9, 95% CI = 1.4–2.5). **Conclusions** Patients with treatment-resistant depression may be at greater risk for substance use disorders compared with other patients with major depressive disorder. Patterns may differ for patients with and without a history of substance use disorders, and for different categories of substance use disorder.

Keywords Addiction, alcoholism, antidepressants, depressive disorder, epidemiology, opioid-related disorders, treatment-resistant.

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent and often recurrent condition with substantial consequences for both the individual and for society in terms of function loss, costs and premature death [1,2]. Far from all depressed individuals respond as intended to treatment, as 10–20% do not tolerate an initial treatment trial, and 25–60% of completers of an adequate trial do not achieve remission [3–5]. During the last decades, several definitions of treatment-resistant depression (TRD) have been proposed for clinical and research

purposes, with a common denominator among them being at least two adequate treatment attempts without achieving remission [6,7].

Substance use disorders (SUD) as defined by DSM-5 are conditions in which the use of one or more psychoactive substances leads to a clinically significant impairment or distress [1], replacing the earlier diagnostic concepts of abuse, addiction and dependence. SUD may lead to various adverse mental, physical and economic outcomes, and account for 5% of the global burden of lost disability-adjusted life-years [8]. In administrative data, the 12-month prevalence of alcohol or drug dependence in MDD patients is

estimated at approximately 12% [9], increasing by to up to 30% in clinical samples [10].

A wide range of studies show a temporal association from depression to SUD, but the relationship appears to be complex. Depression and other mental disorders often precede the presentation of SUDs, regardless of substance being used [11,12]. There is also evidence that the relationship may be temporally reversed or bidirectional, and that it may vary for different types of drug use and during different stages in life [12–15]. Antidepressant effect is generally lower when a comorbid SUD is present [16–18].

In recent years, several novel treatments for TRD have been introduced, including ketamine and hallucinogenic agents such as psilocybin and ayahuasca [19–21]. Although the effect of these treatments may seem superior to current antidepressant medications, one of the unresolved issues regarding these treatments is their known potential for illicit substance use, and whether or not they can be offered safely to patients with or at risk for SUD [22].

As TRD is a clinical concept, studies of long-term outcomes are rare, especially in large cohorts. In a recent systematic review of the literature on medium- to long-term outcomes in TRD, none of the studies reported data on SUD [23]. A possible means of studying long-term outcomes of TRD, including risk for SUD, in sufficiently large cohorts is using public health-care registers. Efforts to adapt clinical criteria of TRD to register data have recently been made in Taiwanese, Danish and Swedish public health-care databases [24–26].

The aim of this study was to investigate in a national register-based setting whether patients with TRD are at higher risk for subsequent SUD than other patients with MDD, among patients with as well as without a previously known SUD.

METHODS

Study population

Using Swedish governmental registers, we identified all residents in Sweden during the study period 2006–14 who: (1) were aged more than 18 years, (2) had filled a prescription for an antidepressant drug (ATC-code N06A) in the Prescribed Drug Register (PDR) [27] and (3) had a diagnosis of depression (ICD-10 codes F32, F33 or F34) in the National Patient Register (NPR) [28], within a time interval of 30 days before and up to 365 days after the filled prescription. The PDR contains data on all dispensed prescriptions in Swedish pharmacies starting from 1 July 2005. As 2006 was the first full year with data coverage it marked the start of the study period, with 2014 being the last year with full data available in our data set. The NPR covers diagnoses from all in- and out-patient specialized care in Sweden, but not primary care/general practice. Excluded were patients with any prescription during 180 days before the

index prescription of antidepressants or of the potential augmenting medications for depression: lithium, antipsychotics, valproate, lamotrigine or carbamazepine. Also excluded were those with procedure codes for electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) and/or with a history of psychosis (ICD-10 F20–F29), mania (F30), bipolar disorder (F31) or dementia (F00–F03). Included patients had to be residents in Sweden according to the Total Population Register [29] for a full 180 days before the first antidepressant prescription filling during the study period. The flow-chart for study population selection is shown in Fig. 1.

Definition of TRD

Patients were classified with TRD if at least two subsequent treatment trials (a different antidepressant ATC-code, antidepressant add-on medication or ECT/rTMS) were recorded within the first year after the first antidepressant prescription filling, with no treatment gap of > 28 days according to the prescription texts and medication package sizes. An adequate treatment trial was defined as lasting for at least 28 days. Lithium, risperidone, olanzapine, aripiprazole and quetiapine were counted as augmentation of MDD treatment, in agreement with recommendations by guidelines for the treatment of TRD [30,31]. Patients were reclassified from MDD to TRD from the first day of the third treatment attempt.

If patients filled a novel drug prescription during ongoing hospitalization, treatment was considered to start on the day of hospital discharge. For patients who received in-patient care after the first antidepressant prescription fill, the assumed duration of the prescription was prolonged with the number of days of care. If in-patient care occurred during a prescription gap, the gap was shortened by the number of days of care.

Outcomes

The outcome of SUD was defined as the occurrence of a SUD diagnosis in specialized care in the NPR, or of a prescription of a medication for SUD in the PDR. Definitions of the different subcategories of SUD are shown in Panel 1.

Covariates

The socio-demographic variables of age, sex, county of residence in Sweden and educational level (≤ 10, 10–12, > 12 years) were taken from the Longitudinal Integration Database for Health Insurance and Labor Market Studies. Subjects with missing data on education level were assigned to the lowest stratum. There were no missing data in other covariates. The psychiatric comorbidities of history of self-harm/suicide attempts (ICD codes X60–X84, Y10–Y34), personality disorders (F60–F61) and anxiety
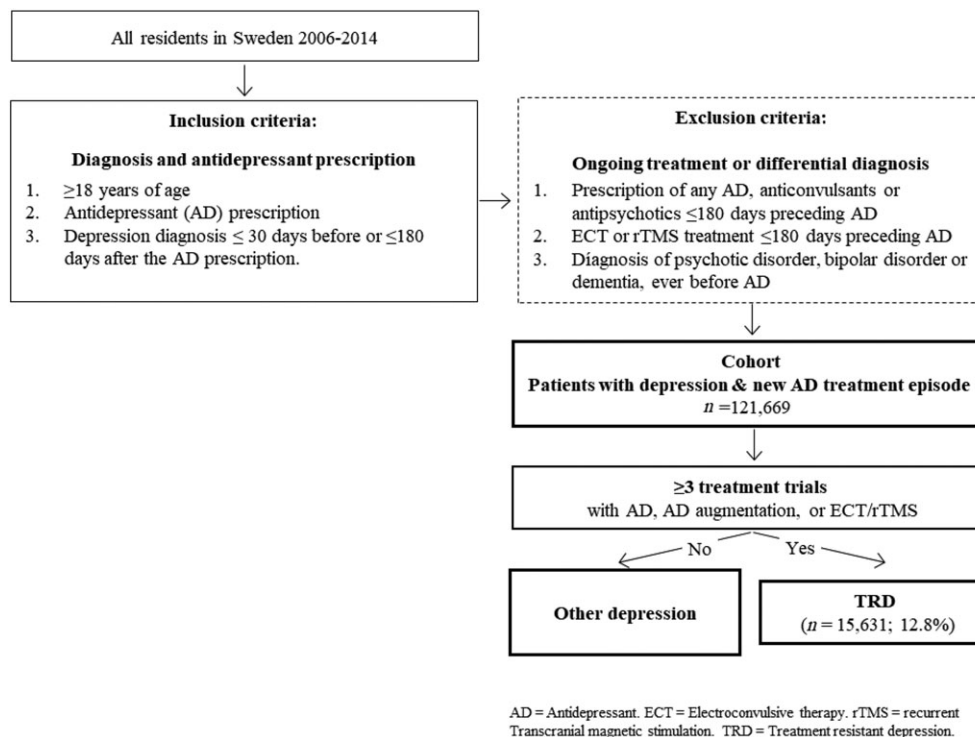
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┌─────────────────────────────────────────┐
│        All residents in Sweden 2006–2014 │
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Inclusion criteria:

Diagnosis and antidepressant prescription

1. ≥18 years of age
2. Antidepressant (AD) prescription
3. Depression diagnosis ≤ 30 days before or ≤180 days after the AD prescription.

Exclusion criteria:

Ongoing treatment or differential diagnosis

1. Prescription of any AD, anticonvulsants or antipsychotics ≤180 days preceding AD
2. ECT or rTMS treatment ≤180 days preceding AD
3. Diagnosis of psychotic disorder, bipolar disorder or dementia, ever before AD

Cohort
Patients with depression & new AD treatment episode
n =121,669

≥3 treatment trials
with AD, AD augmentation, or ECT/rTMS

No — **Other depression**

Yes — **TRD**
(*n* = 15,631; 12.8%)

AD = Antidepressant. ECT = Electroconvulsive therapy. rTMS = recurrent Transcranial magnetic stimulation. TRD = Treatment resistant depression.

Figure I Flow-chart for study population selection

disorders (ICD-10 category of neurotic disorders, F40–F48) at baseline were identified in the NPR.

Statistical analysis

Patients with TRD were compared to the whole MDD study population regarding risk for occurrence of SUD using proportional hazard regression models with the results expressed as hazard ratios (HR) with 95% confidence intervals (CI). Within the cohort, TRD was treated as a time-varying covariate, i.e. an individual moved from the MDD to the TRD group (unexposed to exposed group) when the requirements of TRD were fulfilled. The follow-up stopped at the first occurrence of any SUD as outcome. Due to the assumption of proportional hazards not being met, separate analyses were made for occurrence of SUD ≤ 1 year and > 1 year after the start of the initial antidepressant trial, in which hazards were proportional. The models included the socio-demographic covariates as well as history of self-harm/suicide attempts, personality disorders and anxiety disorders. In order to investigate the temporal impact of TRD on risk for SUD, and with the hypothesis that patients with and without prior SUD would have different risk patterns, separate analyses were conducted for patients with and without history of SUD in the registers (before start of follow-up). Patients with and without previous occurrence of MDD or antidepressants in the registers were also compared in a separate analysis.

All analyses were performed in SAS® version 9.4 (SAS Institute, Cary, NC, USA).

Ethical permission

The study was approved by the regional ethical review board in Stockholm (no. 2017/1236–31/2).

RESULTS

Table 1 shows baseline data for the whole study population and for the proportion that was classified with TRD. Of a total of 121 669 MDD patients, 15 631 (12.8%) fulfilled the TRD criteria. Median age in the whole cohort was 36 years [± standard deviation (SD) = 1] with a higher proportion of TRD patients in the older age strata. Females comprised 58% of patients, both in the whole cohort and among patients with TRD. The proportion of patients with a history of SUD was roughly equal among patients with TRD and the other MDD patients (11.9 versus 11.2%). Patients with TRD had a higher rate of history of anxiety disorders (23 versus 18%). Median time from first antidepressant prescription to classification with TRD was 203 days (± SD = 83.1).

Table 2 shows the result from the survival analysis among the MDD patients without any previous occurrence of SUD in the registers. The adjusted risk was elevated with 23% among TRD patients for the outcome of any SUD ≤ 1 year after treatment start (HR 1.2; 95% CI = 1.1–1.4),

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

ICD codes

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

Table 1 Baseline characteristics of the entire cohort with major depressive disorder (MDD) and the part of the cohort classified with treatment-resistant depression (TRD).

	Entire MDD cohort		TRD	
	N	%	n	%
	121 669	100.0	15 631	100.0
Age (years)				
18–29	43 497	35.8	4879	31.2
30–49	48 383	39.8	6325	40.5
50–69	26 913	22.1	3926	25.1
> 70	2876	2.4	501	3.2
Sex				
Females	70 757	58.2	9018	57.7
Males	50 912	41.8	6613	42.3
Education level				
Missing	1499	1.2	144	0.9
< 10 years	31 766	26.1	3962	25.3
10–13 years	55 275	45.4	7333	46.9
> 13 years	33 129	27.2	4192	26.8
History of SUD[a]	16 953	13.9	2280	14.6
Anxiety disorder[b]	22 077	18.1	3601	23.0
Personality disorder[c]	3235	2.7	464	3.0
Self-harm[d]	7364	6.1	1123	7.2

[a]ICD codes F10.1-F16.9, F18.0-F19.9 and/or ATC codes N07BB01–05, N07BB-BC. [b]ICD codes F40–48. [c]ICD codes F60-F61. [d]ICD codes X60-X84, Y10-Y34.

with a borderline significant elevated risk after > 1 year (HR = 1.15; 95% CI = 1.0–1.3). Risks were also significantly elevated for the SUD subcategories of opioids (≤ 1 year: HR = 3.4; 95% CI = 2.4–4.9; > 1 year: HR = 1.9; 95% CI = 1.4–2.5) and sedatives (≤ 1 year: HR = 3.0; 95% CI = 2.3–3.8; > 1 year HR = 2.7; 95% CI = 2.2–3.2).

Results for patients with previous occurrence of SUD in the registers are presented in Table 3. The adjusted risk was elevated with 23% among TRD patients for the outcome of any SUD ≤ 1 year after treatment start (95% CI = 1.1–1.4), with a borderline significant elevated risk after > 1 year (HR = 1.15; 95% CI = 1.0–1.3). In the SUD subcategories, adjusted relative risks were elevated both ≤ 1 year and > 1 year after treatment start for sedatives (≤ 1 year: HR = 2.4; 95% CI = 1.7–3.4, > 1 year HR = 2.0; 95% CI = 1.3–3.0) and multiple substance use (≤ 1 year HR = 1.4; 95% CI = 1.1–1.8; ≤ 1 year HR = 1.9; 95% CI = 1.4–2.6).

In all analyses, the number of patients in the SUD subcategories of cocaine, hallucinogens and volatile solvents were too small for analysis. There were minor inconsistencies between rates and HRs in some analyses (i.e. the rate for alcohol use disorder ≤ 1 year being higher in the MDD category than in TRD, but HR being positive) due to the assumption of the models being proportional over time not being completely met. No significant effect modifications were found when stratified analyses for all covariates were performed, and there were no significant differences between women and men. When comparing patients with and without previous occurrence of MDD in the registers, no significant differences were found (Supporting information, Table S1).

DISCUSSION

In this population-based cohort study, patients with TRD had an elevated risk for subsequent SUD diagnosis compared to other MDD patients. This risk increase was 51% during the first year after antidepressant initiation and 39% thereafter among patients without any previously registered health-care contact due to SUD, while for patients who had had such contact the risk increase was 15% during the first year.

The strengths of this study include the use of high-quality national registers with high completeness, and a large cohort size granting statistical power to detect several risk differences while allowing adjustment for multiple covariates. The diagnoses in the NPR have a high validity

Table 2 Risk for developing substance use disorders (SUD) among patients with treatment-resistant depression (TRD) compared with patients with major depressive disorder (MDD) not classified with TRD. Patients without previous SUD, time-dependent proportional hazard regression.

	MDD[a]		TRD		Crude HR (95% CI)			Adjusted HR (95% CI)[b]		
	≤ 1 year	> 1 year	≤ 1 year	> 1 year	≤ 1 year[e]	> 1 year	P-value	≤ 1 year	> 1 year	P-value
							Wald χ² test for total effect of TRD			Wald χ² test for total effect of TRD
Total N	101 166	74 962	12 856	10 600						
Time under observation, years	85 669	280 746	8536	36 326						
	n (rate)[c]	n (rate)	n (rate)	n (rate)			of TRD			of TRD
Any SUD[d]	3504 (40.90)	3462 (12.33)	425 (49.79)	607 (16.71)	1.45 (1.31–1.60)	1.34 (1.23–1.46)	< 0.0001	**1.51 (1.36–1.67)**	**1.39 (1.27–1.51)**	**< 0.0001**
Alcohol	2226 (25.98)	2135 (7.60)	202 (23.66)	290 (7.98)	1.10 (0.95–1.27)	1.04 (0.92–1.17)	0.35	1.12 (0.97–1.30)	1.05 (0.93–1.19)	0.24
Opioids	139 (1.62)	279 (0.99)	44 (5.15)	68 (1.87)	3.44 (2.44–4.85)	1.88 (1.44–2.45)	< 0.0001	**3.42 (2.42–4.83)**	**1.87 (1.44–2.45)**	**< 0.0001**
Cannabinoids	229 (2.67)	160 (0.57)	20 (2.34)	12 (0.33)	1.06 (0.67–1.69)	0.57 (0.32–1.02)	0.16	1.41 (0.89–2.23)	0.72 (0.40–1.29)	0.19
Sedatives	312 (3.64)	395 (1.41)	78 (9.14)	136 (3.74)	2.94 (2.29–3.78)	2.61 (2.15–3.18)	< 0.0001	**2.95 (2.29–3.80)**	**2.65 (2.18–3.22)**	**< 0.0001**
Cocaine	13 (0.15)	6 (0.02)	1 (0.12)	3 (0.08)	–	–		–	–	
Stimulants	73 (0.85)	66 (0.24)	9 (1.05)	8 (0.22)	1.34 (0.67–2.69)	0.93 (0.45–1.93)	0.70	1.54 (0.77–3.10)	1.04 (0.50–2.17)	0.48
Hallucinogens	12 (0.14)	13 (0.05)	1 (0.12)	5 (0.14)	–	–		–	–	
Volatile solvents	2 (0.02)	3 (0.01)	0 (0.00)	0 (0.00)	–	–		–	–	
Multiple drugs[f]	498 (5.81)	405 (1.44)	70 (8.20)	85 (2.34)	1.61 (1.25–2.08)	1.60 (1.27–2.02)	< 0.0001	1.12 (0.97–1.30)	1.05 (0.93–1.19)	**< 0.0001**

[a]TRD patients contribute with person-time in both MDD (before fulfilling all criteria for TRD) and TRD. If numbers are added up, the sum is larger than the total cohort. [b]Adjusted for age, sex, area of residence in Sweden and education level (< 10, 10–12 or > 12 years), history of self-harm/suicide attempts, personality disorders and anxiety disorders. [c]Number/1000 person-years. [d]Defined as occurrence of F10.1–16 and F18–19 ICD codes for SUD, and in the categories of alcohol and opioids also pharmacological treatment (ATC codes N07BB-BC). [e]Any inconsistency between rates and ratio is due to disproportionality over time. [f]ICD-10 F19.0–9: mental and behavioural disorders due to multiple drug use and use of other psychoactive substances.

Table 3 Risk for developing substance use disorders (SUD) among patients with treatment-resistant depression (TRD) compared with patients with major depressive disorder (MDD) not classified with TRD. Patients with previous SUD, time-dependent proportional hazard regression.

	Non TRD[a]		TRD		Crude HR (95% CI)			Adjusted HR (95% CI)[b]		
	≤ 1 year	> 1 year	≤ 1 year	> 1 year	≤ 1 year[e]	> 1 year	P-value Wald χ² test for total effect of TRD	≤ 1 year	> 1 year	P-value Wald χ² test for total effect of TRD
Total N	16 058	8026	1803	1075						
Time under observation, years	10 486	23 521	985	2836						
	n (rate)[c]	n (rate)	n (rate)	n (rate)						
Any SUD[d]	5216 (497.44)	1748 (74.32)	466 (473.19)	249 (87.80)	1.26 (1.15–1.39)	1.16 (1.02–1.33)	< 0.0001	1.23 (1.12–1.35)	1.15 (1.00–1.31)	< 0.0001
Alcohol	3658 (348.86)	1170 (49.74)	300 (304.63)	134 (47.25)	1.17 (1.04–1.32)	0.93 (0.78–1.12)	0.02	1.12 (1.00–1.26)	0.90 (0.75–1.08)	0.09
Opioids	384 (36.62)	97 (4.12)	34 (34.52)	18 (6.35)	1.35 (0.95–1.93)	1.52 (0.92–2.52)	0.06	1.32 (0.93–1.89)	1.50 (0.91–2.48)	0.09
Cannabinoids	203 (19.36)	75 (3.19)	16 (16.25)	7 (2.47)	1.09 (0.66–1.83)	0.76 (0.35–1.65)	0.74	1.34 (0.80–2.25)	0.91 (0.42–1.98)	0.52
Sedatives	210 (20.03)	117 (4.97)	43 (43.66)	30 (10.58)	2.69 (1.93–3.74)	2.11 (1.42–3.16)	< 0.0001	2.41 (1.73–3.36)	1.98 (1.32–2.95)	< 0.0001
Cocaine	10 (0.95)	4 (0.17)	1 (1.02)	2 (0.71)	–	–		–	–	
Stimulants	103 (9.82)	48 (2.04)	8 (8.12)	7 (2.47)	0.97 (0.47–2.00)	1.19 (0.54–2.63)	0.91	1.04 (0.50–2.14)	1.22 (0.55–2.70)	0.88
Hallucinogens	12 (1.14)	4 (0.17)	0 (0.00)	2 (0.71)	–	–		–	–	
Volatile solvents	1 (0.10)	4 (0.17)	0 (0.00)	0 (0.00)	–	–		–	–	
Multiple drugs[f]	635 (60.56)	229 (9.74)	64 (64.99)	49 (17.28)	1.34 (1.04–1.74)	1.74 (1.28–2.37)	0.0002	1.37 (1.06–1.77)	1.86 (1.37–2.54)	< 0.0001

[a]TRD patients contribute with person-time in both MDD (before fulfilling all criteria for TRD) and TRD. If numbers are added up, the sum is larger than the total cohort. [b]Adjusted for age, sex, area of residence in Sweden and education level (<10, 10–12 or >12 years), history of self-harm/suicide attempts, personality disorders and anxiety disorders. [c]Number/1000 person years. [d]Defined as occurrence of F10.1–16 and F18–19 ICD codes for SUD, and in the categories of alcohol and opioids also pharmacological treatment (ATC codes N07BB-BC), [e]Any inconsistency between rates and ratio is due to disproportionality over time. [f]ICD-10 F19.0–9; mental and behavioural disorders due to multiple drug use and use of other psychoactive substances.

in general, although the diagnoses of MDD and SUD have not been specifically validated [28]. Limitations to this study include lack of clinical information on patients, such as severity or characteristics of MDD and SUD, or reasons for adherence to, or discontinuation of, a treatment trial. Also, while the PDR covers all dispensed prescriptions in Sweden regardless of prescriber, the NPR only covers specialized care, which excludes all MDD patients who are only diagnosed in primary care. This may, however, have increased the validity and specificity of the cohort. Psychotherapy as a treatment for MDD was not possible to account for, nor was other treatment for SUD than the drugs included in the study, including psychotherapy/rehabilitation programmes. Although the MDD cohort included a large number of patients, numbers in several drug categories were too small to analyse and power may have been insufficient to detect significant risk differences. Furthermore, only first occurrence of a SUD was counted as the outcome, meaning that patients who subsequently develop other or multiple substance use are not counted as such in this study. Patients with SUD are likely to be more prone to loss of follow-up and therefore not eligible for subsequent classification as TRD, which may have lowered the risk differences in this study [32]. Another clinical factor which may lead to misclassification is that patients who present with SUD often do not receive optimal care, meaning that all treatment attempts required for TRD classification in this study may not initialized [33].

The 13% rate of TRD found in the present study is similar to other studies based on administrative health-care data, where numbers are typically lower than in clinical studies [24,25,34]. The patients in this study who were not classified as TRD were likely to consist of a variety of patients, ranging from MDD patients with a successfully treated depression to severely ill patients who decline treatment or who are lost to follow-up. The whole MDD cohort in this study was diagnosed in specialized care, which means that they are most probably suffering from a relatively complicated MDD, as most uncomplicated depressions would be treated in primary care.

The difference in results between occurrence of SUD < 1 year and > 1 year after treatment start were not substantial in most categories, and should be interpreted considering the method of definition of TRD in this study, i.e. multiple registered treatment trials, meaning health-care contacts for the patients and opportunities for registering SUD diagnosis. This method could lead to detection bias and subsequent inflation of SUD rates among patients eligible for health-care contacts and TRD status. However, as mean time to TRD was 203 days, most treatment trials should have been commenced during the first year, meaning that the period > 1 year should be less prone for detection bias. This is also reflected in the difference of observed rates seen, i.e. the rate of any SUD among patients with TRD ≤ 1 year after treatment start being 50/1000 patient years compared to 17 > 1 year. To put this into context, the mean elapsed time between MDD diagnosis and alcohol SUD diagnosis in similar registers in Denmark is 5 years [35].

Somewhat unexpectedly, alcohol use disorder, the largest SUD category by number of patients, was not associated with TRD in this study. A positive association between MDD and future alcohol use has been demonstrated in a meta-analysis [14], while in a study on similar register data from Denmark, 26% of patients with alcohol use disorder had a previous MDD before SUD [35]. However, a 10-year follow-up of the National Comorbidity Survey (NCS) could not establish a temporal association between MDD at baseline and alcohol abuse [36]. Also, alcohol use disorder may not be related to treatment effect in MDD, which is the exposure in this study.

The two- to threefold risk increase for sedative use disorder seen in this study—even though anxiety disorders were adjusted for—may partly be explained by more prescriptions of benzodiazepines among TRD patients, a use which may later progress into a SUD. This could be supported by the fact that nervous traits in depression is a risk factor for TRD [37]. Conversely, benzodiazepine use has been suggested to increase risk for TRD [38].

There are various theories regarding the comorbidity of SUD following MDD, including substance use as self-medication for depressive symptoms [36] or shared predisposing factors [39]. There is, however, a paucity of studies investigating a temporal association of the efficacy of MDD treatment with the occurrence of SUD. The majority of both clinical and large-scale epidemiological data investigating the association between MDD severity and SUD are cross-sectional [40]. In claims data, both mood disorders diagnoses and antidepressant prescriptions are up to five times more common among patients with diagnoses of opioid use disorders, although the temporal association is unclear [41].

Overall, the findings here indicate that TRD not only may increase risk for SUD but also decreases the chance of remission of pre-existing SUD among MDD patients, at least regarding the categories of sedatives and multiple substance use. Our finding of increased risk for the category of multiple substance use disorder may reflect an addition of substances used. The presence of MDD has been shown to reduce the chance of remission of SUD, with 50% among patients with MDD prior to SUD onset and with 90% among patients with SUD-induced MDD [42]. In a study on in-patients treated for SUD, substance-induced MDD increased the risk of continued use of alcohol, cocaine and heroin four to six times, while independent MDD doubled the risk [43].

The results in this study should be considered in the light of findings not only on the negative consequences of TRD on various social and health outcomes [26,44,45], but also on the detrimental impact of the 'dual diagnosis' of depression and SUD. Patients with MDD and SUD are at higher risk of suicide, social and personal impairment and psychiatric comorbidity compared to other MDD patients [10]. MDD more than doubles the risk of suicide among SUD patients, regardless of whether it occurred before or during the SUD [46]. Adjunctive treatment with benzodiazepines or sedatives may contribute to a risk increase regarding sedative SUD as well as development of TRD, and should generally be used with caution [38]. Considering the novel therapies for TRD now under increased study, such as ketamine or hallucinogens and the potential risk for emerging or relapse of SUD with their use, it could be argued, however, that the impact of an unresolved depression or TRD in itself also increases the risk for SUD among patients with an existing SUD diagnosis, and that novel effective treatments should also be considered for this group of patients.

CONCLUSIONS

TRD patients are at higher risk for SUD compared to other MDD patients, with differences depending on category of SUD and whether or not they have a history of SUD. The effects for the patient and for society of SUD should be considered in the management of MDD patients, encouraging early identification and active treatment of TRD.

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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 Risk for diagnosis or treatment of substance use disorders (SUD) among patients with treatment resistant depression compared to other depressed patients. Patients with and without previous occurrence of a depression diagnosis or an antidepressant (AD) prescription in the registers >180 days before index prescription in the study.