Incidence of, Risk Factors for, and Changes Over Time in Treatment-Resistant Depression in Denmark:
A Register-Based Cohort Study

Frederikke Hordam Gronemann, MSc[a]; Martin B. Jorgensen, DMSc[b]; Merete Nordentoft, DMSc[b,c]; Per K. Andersen, DMSc[d]; and Merete Osler, DMSc[a,e,*]

ABSTRACT

Objective: Varying definitions of treatment-resistant depression (TRD) across studies make it difficult to estimate the size of the problem and to identify patients at increased risk. The aim of this cohort study was to examine the incidence of TRD, disease-related risk factors, and changes over time using different definitions of TRD.

Methods: From 1996 through 2014, all patients with a first-time hospital contact for depression (*ICD-10* codes F32 and F33) were identified in Danish National Patient Registries. A total of 211,689 patients were followed for shifts in antidepressant treatment in the Danish Patient and Prescription Registries. TRD was defined at the second shift in treatment during the first 12 months after diagnosis. The associations of year and type of hospital contact, depression subtype, and severity of TRD were analyzed using Cox proportional hazard regression.

Results: A total of 14.0% of patients experienced a second shift in antidepressant treatment during the first year after admission. When applying 3 other common TRD definitions, the proportion varied from 13% to 31%. Psychiatric inpatients and patients with recurrent or severe depression had the highest incidence of TRD. The incidence of TRD was also slightly higher in patients diagnosed after 2001. All associations were replicated when data were reanalyzed using the alternative definitions of TRD.

Conclusions: About 14% of patients with depression developed TRD during the first year after first hospital contact. The incidence was highest in patients with severe depression and was relatively stable over time. Various definitions of TRD provided different estimates of the frequency of TRD but were all associated with disease severity.

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[a]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals, Frederiksberg, Denmark

[b]Mental Health Centre Copenhagen, Copenhagen, Denmark

[c]Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPsych, Copenhagen and Aarhus, Denmark

[d]Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark

[e]Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark

**Corresponding author:* Merete Osler, DMSc, Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark (Merete.osler@regionh.dk).

Depression is one of the leading causes of years lived with disability worldwide,[1] and resistance to treatment is a common problem in clinical practice.[2–6] It has been estimated that about one-third of patients treated for depression do not respond satisfactorily to at least one adequate treatment.[2,5,7] These patients seem to have poorer prognostic outcomes,[3,7] and treatment resistance appears to pose a substantial economic burden to the health care system.[8,9] Treatment-resistant depression (TRD) has been defined as the absence of remission after treatment for depression,[3] and during the past decade a consensus has emerged that at least 2 failed antidepressant treatments can be considered to be TRD,[10] but this definition is not univocal.[2,3,11] Varying definitions of TRD across studies have contributed to different estimates of TRD, with proportions ranging from 12% to 29%.[9,12] However, these estimates are mainly derived from smaller clinical studies, and a diversity in how patients have been sampled hampers the possibilities of determining risk factors for TRD as well as prognostic outcomes.[13] Together, these factors make it difficult to estimate the size of the problem and to identify patients at risk of TRD, who might be candidates for alternative treatment strategies.[2–5,13] It has also been questioned whether TRD exists or simply reflects that depression consists of several disease entities with different etiology and therefore shows varying responses to standard antidepressant treatment.[4] However, clinical studies that have investigated the association of depression subtype or severity or number of previous episodes with TRD have been inconsistent.[13] Large-scale epidemiologic clinical data are required to determine what the rates are and whether there are differences in relation to setting and disease severity and over time.

The overall aim of this study was to determine the incidence of treatment resistance in patients with single-episode or recurrent depression and explore whether it associates with other disease-related risk factors and changes over time (1996–2014). We also explored if the findings could be replicated when data were reanalyzed using other common definitions of TRD. We hypothesized that at least 25% of all patients would be defined as resistant to first-line treatment and that this estimate would be independent of type of hospital contact, depression subtype, and severity. All Danish citizens have free access to psychiatric treatment, and though there were some changes in the available treatment during the study period, we expected that the frequency of TRD would be stable over time. We also expected that the

Clinical Points

- Varying definitions of treatment-resistant depression (TRD) across studies make it difficult to estimate the size of the problem and to identify patients at increased risk.
- At least 14% of depressed patients were defined as treatment resistant during the year after first hospital contact, and the risk was highest in inpatients with severe or recurrent depression.

aforementioned associations would be replicated using other definitions of TRD.

METHODS

Study Population

All citizens in Denmark with a first-time inpatient or outpatient hospital contact due to depression between January 1, 1996, and December 31, 2014, and no prior diagnosis of other affective disorders were included. In total, 254,250 inpatients or outpatients were identified in the Danish Psychiatric Central Research Registry (DPCR)[14] and the Danish National Patient Registry (DNPR)[15] using the *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes F32.0–F32.9 and F33.0–F33.9. Both registers contain information on date, type of contact, and diagnosis for all in-hospital admissions in Denmark since 1969 (DPCR) and 1977 (DNPR). In 1995, the DPCR became an integrated part of DNPR, and data on outpatient contacts in hospital clinics as well as emergency department contacts were added.[14] A total of 31,292 patients with a comorbid diagnosis of manic episode (*ICD-10*: F30; n = 2,991), bipolar disorder (*ICD-10*: F31; n = 9,375), persistent mood disorder (*ICD-10*: F34; n = 8445), other or unspecified mood (affective) disorders (*ICD-10*: F38 and F39; n = 3,416), or a comorbid schizophrenia spectrum disorder (*ICD-10*: F20; n = 7,065) were excluded from the study. Further, 478 individuals not living in Denmark at the time of first hospital contact, with missing information on birth date or age below 10 years, were excluded. This left 222,480 patients for the analyses. The study was approved by the Danish Data Protection Agency. All data were retrieved from the Danish Health Data Authority and located in Statistics Denmark. Access to data can be obtained after approval by the Danish Data Protection Agency and Statistics Denmark.

Data

Each patient's hospital records were linked to information from the National Prescription Registry and the Danish Civil Registration System using the unique Danish person identification (CPR) number.

Outcome: Treatment-Resistant Depression

TRD was defined a priori based on common treatment guidelines[16–18] and a discussion with the participating psychiatric specialists as more than 2 shifts in first-line treatment, which was among the most restrictive definitions. An alteration of treatment was a shift in either antidepressant medication (from one to another group of chemical substances [see Supplementary Table 1]) or electroconvulsive therapy (ECT). The individual patients' refills of prescriptions for antidepressant medication were identified by the Anatomic Therapeutic Chemical (ATC) classification system codes (N06A) in the Danish National Prescription Registry. This register contains information on all prescribed, redeemed drugs sold at Danish pharmacies.[19] Data on use of ECT were extracted from DNPR, which also holds information on specific treatments provided to patients during hospitalization (Danish Health Classification System [SKS] codes: BRXA1* and BRTB1*).[15] Pharmacologic treatment could have been initiated in primary care before the patients were referred to hospital. To distinguish between prevalent and incident TRD, patients were followed in a pre-index period starting 12 months prior to the date of being diagnosed and followed until 12 months after. Prevalent TRD was defined as having obtained 2 shifts in treatment (medication or ECT) at time of study entry (date of first hospital contact with depression), while incident TRD was defined at the second shift in treatment during follow-up. We also explored the frequency and associations of TRD using 3 of the definitions most commonly reported in the existing literature. Here TRD was defined as (1) as at least 1 failed antidepressant treatment,[3,13,20] (2) as at least 2 failed antidepressant treatments,[8,21–24] or (3) by a register-based treatment pattern algorithm including treatment with a monoamine oxidase inhibitor (MAOI) or ECT or at least 2 failed other antidepressant treatments.[9,12,25] Some patients might shift treatment after only a few weeks due to side effects. In a series of sensitivity analyses, we explored the frequency of shift in antidepressant treatment within 4 weeks of initiating treatment and whether exclusion of such shifts influenced our findings. The same was done for treatment gaps of more than 6 weeks based on volume (defined daily dose dispensed) and number of refills. Further, inpatients might receive their antidepressant medication at the hospital, and this is not recorded in the Danish National Prescription Registry. Consequently, we examined whether length of hospitalization was associated with an unexpected lower rate of TRD.

Covariables

The *ICD-10* codes provided information on depression subtypes (single [F32] or recurrent [F33]) and reflect disease severity.[26] Disease severity was categorized as mild (*ICD-10*: F32.0, F32.8, F32.6, F33.0, F33.4, F33.8, F33.9), moderate (*ICD-10*: F32.1, F33.1), or severe (*ICD-10*: F32.2–F32.3, F33.2–F33.3). If multiple diagnoses were registered, the most severe was chosen. If both an F32 and an F33 diagnosis were registered, F33 was chosen. From DNPR, we also obtained information on whether the patients were diagnosed with depression at a psychiatric or medical ward as an inpatient (full or daytime), outpatient, or emergency contact. Since many of those diagnosed with depression

Table 1. Distribution and Associations of Disease Characteristics in 211,689 Danish Patients With a First-Time Hospital Contact for Depression From 1996 Through 2014

Variable	Patients, n (%)	Incident TRD Cases, No. (%)	Unadjusted HR (95% CI)	Mutually Adjusted HR (95% CI)
Type of depression				
Single episode	156,320 (73.8)	20,600 (13.2)	1 (reference)	1 (reference)
Recurrent	55,369 (26.2)	9,091 (16.4)	1.24 (1.22–1.28)	1.28 (1.25–1.31)
Severity of depression				
Mild	120,093 (56.7)	12,234 (10.2)	1 (reference)	1 (reference)
Moderate	65,441 (30.9)	10,974 (16.8)	1.65 (1.60–1.69)	1.44 (1.40–1.48)
Severe	26,155 (12.4)	6,483 (24.8)	2.58 (2.51–2.67)	2.17 (2.10–2.24)
Type of admission				
Inpatient	108,407 (51.7)	16,181 (14.9)	1 (reference)	1 (reference)
Outpatient	103,282 (48.8)	13,510 (13.1)	0.84 (0.82–0.86)	0.78 (0.76–0.80)
Type of contact				
Psychiatric	138,077 (65.2)	23,241 (16.8)	1 (reference)	1 (reference)
Somatic	73,612 (34.7)	6,450 (8.8)	0.53 (0.52–0.55)	0.64 (0.62–0.66)
Comorbid anxiety				
No	172,619 (81.5)	23,883 (13.8)	1 (reference)	1 (reference)
Yes	39,070 (18.5)	5,808 (14.9)	1.04 (1.01–1.07)	0.88 (0.85–0.91)
Year of diagnosis				
1996–2001	45,233 (21.4)	6,001 (13.3)	1 (reference)	1 (reference)
2002–2007	68,146 (32.2)	10,204 (15.0)	1.14 (1.11–1.18)	1.22 (1.18–1.26)
2008–2014	98,310 (46.4)	13,486 (13.7)	1.05 (1.02–1.09)	1.14 (1.11–1.18)

Abbreviations: CI = confidence interval, HR = hazard ratio.

in an emergency department were admitted as inpatients afterward, we dichotomized this variable as inpatients (full-time, daytime, or emergency department contact) or outpatients seen in hospital clinics. Further, information on comorbid anxiety (*ICD-10*: F41–F43) was included. We extracted the year of diagnosis from the data of first admission for each patient in DNPR. This information was collapsed into 3 periods; 1996–2001, 2002–2007, and 2008–2014. Finally, information on patients' date of birth, sex, vital status, and migration status were obtained from the CPR.

Statistical Analysis

Incidence rates (IRs) of TRD and 95% confidence intervals (CIs) were calculated using time-to-event analysis. Individuals were followed from the date of first registered depression diagnosis until the date of complying with the TRD definition, emigration, death, or end of follow-up (defined as 12 months after study entry), whichever came first. The 12 months of follow-up was chosen as it was expected that treatment resistance would manifest itself within this period and we would avoid treatments initiated due to a new depressive episode. Individuals with prevalent TRD were excluded, as they were not at risk of developing TRD. We examined the association of disease severity, type of depressive episode, and year of diagnosis with incidence of TRD using Cox proportional hazard (hazard ratio [HR] and 95% CI) regression analysis. The proportional hazard assumption was examined graphically, which indicated a slight violation of the assumption for the variable year of diagnosis. However, splitting the model with year of diagnosis as covariable on follow-up time showed only minor differences in the HR for TRD with early (< 6 months) and later (6–12 months) onset. We also completed all analyses for each of the 3 TRD definitions.

RESULTS

Frequency of TRD

Of 222,480 patients included in the study, 62.8% (n = 139,622) were women, and the mean age was 50.4 years (range, 10–110 years) at time of study entry. Overall, 135,200 patients had a prescription filled for antidepressant medication before they were diagnosed with depression at a hospital ward, and 10,791 (8%) of these were defined as having prevalent TRD, which corresponded to 4.9% of the study population. Patients with prevalent TRD were excluded from further analysis, which left 211,689 patients at risk for developing incident TRD. Of these, 31,415 patients (14.8%) initiated no treatment with antidepressants or ECT during the pre-index period or the 12 months of follow-up (Supplementary Table 2). During follow-up, 14.0% (n = 29,691) of the patients developed TRD, and the IR was 163.6 per 1,000 person years (95% CI, 161.8–165.6).

Disease Related Risk Factors

Table 1 shows the distribution of disease characteristics. Patients with recurrent depression had higher incidence of TRD compared to individuals with a single depressive episode (HR = 1.28; 95% CI, 1.25–1.31). Patients with a moderate or severe depression diagnosis also had higher incidence of TRD when compared to patients diagnosed with mild depression. Patients diagnosed with depression at a medical ward had a much lower incidence of TRD compared to patients diagnosed within a psychiatric ward (HR = 0.64; 95% CI, 0.62–0.66). Further, outpatients had lower incidence of TRD than inpatients (daytime or full-time) or those diagnosed at an emergency department contact (HR = 0.78; 95% CI, 0.76–0.80). Patients with comorbid anxiety showed lower risk of TRD (HR = 0.88; 95% CI, 0.85–0.91) when other covariables were included in the model.

Table 2. Frequency (Prevalence and Incidence) of Treatment-Resistant Depression (TRD) at Time of First Diagnosis (Study Entry) in 222,480 Danish Patients Using 3 Other Definitions of TRD

Definition of TRD	Reference Studies	Patients With TRD at Study Entry (Prevalent Cases), n (%)	Patients Who Developed TRD During Follow-Up (Incident Cases), n (%)
At least 1 failed AD treatment	De Carlo et al, 2016,[13] Fekadu et al, 2009,[3] Fava, 2003[20]	44,250 (19.9)	55,041 (30.9)
At least 2 failed AD treatments	Kubitz et al, 2013,[8] Mandelli et al, 2016,[21] Rane et al, 2010,[22] Rizvi et al, 2014,[23] Souery et al, 1999[24]	10,776 (4.8)	28,139 (13.3)
One MAOI or 1 treatment with ECT or at least 2 failed AD treatments	Corey-Lisle et al, 2002,[9] Gibson et al, 2010,[12] Scherrer et al, 2012[25]	11,172 (5.0)	31,174 (14.7)

Abbreviations: AD = antidepressant medication, ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor.

Table 3. Distribution and Associations of Disease Characteristics in Danish Patients With a First-Time Hospital Contact for Depression Between 1996 and 2014 per 3 Definitions of TRD

	At Least 1 Failed AD Treatment		At Least 2 Failed AD Treatments		1 MAOI or 1 ECT Treatment or at Least 2 Failed AD Treatments	
Variable	Incident TRD Cases, No. (%)[a]	Adjusted[b] HR (95% CI)	Incident TRD Cases, No. (%)[c]	Adjusted[b] HR (95% CI)	Incident TRD Cases, No. (%)[d]	Adjusted[b] HR (95% CI)
Type of depression						
Single episode	41,087 (30.5)	1 (reference)	19,472 (12.5)	1 (reference)	21,656 (13.8)	1 (reference)
Recurrent	13,954 (32.2)	1.09 (1.07–1.11)	8,667 (15.7)	1.28 (1.25–1.32)	9,518 (17.2)	1.25 (1.22–1.29)
Severity of depression						
Mild	26,245 (25.6)	1 (reference)	11,900 (9.9)	1 (reference)	12,520 (10.4)	1 (reference)
Moderate	18,478 (35.8)	1. 41 (1.39–1.44)	10,658 (16.3)	1.44 (1.41–1.49)	11,264 (17.2)	1.43 (1.39–1.47)
Severe	9,318 (43.7)	1. 75 (1.70–1.79)	5,581 (21.3)	1.89 (1.83–1.95)	7,390 (28.0)	2.35 (2.29–2.43)
Type of admission						
Inpatient	30,534 (32.9)	1 (reference)	14,907 (13.8)	1 (reference)	17,393 (16.0)	1 (reference)
Outpatient	24,507 (28.7)	0.80 (0.79–0.82)	13,232 (12.8)	0.83 (0.81–0.85)	13,598 (13.4)	0.74 (0.73–0.76)
Type of contact						
Psychiatric	38,752 (33.9)	1 (reference)	21,852 (15.8)	1 (reference)	24,597 (17.8)	1 (reference)
Somatic	16,289 (25.5)	0.87 (0.85–0.89)	6,287 (8.5)	0.65 (0.63–0.68)	6,577 (8.9)	0.63 (0.61–0.65)
Comorbid anxiety						
No	45,167 (30.9)	1 (reference)	22,657(13.1)	1 (reference)	25,044(14.5)	1 (reference)
Yes	9,874 (30.6)	0.86(0.84–0.88)	5,482(14.1)	0.90(0.87–0.93)	6,130(15.7)	0.88(0.85–0.91)
Year of diagnosis						
1996–2001	12,520 (31.7)	1 (reference)	5,951 (13.2)	1 (reference)	6,038 (13.4)	1 (reference)
2002–2007	18,516 (32.2)	1. 07 (1.05–1.10)	9,545 (14.0)	1.14 (1.09–1.17)	10,864 (15.9)	1.29 (1.25–1.33)
2008–2014	24,005 (29.6)	1.00 (0.98–1.02)	12,643 (12.9)	1.06 (1.03–1.10)	14,272 (14.5)	1.21 (1.18–1.25)

[a]Total n = 178,230.
[b]The covariables in the table are mutually adjusted.
[c]Total n = 211,704.
[d]Total n = 211,308.
Abbreviations: AD = antidepressant medication, CI = confidence interval, ECT = electroconvulsive therapy, HR = hazard ratio, MAOI = monoamine oxidase inhibitor.

Year of Diagnosis

The number of patients with a hospital contact for depression increased steadily over time from 6,260 (2.8%) in 1996 to 14,218 (6.4%) in 2014. The incidence of TRD was higher during both the second (HR = 1.22; 95% CI, 1.18–1.26) and the third period (HR = 1.14; 95% CI, 1.11–1.18) (Table 1).

Other Definitions of TRD

When the analyses were repeated using the 3 other common TRD definitions, the corresponding estimates of both prevalent and incident TRD were similar, apart from the estimates for the least restrictive definition of 1 failed treatment, for which the prevalence and incidence of nonresponse were higher (Table 2). Further, the associations between depression diagnosis and TRD were similar (Table 3), whereas the associations between year of diagnosis and TRD differed slightly. Thus, when 1 failed AD treatment was used as the definition of TRD, there was no difference in incidence of TRD over time (Table 3).

Sensitivity Analysis

Overall, 100,126 patients altered their first antidepressant treatment during follow-up. Of these, 20.4% (n = 20,413) did so within 4 weeks after start of treatment. Further, 40,482 patients changed their second treatment, and 19.9% (n = 8,050) did so within 4 weeks after initiation. When antidepressant treatments lasting less than 4 weeks or with insufficient coverage were excluded, the numbers of both prevalent and incident cases of TRD were smaller; however, this exclusion did not influence the aforementioned patterns of association (Supplementary Table 3). Further, long-term inpatients did not have lower TRD rates than those with a hospital stay of only a few days.

DISCUSSION

In this nationwide register-based study of 211,689 patients with a first-time hospital contact for depression in Denmark, we found that 14.0% of patients fulfilled our definition of TRD (IR = 163.6 per 1,000 person years). When we used the other common definitions of TRD, the incidence ranged from 13% to 31%. Further, psychiatric inpatients and patients with recurrent or severe depression had the highest incidence of TRD as compared to the opposed patient groups. The incidence of TRD was slightly lower in patients diagnosed before 2001 than among those diagnosed from 2002 through 2014. Most associations were replicated when data were reanalyzed using the 3 alternative definitions of TRD.

The incidence of TRD was lower than we had expected. Previous studies[8,9,12,23,25,27] have estimated the frequency of TRD between 12% and 29% among patients with depression. The incidence in our study was within but in the lower end of this range of variation, possibly due to the unselected patient sample and a relatively strict TRD definition. Contrary to our study, both Gibson et al[12] and Kubitz et al[8] included only patients with both a depression diagnosis and at least one prescription of antidepressants in their analyses. These patients may represent a subpopulation of depressed patients who are already at greater risk of developing TRD than patients being treated exclusively with psychotherapy or other treatment regimens not reflected when filled antidepressant prescriptions are used as inclusion criteria. Rizvi et al[23] estimated the prevalence of TRD in primary care in Canada at 21.7%. In Denmark, up to 85% of all antidepressants are prescribed by general practitioners, and it could therefore be expected, as shown by the TRD prevalence in the present study, that some patients treated in this sector already had developed TRD. Unfortunately, a Danish Register for General Practice (the Danish Health Service register) and the Danish National Prescription Registry do not contain information on diagnosis. Identifying patients with depression through filled prescriptions for antidepressant medication would lead to misclassification since approximately 50% of all antidepressants are prescribed for purposes other than depression.[28] However, we assumed that patients not responding to first-line antidepressant treatments in the primary sector would, as recommended in the clinical guidelines,[16,17] be referred to the secondary health care sector for further evaluation and hence be included in our study population. As such, it could be expected that including all patients treated for less severe depression would entail a further reduction of the incidence. Another difference between ours and other studies was the inclusion only of patients with a first-time diagnosis of depression independent of disease severity.

Few studies have investigated the association of depression subtype with TRD, and most of these were clinical studies reporting no association.[13] However, a European multicenter study of 702 patients[29] found that the risk of TRD was associated with melancholic but not psychotic features. Similar to our results, a subsequent analysis of data from this multicenter study[30] showed that TRD was associated with disease severity. It has been reported that patients not responding to their first antidepressant treatment might already be at increased risk of developing TRD.[31] However, we also wondered whether treatment resistance exists or is merely a reflection of more severely ill patients, who have not yet been offered the appropriate treatment for their specific disease pattern or who do not respond to the standardized first-line treatment regimens for depression. The substantial symptom variation among patients diagnosed with depression indicates difference in etiology and might explain the difficulties in obtaining treatment effects.[32] It is also likely that patients with severe symptoms are much more motivated to try different treatments compared to their counterparts and, as such, the association of TRD and disease severity becomes a self-fulfilling prophecy when TRD is defined by shifts in treatment.[33] Severe cases could also show psychotic symptoms or suicidality, which might lead to reluctance to treatment. Consequently, it was not surprising that patients diagnosed with depression at medical wards had lower hazard ratios of TRD, since these patients had depression as a secondary diagnosis. Neither was it unexpected that inpatients had higher hazard ratios of TRD than outpatients, since the latter can be regarded as having less severe cases. In contrast to previous studies,[34] we found that comorbid anxiety was associated with a lower risk of TRD after adjustment for other measures of depression severity.

Time trends in TRD rates have not been investigated previously, but our study indicated that the incidence of TRD was slightly higher after 2001. During the study period, the use of antidepressants changed from tricyclic antidepressants to selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, which might be less efficacious.[6,11] Further, the introduction of more antidepressants might have led to more shifts. However, some of the increase might reflect that ECT was insufficiently registered before 2003 in the DNPR.[35]

The primary strength of this study was the use of nationwide population-based registers in a country with free access to health care, which provided us with a large, relatively unselected group of patients. Our study was restricted to patients with a first-time diagnosis based on clinical assessments, which reduces the risk of misclassification of index diagnosis. Thus, although the diagnoses might rely on assessments made by a variety of different clinicians, the information on depression in the DNPR has been shown to have high validity.[36] However, as we based our study on patients with a first-time hospital contact for depression, it might not include the presumed milder cases of depression diagnosed in primary care in Denmark. A further advantage was the CPR number, which allowed us to link individual patient data with other registries and obtain complete follow-up on information for purchase of medicine, migration, and death, which reduces potential selection biases. The data were flexible and made it possible to study

different definitions of TRD. We used common treatment guidelines and switches in first-line antidepressant treatment as primary outcome measures. The registration of purchased medicine and ECT is mandatory and has a high degree of completeness, reducing the risk of underreporting.[18,35] It is, however, a limitation that our TRD measures are based solely on information from registers on shifts in antidepressant treatments, because use of ratings scales would have allowed a more precise assessment of symptom severity and treatment response. Further, we did not have information on reasons for changes in antidepressant treatment or measures of adherence to treatment, and the pharmacologic definitions of TRD do not incorporate psychotherapy, which is an important consideration.[37] Combination and augmentation approaches are typically used when switching antidepressant medications has failed. Consequently, we considered this as the next step for patients defined as treatment resistant in our study and did not include medications such as lithium or quetiapine. Additionally, other factors such as the length of the episode are clinically significant but not captured by our outcome measure.

The use of various definitions of TRD in the literature has been criticized since it makes it difficult to compare findings and pool estimates for meta-analysis to improve knowledge of risk factors and patient outcomes. We chose to apply a definition of TRD reflecting the clinical guidelines and practices in Denmark, adding yet another definition to the pack. Reassuringly, we found nearly the same patterns of associations when we used other definitions of TRD. However, more studies on potential genetic and sociodemographic factors, comorbidities, and treatments that might increase the risk of TRD are needed to produce a better tool to predict patients at risk. Further, studies on short- and long-term consequences of TRD with sufficient adjustment for disease-related risk factors could shed light on the question of whether TRD is just a proxy measure for disease severity.

In conclusion, about 14% of patients with a first-time hospital contact for depression developed TRD during the first year after admission. The risk of TRD was highest in patients with the most severe depression. The rates of TRD have been relatively stable over the last decade—a period with relatively small changes in antidepressant treatment. The various definitions of TRD provided different estimates of the frequency of TRD but were all associated with disease severity.

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Supplementary Material

Article Title: Incidence of, Risk Factors for, and Changes Over Time in Treatment-Resistant Depression in Denmark: A Register-Based Cohort Study

Author(s): Frederikke Hordam Gronemann, MSc; Martin B. Jorgensen, DMSc; Merete Nordentoft, DMSc; Per K. Andersen, DMSc; and Merete Osler, DMSc

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Supplementary Table 1. Overview of dispensed prescribed antidepressants according to their chemical substance as well as number of redeemed Defined Daily Doses ((DDD)[a] per 1000) of antidepressants and ECT procedures within the study population (N=222 480) in three year intervals

	Year					
ATC code (Generic group)	**1996-1998**	**1999-2001**	**2002-2004**	**2005-2007**	**2008-2010**	**2011-2014**
TriCyclic Antidepressants (TCA)						
N06AA02 (Imipramine)	173	182	186	205	220	271
N06AA03 (Imipramin oxide)	3·5	-	-	-	-	-
N06AA04 (Clomipramine)	573	699	732	818	893	1365
N06AA05 (Opipramol)	34	-	-	-	-	-
N06AA06 (Trimipramine)	11·4	10·3	9·3	6·2	3·7	-
N06AA07 (Lofepramine)	120	113	29·1	-	-	-
N06AA09 (Amitriptyline)	1267	1409	1593	1685	1943	2752
N06AA10 (Nortriptyline)	849	1539	2190	3044	4295	6910
N06AA11 (Protriptyline)	0·3	0·05	-	-	-	-
N06AA12 (Doxepin)	228	192	157	121	91	102
N06AA16 (Dosulepin)	201	224	235	218	158	147
N06AA17 (Amoxapine)	141	127	29	-	-	-
N06AA21 (Maprotiline)	99	69	56	49	24	11
Selective Seretonin Reuptake Inhibitors (SSRI)						
N06AB03 (Fluoxetine)	3039	3242	3984	4273	4347	5506
N06AB04 (Citalopram)	9082	15 663	29 087	41 794	54 943	82 549
N06AB05 (Paroxetine)	1928	3814	4736	4432	4072	5271
N06AB06 (Sertraline)	2903	6757	10 223	12 257	17 021	37 783
N06AB08 (Fluvoxamine)	98	110	90	78	75	72
N06AB10 (Escitalopram)	-	-	3347	15 024	25 827	20 268
Monoamine Oxidase Inhibitors (MAOI)						
N06AF01 (Isocarboxazid)	117	88	109	140	141	169
N06AG02 (Moclobemide)	181	125	91	66	64	78
Noradrenaline Reuptake Inhibitors, Serotonin and Noradrenaline Reuptake Inhibitors (SNRI) and Specific serotonergic antidepressants.						
N06AX03 (Mianserin)	680	1178	1529	2007	2206	2594
N06AX06 (Nefadozone)	25	84	35	-	-	-
N06AX11 (Mirtazapine)	821	4625	9276	16 362	28 739	40 280
N06AX12 (Bupropion)	-	71	80	127	100	129
N06AX16 (Venlafaxine)	918	3771	10 634	17 563	23 631	41 291
N06AX18 (Reboxetine)	1·6	162	196	195	194	175
N06AX21 (Duloxetine)	-	-	0·1	2290	5716	8880
N06AX22 (Agomelatine)	-	-	-	-	641	3259
N06AX26 (Vortioxetine)	-	-	-	-	-	24
SKS code (procedure)						
BRTB1* & BRXA1* (Voluntary and involuntary ECT)		0·2	1·3	1·9	2·0	2·4

[a]As defined by WHO's DDD-index, not individual patient treatment regiment

ATC, Anatomical Therapeutic Chemical Classification System; ECT, electro convulsive therapy

Supplementary Table 2 Distribution of treatment switch classes among 211,689 Danish patients with first time hospital contact for depression between 1996 and 2014							
		Second treatment					
First treatment	**Total (first treatment)**	SSRI	*SNRI*	*TCA*	*MAOI*	*ECT*	*No second*
SSRI	124,465(58.8)	15,000 (12.1)	38,080(30.6)	4,715(3.8)	84(0.1)	1,021(0.8)	65,565(52.7)
SNRI	45,702(21.6)	13,627(30.0)	7,786(17.0)	1,974(4.3)	36(0.1)	512(1.1)	21,767(47.6)
TCA	8,957(4.2)	3,053(34.1)	1,789(20.0)	634(7.1)	19(0.2)	70(0.8)	3,392(37.9)
MAOI	291(0.1)	80(27.5)	74(25.4)	25(8.6)	2(0.7)	3(1.0)	107(36.8)
ECT	859(0.4)	246(28.6)	355(41.3)	149(17.3)	1(0.7)	-	108(12.6)
No first	31,415(14.8)						
		Third treatment					
Second treatment	**Total (second Treatment)**	*SSRI*	*SNRI*	*TCA*	*MAOI*	*ECT*	*No third*
SSRI	32,006(15.1)	2,126(6.6)	6,609(20.7)	1,214(3.8)	21 (0.1)	400 (1.3)	21,636(67.6)
SNRI	48,084(22.7)	4,863(10.1)	7,739(16.1)	2,242(4.7)	39(0.1)	726(1.5)	32,475(67.5)
TCA	7,497(3.5)	748(10.0)	1,103(14.7)	422(5.6)	22(0.3)	114(1.5)	5,088(3.5)
MAOI	142(0.1)	21(19.8)	31(21.8)	13(9.2)	1(0.7)	1(0.7)	75(52.8)
ECT	1,606(0.8)	287(17.9)	666(41.5)	282(17.6)	1(0.1)	-	370(23.0)
No second	122,354(57.8)						

Supplementary Table 3 **The association (Hazard Ratios (HR) with 95 % (CI)) of type (single vs. recurrent), severity of depression, type of admission, type of contact and year of diagnosis with incident Treatment-Resistant Depression (TRD) in Danish patients with a first-time hospital contact for depression between 1996 and 2014**

	With antidepressant treatments lasting less than four weeks excluded*		With treatment gabs > 6 weeks excluded**	
	No. of Incident TRD cases *n* (%)	Adjusted* HR with 95 % CI	No. of Incident TRD cases *n* (%)	Adjusted* HR with 95 % CI
All	22,084 (10.3)		20,550 (9.4)	
Type of depression				
Single depressive episode	14,807(9.3)	1	15,595 (9.8)	1
Recurrent depression	7,277 (12.8)	1.40 (1.37-1.45)	4,955 (8.5)	0.88 (0.85-0.91)
Severity of depression				
Mild	8,703 (7.2)	1	7,616(6.14)	1
Moderate	8,207 (12.3)	1.46 (1.42-1.52)	8,142 (11.9)	1.55(1.49-1.60)
Severe	5,174 (19.3)	2.33 (2.25-2.42)	4,792 (18.7)	2.46 (2.32-2.55)
Type of admission				
Inpatient	12,101 (11.0)	1	10,995 (9.9)	1
Out-patient	9,983 (9.5)	0.76 (0.74-0.78)	9,553 (9.0)	0.80 (0.77-0.84)
Type of contact				
Psychiatric	17,630 (12.5)	1	16,977(11.9)	1
Somatic	4,454(6.0)	0.60 (0.58-0.63)	3,573 (4.8)	0.54 (0.52-0.57)
Comorbid anxiety				
No	17,780 (10.1)	1	16,865 (9.5)	1
Yes	4,304 (10.8)	0.85(0.82-0.88)	3,685 (9.1)	0.80(0.77-0.83)
Year of diagnosis				
1996-2001	4,083 (8.9)	1	4,675 (10.1)	1
2002-2007	7,554 (10.9)	1.33 (1.28-1.39)	7,340 (10.5)	1.10 (1.06-1.14)
2008-2014	10,447 (10.4)	1.31 (1.27-1.36)	8,535 (8.4)	0.90 (0.87-0.94)

*222,480-6,949 prevalent TRD=215,531 patients;** 222,480-4,439prevalent TRD=218,141