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Published in:
Journal of Affective Disorders

DOI:
10.1016/j.jad.2021.03.029

Publication date:
2021

Document version
Publisher's PDF, also known as Version of record

Document license:
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Citation for published version (APA):
Gronemann, F. H., Petersen, J., Alulis, S., Jensen, K. J., Jesper, R., Ankarfeldt, M. Z., Solem, E. V. J., Bødker, N., & Osler, M. (2021). Treatment patterns in patients with treatment-resistant depression in Danish patients with major depressive disorder. Journal of Affective Disorders, 287, 204-213. https://doi.org/10.1016/j.jad.2021.03.029
Treatment patterns in patients with treatment-resistant depression in Danish patients with major depressive disorder

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ARTICLE INFO

Keywords:
treatment-resistant
treatment patterns
antidepressants
major depressive disorder

ABSTRACT

Objective: To describe treatment patterns in patients with treatment-resistant depression (TRD) and major depressive disorder (MDD) stratified by depression severity and year of diagnosis. Patterns of treatment were also compared to country-specific guidelines.

Methods: All adults registered first time with a hospital contact due to MDD from 1996 through 2015 were identified and followed for all dispensed prescriptions of antidepressants, antipsychotics, lithium, initiation of electroconvulsive therapy (ECT), and psychotherapy in Danish registers 12 months before and after their hospital MDD diagnosis. TRD was characterized by two shifts in treatment.

Results: We identified 197,615 patients of whom 15% developed TRD. In total, 88% of patients started treatment with antidepressants or ECT. Selective serotonin reuptake inhibitors (SSRIs) were the most frequently used treatment during the study period and more than half (50.7%) of patients changed treatment at least once. Among patients with TRD, serotonon and noradrenaline reuptake inhibitors (SNRIs) were the most frequently used treatment (55.9%), and 37.0% initiated a new treatment the following year. SSRIs and SNRIs were part of most combinations of treatment, regardless of depression severity, year of diagnosis, or presence of TRD.

Conclusion: 15% of patients met the criteria for TRD. Irrespective of patient characteristics and year of diagnosis, SSRIs and SNRIs are the most used treatments for depression, even after patients met the criteria for TRD. We confirm that guidelines for first treatment were followed for most patients diagnosed with MDD in Denmark, but for patients with TRD, choice of treatment was arbitrary.

Introduction

Major depressive disorder (MDD) is one of the leading causes of years lived with disability worldwide (James et al., 2018) and is associated with higher mortality (Cuijpers et al., 2014), including an increased risk of suicide (Hawton et al., 2013), and reduced quality of life (Barge-Schaapveld et al., 1999).

There are different modalities available for treating MDD; and Danish and international guidelines recommend that selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are usually among first choice pharmacotherapeutic agents used to treat adults with MDD (American Psychiatric Association, 2010; Bauer et al., 2019; Danske Regioner, 2016; “NICE. Depression in adults: recognition and management,” 2009). However, it has been estimated that about one-third of patients do not respond satisfactorily to at least one treatment with antidepressants (Bartova et al., 2010).
Studies based on register data from Denmark (Gronemann et al., 2018) and Sweden (Reutors et al., 2018) have estimated the incidence of TRD to be around 15%. This estimate is in line with most studies based on US claims databases (Amos et al., 2018; Corey-Lisle et al., 2002). However, one study estimated the incidence of TRD to be as low as 6% of MDD episodes among patients with MDD (Kubitz et al., 2013).

Despite the increased focus, only a few treatment guidelines offer specific guidance on treatment of patients with TRD, and they are inconsistent and lack clarity (MacQueen et al., 2017). The Danish guideline does not use a specific definition for TRD but it addresses very briefly in one sentence options for treating treatment resistance (Danske Regioner, 2016). The National Institute for Health and Care Excellence (NICE) guidelines and guidelines from the American Psychiatric Association (APA) are usually integrated into the Danish treatment guidelines. The printed guidelines from NICE do not address TRD at all (NICE, 2009) but APA guidelines do address treatment options (American Psychiatric Association, 2010). Further, the World Federation of Societies of Biological Psychiatry (WFSBP) (Bauer et al., 2017) includes a brief section on TRD, but with no specific guidance for treatment. Studies based on electronic healthcare databases have also described real-world prescription patterns of first-line antidepressants for MDD in five European countries (Abbing-Karahogopian et al., 2014), USA (Hassan et al., 2016) and Japan (Furukawa et al., 2013). These indicated that approximately 80% of treatments follow the existing national guidelines for MDD. However, treatment strategies for second-line treatments and patients with TRD in real-world settings are poorly investigated and vary considerably (Hassan et al., 2016). Better knowledge of how antidepressant treatments are combined, as well as patterns of switching, could help to identify reasons for failure to respond and assess the magnitude of the problem. Further, it would contribute to our understanding of TRD to identify if specific treatment patterns characterize patients who become treatment resistant. Finally, knowledge on treatments used for TRD could be used to identify gaps in treatment options.

Aims of the study

The aim of this study was to describe treatment patterns in patients with TRD and MDD stratified by depression severity and year of diagnosis. Observed treatment patterns were also compared to national guidelines for treatment of MDD.

Methods

Study population

In this register-based cohort study, the study population was identified through the Danish National Patient Register (DNPR) (Lynge et al., 2011). All citizens in Denmark aged 18 or above registered first time with an MDD diagnosis at a Danish hospital, either as in- or outpatient, between January 1, 1996 and December 31, 2015 were included. Diagnoses were identified using the International Classification of Diseases, Tenth Revision (ICD-10) codes for single depressive episode (F32.0-F32.9) and recurrent depressive episode (F33.0-F33.9). Patients with a prior hospital contact due to a comorbid diagnosis of bipolar affective disorder, other affective mood disorders, persistent mood disorder, schizophrenia spectrum disorder, or dementia registered in the Danish Psychiatric Central Research Register (DPCRR) (Mors et al., 2011) or DNPR using ICD-10 or ICD-8 codes were not included. The specific ICD codes are found in Supplementary Table S1.

In line with previous studies (Gronemann et al., 2020, 2018), TRD was defined as two shifts in treatment for MDD, which was assessed by patients’ use of antidepressants or electroconvulsive therapy (ECT) 12 months before and after first hospital contact with MDD. A change in treatment was defined as a shift in either antidepressant treatment (from one to another group of chemical substances of N06A, Anatomic Therapeutic Chemical [ATC] level 5) or to electroconvulsive therapy (ECT). An add-on treatment to the existing antidepressant with an antidepressant from a different chemical substance class was also considered a treatment shift. Pharmacological treatment could have been initiated in primary care before the patients were referred to a hospital. To distinguish between prevalent and incident TRD patients, they were followed from 12 months prior the date of being diagnosed at hospital until 12 months after. Patients who met the criteria for TRD before or at the first hospital contact with MDD were not included in the population. In addition, we further constructed a subpopulation consisting only of patients characterized with TRD 12 months after the initial hospital contact for MDD. For a flow chart of the population see Supplementary Figure S1. Each patient’s hospital records were linked to several national registries using the unique Danish person identification number.25

Measures of treatment

Individual patients’ redemption of antidepressant prescriptions was identified by their ATC codes in the Danish National Prescription Registry. This register contains information on all prescribed medicines redeemed at Danish community pharmacies (Wallach Kildemoes et al., 2011). For ECT, data was extracted from the DNPR as specific treatments (procedure codes) provided to patients during hospitalization (Danish Health Classification System [SKS] codes: BRXAI* and BRTBI*). Before 2001 it was not mandatory to register ECT treatment.

Covariables

Patients’ age, sex, migration, and vital status were obtained from the Danish Civil Registration System (CRS) (Schmidt et al., 2014). Data on depression subtype was based on the ICD-10 codes and dichotomized as single depressive episode (F32.0-F32.9) or recurrent depressive episode (F33.0-F33.9). Disease severity was categorized as mild (F32.0, F32.8, F32.9, F33.0, F33.4, F33.8, F33.9), moderate (F32.1, F33.1), or severe (F32.2, F33.3, F33.0, F33.8). Concomitant use was defined as patients redeeming prescriptions of antipsychotics (ATC-code: N05A, except N05AN), lithium (ATC-code: N05AN), or treatment with psychotherapy (SKS-code BRS*-BRSP50*) within the same period of time with treatment of antidepressants or ECT.

Ever-use was defined as having redeemed at least one prescription of either an SSRI, SNRI, tricyclic antidepressants (TCA), monoamine oxidase inhibitor (MAOI), lithium, an antipsychotic agent, or having treatment with ECT assessed within 12 months before and after first hospital contact for MDD. For the TRD subpopulation, ever-use was further assessed within one year after the date of meeting the criteria for TRD. Lastly, the year of MDD diagnosis was examined in four pre-specified periods, 1996-2000, 2001-2005, 2006-2010, and 2011-2015.

Statistical analyses

All analyses were conducted both on the MDD population and the subgroup of patients with TRD. Results were reported as frequency of
patients in absolute numbers and percentages. We identified all combinations of the first three treatment shifts among all patients (first, second, and third treatment). In patients with TRD, we further assessed two subsequent switches after the TRD-defining treatment (fourth and fifth treatment). Because of the substantial amount of combinations of treatment shifts, only the ten most frequent within each population are reported. To identify potential differences in treatment patterns between patients and to evaluate possible time trends, treatment patterns were stratified on depression severity and year of depression diagnosis (2001-2005, 2006-2010, and 2011-2015), respectively. In supplementary analyses, we also explored treatment patterns stratified by age, sex and depression subtype (single versus recurrent depressive episode).

To assess changes during the study period in the risk of initiating treatment with an SSRI, SNRI, TCA, MAOI, ECT, lithium, antipsychotic agents, or psychotherapy, one-year treatment rates were calculated. For estimation of one-year treatment rates in the MDD population, patients were followed from date of first registered MDD contact (index date) until the day of meeting the TRD criteria, being registered with a comorbid diagnosis listed in Supplementary Table S1, emigration, death, or end of follow-up (12 months after index date), whichever came first. The TRD population was followed from the date of TRD (index date) until the end of follow-up (12 months after index date) or censoring due to being registered with a comorbid diagnosis listed in Supplementary Table S1, emigration, or death, whichever came first. Further, initial drug classes after meeting the TRD criteria were estimated. Cumulative incidences of newly initiated treatments listed in Supplementary Table S2 were calculated, considering the competing risk of death from time of MDD onwards. The analyses were performed in STATA 15.1, SAS 9.4 and R using the package SunburstR.

### Results

A total of 197,615 patients with an MDD diagnosis were included in the MDD population. Within the first year after MDD diagnosis, 29,212 patients met the criteria for TRD (Table 1, Supplementary Figure 1). In both populations, the majority were women (MDD: 62%; TRD: 64.5%) and the mean age of the patients was 51.2 and 51.4, respectively (Table 1). During the study period, the number of patients diagnosed with MDD and TRD increased, and in both groups most patients were diagnosed with mild depression. Most patients with MDD or TRD had been treated with an SSRI and an SNRI within the study period. The proportions of patients having been treated with TCA, ECT, antipsychotic agents, lithium, or psychotherapy were higher within patients with TRD.

**Figure 1** illustrates the treatment patterns of patients according to the antidepressant drug class redeemed and treatment with ECT. Overall, 69.5% of MDD patients initiated their first treatment with an SSRI, out of which 30.7% of patients did not switch to any other antidepressant treatment during the study period (Figure 1a, Table 2). A further 25.1% of patients started their first treatment with an SNRI, out of which 10.8% did not switch to any other antidepressant treatment during the study period. As such, SSRIs and SNRIs were the most commonly prescribed antidepressants, administered in different orders. Only 4.8% of the patients initiated treatment with TCA, out of which 1.6% of patients did not switch to any other antidepressant treatment during the study period (Table 2) shifts. Further, 12.3% of the patients with MDD (n=24,376) never initiated any treatment with either an antidepressant or ECT during the assessment period 12 months before and after first hospital contact for MDD. This was the third most frequently occurring treatment pattern overall. All in all, 49.3% of patients did not shift to a second treatment during the assessment period. Table 2 further shows that these treatment patterns were not associated with depression severity or year of depression diagnosis (Figure 2, Table 2). The treatment patterns only differed marginally across age, sex and depression subtype (Single versus recurrent depressive episode) (Supplementary Table S3).

Prior to being diagnosed with TRD, patients most commonly initiated their first treatment for MDD with an SSRI, then switching to an SNRI, with their third treatment being an SNRI of another chemical substance (24.0%) (Figure 1b, Table 2). The ten most prescribed treatment patterns in patients developing TRD predominantly consisted of combinations of SSRIs and SNRIs as first, second, and third administered treatment (Table 2). When grouped by depression severity, patients with severe depression shifted to treatment with TCA or ECT slightly more often as their second or third treatment option. Figure 1b further shows that SNRIs were most commonly the TRD-defining treatment (55.9%), with SSRI being second (25.6%). Of the 29,212 patients with TRD, 63.0% did not initiate a fourth treatment with antidepressants or ECT within one year after meeting the TRD criteria. As displayed in Table 2 and Figure 1c, the remaining 37% of patients with TRD that initiated a fourth or fifth treatment most commonly shifted to another SNRI (52.2%). Supplementary Table S4 shows that concomitant use of antipsychotic agents was common in all treatment lines with quetiapine being used most often. Use of concomitant lithium increased with increasing number of treatment lines, while the pattern of use of psychotherapy was less clear.

**Figure 3** presents the one-year treatment rates during the study period. Only minor changes occurred, with a slight increase in the prescription rates of SSRIs the first few years of the study period and a slight decrease in SNRI prescriptions for MDD patients (Figure 3, left). Treatment rates increased to a minor degree for ECT, while the rates of lithium were stable. The treatment rates of antipsychotics agents increased from 0.8 in 2000 to 1.2 in 2014 and for psychotherapy from 0.2 to 1.3 during the study period. In patients with TRD, the prescription rate of all drug classes seemed rather stable (Figure 3, right). The treatment rates of ECT, antipsychotics, and psychotherapy increased to a minor degree.

In Supplementary Table S5, we show the sequence of initial treatment after meeting the criteria for TRD. TRD patients most commonly initiated treatment with SNRI after complying with the TRD criteria from 2000 through 2006. From 2007 onwards, antipsychotics were the

| Severity of depression | MDD | TRD |
|-------------------------|-----|-----|
| Mild                    | 112,385 (56.9) | 11,784 (40.3) |
| Moderate                | 61,112 (30.9)  | 11,133 (38.1)  |
| Severe                  | 24,118 (12.2)  | 6,295 (21.6)   |

### Table 1

Demographic and clinical characteristics of all patients with first-time diagnosis of major depressive disorder and patients meeting the criteria for treatment-resistant depression (TRD)

| Characteristics | All patients with MDD (n=197,615) | Patients with TRD (n=29,212) |
|-----------------|-----------------------------------|------------------------------|
| Age, mean (quartiles) | 51.2 (32.9-69.8) | 51.4 (36.2-66.8) |
| Sex              |                                    |                              |
| Male             | 75,178 (38.0) | 10,366 (35.5) |
| Female           | 122,437 (62.0) | 18,846 (64.5) |
| Type of depression |                                |                              |
| Single episode   | 141,967 (71.8) | 19,949 (68.3) |
| Recurrent episode| 55,648 (28.2) | 9,263 (31.7) |

### Table 2

In Supplementary Table S5, we show the sequence of initial treatment after meeting the criteria for TRD. TRD patients most commonly initiated treatment with SNRI after complying with the TRD criteria from 2000 through 2006. From 2007 onwards, antipsychotics were the
most commonly initiated treatment. Psychotherapy was only fifth in ranking of initiated treatments in 2000, however, it increased over time to the third most commonly initiated treatment after meeting the TRD criteria. The cumulative incidence plot in Supplementary Figure S2a shows the proportion of patients initiating new treatment within one year after MDD diagnosis. Almost 50% of the patients initiated treatment with SSRIs or SNRIs, while almost 30% redeemed a new prescription for antipsychotic agents. Among TRD patients, 20% of individuals initiated an SNRI and 15% initiated treatment with an antipsychotic agent within one year of TRD defining date.

Figure 1. Sunburst plot of treatment patterns in patients with MDD and TRD one year before MDD diagnosis to one year after, respectively. Each ring represents a new modality of treatment initiated. For patients with MDD and patients with TRD – before, the innermost ring symbolizes the first treatment line and the outermost ring the third treatment – the TRD-defining treatment. For patients with TRD – after, the innermost ring symbolizes the third treatment line, the TRD-defining treatment with the fifth treatment line being the outermost ring.
Table 2
The most common combinations of treatment with SSRI, SNRI, TCA, MAOI, and ECT in Danish patients diagnosed with MDD during 1996 through 2015, ranked by frequency

| Patients with MDD (N=197,615) | 2nd treatment | 3rd treatment* | All rank | Mild rank | Moderate rank | Severe rank | 2001-2005 rank | 2006-2010 rank | 2011-2015 rank |
|--------------------------------|---------------|---------------|----------|-----------|--------------|------------|---------------|---------------|---------------|
| SSRI . . | 1 (30.7%) | 1 (34.4%) | 1 (28.1%) | 1 (19.8%) | 1 (32.3%) | 1 (30.6%) | 1 (28.1%) |
| SSRI SNRI . | 2 (13.8%) | 3 (12.5%) | 2 (16.0%) | 2 (14.4%) | 2 (14.0%) | 2 (15.0%) | 2 (13.4%) |
| . . . | 3 (12.3%) | 4 (14.5%) | 4 (9.8%) | 4 (8.6%) | 3 (11.2%) | 4 (10.5%) | 2 (13.9%) |
| SNRI . . | 4 (10.8%) | 4 (11.4%) | 4 (10.2%) | 3 (9.6%) | 4 (10.3%) | 3 (10.6%) | 3 (13.7%) |
| SSRI SNRI . | 5 (13.8%) | 6 (13.8%) | 5 (14.4%) | 5 (14.0%) | 5 (14.0%) | 5 (14.0%) | 5 (14.0%) |
| . . . | 6 (12.3%) | 7 (14.5%) | 7 (13.1%) | 6 (12.6%) | 7 (13.1%) | 6 (12.6%) | 7 (13.1%) |
| SNRI SNRI . | 7 (12.3%) | 7 (12.3%) | 8 (2.3%) | 8 (2.3%) | 8 (2.3%) | 8 (2.3%) | 8 (2.3%) |
| SSRI SNRI SNRI | 8 (2.7%) | 10 (2.3%) | 9 (2.3%) | 9 (2.3%) | 9 (2.3%) | 9 (2.3%) | 9 (2.3%) |
| . . . | 11 (1.6%) | 12 (1.6%) | 10 (2.1%) | 10 (2.1%) | 10 (2.1%) | 10 (2.1%) | 10 (2.1%) |

Subpopulation of patients with TRD (N=29,212)

| 1st treatment | 2nd treatment | 3rd treatment* | All rank | Mild rank | Moderate rank | Severe rank | 2001-2005 rank | 2006-2010 rank | 2011-2015 rank |
|---------------|---------------|---------------|----------|-----------|--------------|------------|---------------|---------------|---------------|
| SSRI . . | 1 (24.0%) | 1 (24.0%) | 1 (25.1%) | 1 (24.0%) | 1 (25.1%) | 1 (26.6%) | 1 (26.6%) |
| SSRI SNRI . | 2 (12.1%) | 2 (13.0%) | 2 (12.4%) | 2 (12.4%) | 2 (12.4%) | 2 (12.4%) | 2 (12.4%) |
| . . . | 3 (10.9%) | 3 (11.9%) | 3 (12.2%) | 3 (12.2%) | 3 (12.2%) | 3 (12.2%) | 3 (12.2%) |
| SNRI SNRI . | 4 (7.1%) | 4 (7.0%) | 4 (7.0%) | 4 (7.0%) | 4 (7.0%) | 4 (7.0%) | 4 (7.0%) |
| SSRI SNRI . | 5 (5.8%) | 5 (5.6%) | 5 (5.6%) | 5 (5.6%) | 5 (5.6%) | 5 (5.6%) | 5 (5.6%) |
| SNRI SNRI . | 6 (3.7%) | 6 (3.6%) | 6 (3.6%) | 6 (3.6%) | 6 (3.6%) | 6 (3.6%) | 6 (3.6%) |
| SNRI SNRI . | 7 (3.2%) | 7 (3.3%) | 7 (3.3%) | 7 (3.3%) | 7 (3.3%) | 7 (3.3%) | 7 (3.3%) |
| SNRI SNRI . | 8 (2.7%) | 13 (1.7%) | 10 (2.3%) | 10 (2.3%) | 10 (2.3%) | 10 (2.3%) | 10 (2.3%) |
| TCA . . | 9 (2.7%) | 9 (2.7%) | 9 (2.7%) | 9 (2.7%) | 9 (2.7%) | 9 (2.7%) | 9 (2.7%) |
| SSRI SNRI . | 10 (2.5%) | 10 (2.4%) | 10 (2.4%) | 10 (2.4%) | 10 (2.4%) | 10 (2.4%) | 10 (2.4%) |
| . . . | 11 (2.5%) | 11 (2.5%) | 8 (2.6%) | 8 (2.6%) | 8 (2.6%) | 8 (2.6%) | 8 (2.6%) |
| SSRI SNRI . | 12 (1.8%) | 12 (1.8%) | 9 (2.4%) | 9 (2.4%) | 9 (2.4%) | 9 (2.4%) | 9 (2.4%) |

Subpopulation of patients with TRD (N=29,212)

| 3rd treatment | 4th treatment | 5th treatment* | All rank | Mild rank | Moderate rank | Severe rank | 2001-2005 rank | 2006-2010 rank | 2011-2015 rank |
|---------------|---------------|---------------|----------|-----------|--------------|------------|---------------|---------------|---------------|
| SNRI . . | 1 (42.1%) | 1 (43.8%) | 1 (43.4%) | 1 (36.4%) | 1 (42.2%) | 1 (41.4%) | 1 (44.3%) |
| SSRI . . | 2 (18.9%) | 2 (22.4%) | 2 (18.5%) | 3 (13.1%) | 2 (20.4%) | 2 (19.9%) | 2 (16.3%) |
| . . . | 3 (10.9%) | 3 (9.3%) | 3 (10.4%) | 3 (8.7%) | 3 (9.6%) | 3 (11.7%) | 3 (9.7%) |
| SNRI . . | 4 (5.3%) | 4 (4.9%) | 4 (5.6%) | 4 (5.5%) | 4 (5.1%) | 4 (5.7%) | 4 (5.8%) |
| SSRI . . | 5 (3.6%) | 5 (3.8%) | 5 (3.5%) | 7 (3.2%) | 5 (3.6%) | 5 (3.4%) | 5 (3.2%) |
| SNRI . . | 6 (2.5%) | 6 (2.8%) | 6 (2.5%) | 9 (2.1%) | 6 (3.0%) | 6 (2.5%) | 6 (2.5%) |
| SNRI . . | 7 (2.5%) | 7 (2.0%) | 7 (2.5%) | 5 (3.6%) | 7 (2.2%) | 7 (2.5%) | 6 (2.9%) |
| ECT . . | 8 (1.5%) | 9 (0.8%) | 8 (1.2%) | 6 (3.2%) | 8 (1.8%) | 8 (2.0%) | 8 (1.4%) |
| TCA . . | 9 (1.1%) | 8 (1.0%) | 9 (1.0%) | 11 (1.4%) | 12 (0.8%) | 10 (1.0%) | 9 (1.3%) |
| ECT . . | 10 (0.9%) | 10 (1.0%) | 10 (1.0%) | 10 (1.0%) | 10 (1.0%) | 10 (1.0%) | 10 (1.0%) |
| SSRI . . | 11 (0.8%) | 11 (0.8%) | 11 (0.8%) | 11 (0.8%) | 11 (0.8%) | 11 (0.8%) | 11 (0.8%) |
| TCA . . | 12 (0.8%) | 12 (0.8%) | 12 (0.8%) | 12 (0.8%) | 12 (0.8%) | 12 (0.8%) | 12 (0.8%) |
| ECT . . | 14 (0.6%) | 14 (0.6%) | 14 (0.6%) | 14 (0.6%) | 14 (0.6%) | 14 (0.6%) | 14 (0.6%) |

*TRD-defining treatment
Abbreviations: MDD: major depressive disorder; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and noradrenaline reuptake inhibitors; TCA: tricyclic antidepressants; MAOI: monoamine oxidase inhibitor; ECT: electroconvulsive therapy; TRD: treatment-resistant depression
Discussion

In this study, we examined treatment patterns in a cohort of 197,615 patients diagnosed with MDD at Danish hospitals between 1996 and 2015. We found that most patients with MDD initiated treatment with an SSRI during the assessment period and those that switched treatment most often shifted to another SSRI or an SNRI. SNRIs were most often the TRD-defining treatment and 37% of patients with TRD shifted to a fourth treatment or more. Treatment patterns were not dependent on depression severity nor year of diagnosis, except for increasing rates of

(Supplementary Figure S2b).

Figure 2. Sunburst plot of treatment patterns by depression severity (mild, moderate, severe) in patients with MDD and TRD one year before MDD diagnosis to one year after, respectively. Each ring represents a new modality of treatment initiated. For patients with MDD and patients with TRD – before, the innermost ring symbolizes the first treatment line and the outermost ring the third treatment – the TRD-defining treatment. For patients with TRD – after, the innermost ring symbolizes the third treatment line – the TRD defining treatment with the fifth treatment line being the outermost ring.
antipsychotics and psychotherapy over the study period.

Our study also showed that existing guidelines (American Psychiatric Association, 2010; Danske Regioner, 2016; “NICE. Depression in adults: recognition and management,” 2009) for first-line treatment seem to be followed for most MDD patients, with SSRIs being the most frequently used first-choice drug during the whole study period. However, currently there is limited guidance for treatment of patients with TRD (MacQueen et al., 2017). The Danish guideline describes that MAOI might be indicated in patients with TRD and that lithium is considered first choice in treatment resistant patients to prevent development of bipolar disease (Danske Regioner, 2016). APA also consider MAOI to be exclusively reserved for TRD and describes transcranial magnetic stimulation, vagus nerve stimulation and ECT as potential treatment of TRD (American Psychiatric Association, 2010). The two latter treatments options were not offered during follow-up of this study. Our study shows that most patients either do not initiate any further treatment with antidepressants or ECT (63.0%) or mainly shift between SNRI and SSRI within one year after meeting the criteria for TRD. As such, no systematic pattern in choice of treatment modalities was evident. This possibly reflects that treatments become more individualized when patients do not benefit from standard treatment. However, our findings could also reflect that no specific guidance is offered for TRD in the Danish guidelines, which may lead to individualized treatment based on the subjective preferences of the psychiatrist or patient that may or may not always be evidence-based treatment choices. Recent studies (Adli et al., 2017; Bauer et al., 2019) have shown that algorithm-guided treatment of MDD may lead to better outcomes than treatment as usual, which underlines the need for both treatment-specific guidelines and the importance of adhering to these.

The lack of systematic pattern in choice of treatment modalities could also be explained by off-label drug use by psychiatrists, e.g. antiepileptics not covered by our analyses. Lastly, though not included in our definition of TRD, augmentation and psychotherapy are also part of treating MDD. Patients not progressing from third treatment might have initiated augmentation or psychotherapy alongside antidepressant treatment before starting a new antidepressant treatment shift. In line with this, our findings suggest that approximately 15% of patients meeting the TRD criteria initiate treatment with antipsychotic agents within one year after TRD diagnosis. Correspondingly, results from a clinical cross-sectional European multicenter study investigating pharmacological treatment strategies in 1,181 MDD patients showed that 24.2% of patients were prescribed at least one antipsychotic drug in addition to ongoing antidepressant medication (Dold et al., 2016). Atypical antipsychotic augmentation is an established approach in the pharmacotherapy of TRD and might have been used to target residual symptoms such as sleeping disturbances or minimize side-effects, and they have increasingly been used since the introduction of quetiapine to Denmark in the early 2000s. The main reasons for the fluctuations in the use of psychotherapy is because its registration was not complete in the registers during the first study period. Further, information on the use of private psychotherapists is not available in the registers.

It is noteworthy, that only minor differences in treatment patterns were observed when grouping patients according to the severity of their depression, as we would have expected that patients with severe depression had other modalities of treatment, e.g. TCA, MAOI, or ECT as recommended in existing treatment guidelines (American Psychiatric Association, 2010; Bauer et al., 2017; Danske Regioner, 2016; “NICE. Depression in adults: recognition and management,” 2009). Actually, 8.6% of the patients with severe depression included in our cohort never initiated any of the included treatments during one year prior to one year after MDD diagnosis. This might be explained by low registration of ECT during the first part of the study period and missing information on drug administration during hospitalization. On the other hand, one would expect that patients would continue treatment after discharge and have redeemed prescriptions from the community pharmacy, thus be registered in the National Prescription Registry. Further, we only considered the lack of information on drugs administered during hospitalization to be a minor problem since previous analyses did not reflect these concerns (Gronemann et al., 2018).

With regard to first-line treatment, our study is in accordance with previous studies from five European countries including Denmark, Germany, the Netherlands, Spain, and the UK (Abbing-Karahagopian et al., 2014), showing that SSRIs are the most commonly prescribed antidepressants. Few studies have examined treatment patterns following first-line treatment. A study from a primary care database in the UK following 262,844 patients who initiated antidepressant treatment between 2005 and 2011 (Mars et al., 2017) found that most patients with MDD initiated treatment with an SSRI (87%) and that 9% of patients switched to another antidepressant, prevalently another SSRI. A Japanese study following 1,592 MDD patients identified in a health insurance claims database found that 17% of patients with a first-time treatment switched to another antidepressant after an average of 3 months (Furukawa et al., 2013). The proportion of patients switching antidepressant treatment in these studies (Furukawa et al., 2013; Mars et al., 2017) is much lower than in the present study, in which more than 50% of MDD patients switched from a first to a second treatment. These differences could be due to our cohort representing a population with a hospital contact with MDD, whereas the UK and Japanese cohorts were from the general population. Our study analyzed patients with a first-time hospital contact for depression and therefore might not have included the presumed milder cases of depression, as they are only treated in primary care in Denmark. Findings from the clinical cross-sectional European multicenter study by Dold et al. (2016) yielded a slightly higher proportion, 29% of patients received at least one adjunctive antidepressant in addition to their first line therapy (Dold et al., 2016). Here patients were recruited in both in- and outpatient
One US-based study characterized differences in treatment patterns between TRD and non-TRD episodes in MDD patients (Kubitz et al., 2013). In this study, 82,742 MDD patients were identified in the US PharMetrics Integrated Database. 52% of MDD episodes were not treated with pharmacotherapy and 6% were defined with TRD (two distinct failed treatments). SSRIs were the most frequently used drug class for both TRD and non-TRD episodes, comprising more than 60% of the treatments. Usage of all other drug classes, such as SNRI, TCA, atypical antidepressants (buspirone), and concomitant antipsychotics was more prevalent for TRD than for non-TRD episodes. Surprisingly, ECT did not seem to be included in the analyses. Also, there was a large proportion of non-treated patients in this study, which can indicate that the cohort included many milder cases of depression, which is not very representative of our cohort. Finally, 12.3% of patients did not initiate treatment with either antidepressants or ECT. However, they could have initiated psychotherapy or other treatment options. Further, 3,177 patients died, and 29 patients emigrated within 30 days after MDD diagnosis leading to no registration of redemption of antidepressants within Danish registers.

There are some strengths and limitations to our study that must be taken into consideration when interpreting the results. An advantage was the use of population-based registers in a country with a tax-based national health care system, which minimizes the risk of selection bias. Further, the registers contain documentation of diagnoses that are based on clinical assessments, which, in turn, reduces the risk of misclassification of the population. Additionally, the unique personal identification number that all Danish citizens are assigned allowed us to link individual patient data with other registries to obtain complete follow-up information for the purchase of medicine, hospital treatments, migration, and death. Thus, the registers ensure a complete follow-up, reduce the potential for selection bias, and increases the validity of this study.

A limitation applicable to many studies using treatment algorithms to identify disease is whether the applied method captures all patients intended. In our study some of the shortcomings are the lack of information on why patients changed antidepressant treatment (e.g. lack of efficacy, adverse events, or patient’s choice) and there were no measures of treatment adherence. However, in sensitivity analyses, we explored the effect of treatments lasting less than 4 weeks (and possible alterations due to side effects) and treatment gaps of more than 6 weeks (based on dose and number of refills) and their influence on associations of depression-related covariates with TRD. These analyses showed that this was not the case (Gronemann et al., 2018). It has also been shown that more restrictive definitions of TRD result in slightly lower proportions of patients with TRD, but overall it does not change the pattern of associations with risk factors and outcomes (Gagnon et al., 2020).

Another limitation of our definition of TRD is that we did not incorporate augmentation approaches. However, the Danish treatment guidelines first recommend antipsychotic or lithium augmentation as a 4th option after 3 failed antidepressants so it should not affect the TRD definition per se. Thus, it is expected to have limited impact on the definition of treatment resistant depression. Although prescriptions were redeemed and paid for, we cannot be certain that the patients ingested the medicines. However, because the Danish National Prescription Register holds information on redeemed prescriptions, we do know that the patient purchased the drugs and hence the medication can be considered one step closer to ingestion than in studies investigating data on prescriptions only. Furthermore, information on drug administration for hospitalized patients was not available; and use of ECT, as well as of psychotherapy, was not fully registered before 2001 (Hundrup et al., 2017). Moreover, our study was based on patients with a first-time hospital contact with depression and therefore the treatment patterns might not be similar in the presumed milder cases of depression mainly treated in primary care in Denmark. Consequently, though we included patients at their first-time hospital contact, it might not reflect the first time the patient presented with depression since milder episodes of depression in the patient could have been treated at the general practitioner. The validity of depression severity in the DNPR has been shown to be low for milder cases (Gock et al., 2009) and we cannot exclude that misclassification has made it difficult to detect small differences in treatment. In this study, patients were sampled at first hospital contact with depression. This may lead to a higher mean age at first depression diagnosis than in studies using prescription data only. Using prescription data only, however, comes with some limitations since indication for antidepressant use was not available in the Danish National Prescription Register during the study period. Hence, using this approach we would not have been able to distinguish whether antidepressants were prescribed for other conditions than depression. Finally, the project was ended in 2016 and did not include newer antidepressant treatments introduced, such as esketamine.

In conclusion, we find that 15% of patients with a hospital contact with MDD meet the TRD criteria. Irrespective of depression severity or TRD, SSRIs, and SNRIs are the most commonly used antidepressant treatments for depression in Denmark, administered in different order. Our findings confirm that the guidelines for first treatment of MDD seem to be followed for most patients, whereas treatment of patients meeting the TRD criteria is arbitrary, possibly due to lack of specific guidelines.

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Funding
This study was financed by Janssen Cilag A/S.

Author Contribution
All listed authors contributed to the design and planning of this study. Collection of and access to data was obtained by FHG and MO. Data management and data analyses were performed by FHG with support from MO and JP. FHG drafted the article. All co-authors contributed to data interpretation, critical revision of the manuscript, and final approval of the manuscript.

Declaration of Competing Interest
SA, JR, NB are employed by Janssen Cilag A/S, which holds the license to antidepressant medicine. Janssen.

Acknowledgements
This study was financed by Janssen Cilag A/S.

Supplementary materials
Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.jad.2021.03.029.

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