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# Real-world characteristics of European patients receiving SNRIs as first-line treatment for major depressive disorder

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ABSTRACT

*Background:* Serotonin-norepinephrine reuptake inhibitors (SNRIs) are among the most frequently prescribed antidepressants (ADs) for major depressive disorder (MDD), with an increasing trend in the last decade. Given the relative dearth of information regarding rationales for their preferred use as first-line ADs in the broad clinical routine, the present study systematically investigated real-world characteristics of MDD patients prescribed either SNRIs or other AD substances across different countries and treatment settings.

*Methods:* In the present secondary analyses based on a large European, multi-site, naturalistic and cross-sectional investigation with a retrospective assessment of treatment outcome, we firstly defined the proportion of MDD patients receiving SNRIs as first-line AD psychopharmacotherapy and secondly compared their sociodemographic and clinical characteristics to those patients prescribed alternative first-line ADs during their current major depressive episode (MDE).

*Results:* Within the total sample of 1410 MDD patients, 336 (23.8 %) received first-line SNRIs. Compared to other ADs, SNRIs were significantly associated with inpatient care, suicidality and treatment resistance during the current MDE, and a longer lifetime duration of psychiatric hospitalizations. Moreover, greater severity of depressive symptoms at study entry, higher daily doses of the administered ADs, as well as more frequent prescriptions of psychopharmacotherapeutic add-on strategies in general and antipsychotic augmentation in particular, were significantly related to first-line SNRIs.

*Conclusions:* Considering the limitations of a cross-sectional and retrospective study design, our data point towards a preferred use of first-line SNRIs in a generally more severely ill MDD patients, although they did not lead to superior treatment outcomes compared to alternative ADs.

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## 1. Introduction

Venlafaxine, duloxetine and milnacipran are serotonin-norepinephrine reuptake inhibitors (SNRIs) that are often referred to as dual antidepressants (ADs) since their common mechanism of action involves elevation of the monoamines serotonin and noradrenaline in the synaptic cleft by selectively inhibiting their reuptake (Dell'Osso et al., 2011). A previous pharmaco-epidemiological study conducted in twelve European countries found out that, depending on the geographical region, SNRIs were administered in 6–25 % of patients with major depressive disorder (MDD). Based on this and further international evidence, SNRIs are ranked as the most commonly prescribed ADs after selective serotonin reuptake inhibitors (SSRIs) (Bauer et al., 2008; Dold et al., 2016a, 2016b; Bauer et al., 2017; Dold and Kasper, 2017; Fugger et al., 2022a, 2022b).

In terms of efficacy, international literature reported an advantageous role of SNRIs in the treatment of severe depression (Dell'Osso et al., 2011; Bradley and Lenox-Smith, 2013) and of additional melancholic features (Dold et al., 2021). Hereby, the amelioration of social functioning by enhancing patients' energy and consecutively their motivation (Eriksson, 2000; Bradley and Lenox-Smith, 2013) or the potency to combat comorbid anxiety (Baldwin, 2006; Bradley and Lenox-Smith, 2013) have been considered important aspects that are thought to be targeted by substances exerting effects in and beyond the serotonergic system more accurately (Dold et al., 2021; Fugger et al., 2022a, 2022b). It might be noteworthy in this context that earlier meta-analyses confirmed superior overall AD efficacy of SNRIs as compared to SSRIs, which was particularly evident for venlafaxine and duloxetine but not milnacipran (Machado and Einarson, 2010; Bradley and Lenox-Smith, 2013). Despite statistical significance of the latter findings, the clinical relevance has been questioned (Machado and Einarson, 2010). In a more recent, large network meta-analysis venlafaxine ranked among the most efficacious of the 21 studied AD compounds (Cipriani et al., 2018). However, venlafaxine and duloxetine were concurrently associated with the highest drop-out rates (Cipriani et al., 2018). Adequately powered randomized-controlled trials (RCTs) focussing on specific MDD symptoms as outcome measures would be of utmost interest but have not yet been executed.

Despite the broad use of SNRIs in real-world settings (Luo et al., 2020; Seifert et al., 2021), little is known about the rationale and implications guiding clinicians in the prescriptions of these particular ADs. Psychopharmacotherapeutic prescription patterns in general have already been shown to depend on heterogeneous pharmacological- and socio-economic factors as well as patient- and physician-related aspects (Dold et al., 2016a, 2016b; Dold et al., 2017; Dold and Kasper, 2017; Winkler et al., 2019; Bartova et al., 2021). While biological determinants guiding the choice of a specific AD in terms of precision medicine are still to come (Bartova et al., 2015), existing clinical evidence, which has for example linked SNRI prescriptions to female physicians (Bauer et al., 2008), remains scarce. Hence, the present study aimed to reveal the still unacquainted facets related to the use of SNRIs as first-line AD treatment in a large, naturalistic, international sample of MDD patients with heterogeneous clinical manifestations and different treatment settings. Hereby, sociodemographic and clinical features, that can be promptly and easily evaluated in the broad clinical routine (Serretti, 2018; Bartova et al., 2019), were systematically investigated in that respect.

## 2. Materials and methods

### 2.1. Study design

The present work represents a secondary analysis of an international, multicenter, observational, cross-sectional and non-interventional study with a retrospective evaluation of treatment outcome that was performed by the European Group for the Study of Resistant Depression (GSRD) (Bartova et al., 2019). These *post-hoc* analyses refer to the project "Clinical and biological correlates of resistant depression and related phenotypes" that was conducted between 2011 and 2016 in ten research centers located in Vienna, Brussels, Toulouse, Elencourt, Halle, Athens, Tel Hashomer, Siena, Bologna/Milan, and Geneve. Local ethics committees of the abovementioned research centers approved the study design and all study procedures that were introduced comprehensively in our previous reports (Bartova et al., 2019).

### 2.2. Patient sample

The recruitment of adult, male and female in- and outpatients was performed in both university and non-academic clinical routine centers of the aforementioned research sites in Austria, Belgium, France, Germany, Greece, Israel, Italy and Switzerland. Patients who were eligible to study participation signed written informed consent after a thorough explanation of the study procedures.

Present single or recurrent major depressive episodes (MDEs) occurring in the course of MDD, which was diagnosed based on the DSM-IV-TR (Wittchen et al., 1997) as the primary psychiatric diagnosis, was mandatory for study enrollment. Ongoing and adequate psychopharmacotherapy comprising a first-line AD agent that was administered in sufficient daily doses for at least four weeks during the current MDE represented a further inclusion criterion (Bartova et al., 2019). Any primary psychiatric diagnosis other than MDD, the presence of severe personality disorders, as well as comorbid substance (with exception of caffeine and nicotine) use disorders present in the previous six months represented exclusion criteria. Other psychiatric- as well as somatic comorbidities and the presence of additional features occurring during the current MDE, such as psychotic symptoms, melancholia, and/or suicidality were allowed in the course of the naturalistic character of the present study (Bartova et al., 2019).

### 2.3. Clinical evaluation

Socio-demographic and clinical patterns of MDD patients were evaluated in the course of a comprehensive clinical assessment by exclusively experienced psychiatrists with academic/university as well as non-academic background who underwent specific rater trainings to assure a high standard of inter-rater reliability. Hereby, medical records of the patients were considered, and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was employed to establish the primary psychiatric diagnosis and the presence of potential psychiatric comorbidities as well as additional features occurring during the current MDE. Furthermore, the presence of potential somatic comorbidities and all treatment strategies that were employed during the current MDE were rigorously evaluated. Hereby, daily doses of the first-line AD agents administered during the current MDE were calculated as fluoxetine dose equivalents according to (Hayasaka et al., 2015). The severity of depressive symptoms at study initiation was measured using the 21-item Hamilton Rating Scale for Depression (HAM—D) (Hamilton, 1960) and the Montgomery and Åsberg Depression Rating Scale (MADRS; current MADRS, cMADRS) (Montgomery and Asberg, 1979). The severity of depressive symptoms at the onset of the current MDE (i.e., at the beginning of the first-line AD treatment initiated minimally four weeks before study enrollment) was assessed employing the retrospective MADRS (rMADRS) scores that were calculated according to the MDD patients' assertions together with clinical data derived from the medical records of the patients.

Based on the GSRD staging model for treatment outcome, the MADRS total score change (rMADRS – cMADRS) was gathered after at least one adequate AD trial administered at sufficient daily dosages for at least four weeks (Bartova et al., 2019). Treatment response was characterized by a MADRS total score of $<22$ and a $\geq 50$ % reduction of the MADRS total score after an adequate AD trial. Non-response was defined as a total score of $\geq 22$ at the MADRS and a $<50$ % MADRS total

score reduction after one AD trial of adequate daily dosing and duration. The so-called treatment resistant depression (TRD) was diagnosed in case of a non-response to two or more consecutive AD trials of adequate daily dosing and duration (Bartova et al., 2019).

The presence of the current suicidal risk, as well as its extent, were assessed based on the HAM-D item 3 focusing exclusively on suicidality (Kasper et al., 2010; Dold et al., 2018). In accordance with our previous reports, the item-score 1 characterized low levels of the current suicidal risk, while the item-scores 2–4 represented moderate to high degree of the current suicidal risk (Dold et al., 2018).

### 2.4. Statistical procedure

All eligible MDD patients derived from a subject pool of the GSRD (Bartova et al., 2019) were subdivided into two groups based on whether they underwent first-line AD psychopharmacotherapy with SNRIs or other AD agents during the current MDE. The related socio-demographic and clinical patterns of the whole sample, as well as the two patient groups are reported using means and standard deviation (SD) for continuous variables and percentages for categorical variables (Table 1). Differences between both patient groups were analyzed using chi-squared tests for categorical variables and analyses of covariance (ANCOVAs) for continuous variables with the respective AD first-line treatment as fixed effect and recruitment center as covariate (Table 1). Hereby, we corrected for multiple comparisons according to the method of Bonferroni, whereby the alpha level was set at alpha = 0.001, as a total of 50 variables were tested (alpha = 0.05/50 = 0.001). In case of statistical significance, binary logistic regression analyses with the relevant independent variables were conducted to analyze their relation to the employed first-line AD treatment with SNRIs as dichotomous dependent variable, whereby the recruitment center served as covariate (Supplementary Table). The present analyses were performed employing the version 27 of IBM SPSS Statistics.

## 3. Results

The total sample of the analyzed GSRD patients included 1410 subjects (Bartova et al., 2019) who were treated with either SNRIs (N = 336, 23.8 %) or with other AD substances (N = 1074, 76.2 %) as their first-line AD psychopharmacotherapy during their current MDE (Fugger et al., 2022a, 2022b). In detail, other ADs comprised SSRIs, n = 734, (52.0 %); Noradrenaline and Specific Serotonergic Antidepressants (NaSSAs), n = 121, (8.6%); Tricyclic Antidepressants (TCAs), n=74 (5.2%); Norepinephrine Dopamine Reuptake Inhibitors (NDRIs), n = 32 (2.3 %); Agomelatine, n = 69 (4,9 %); Serotonin Antagonist/Reuptake Inhibitors (SARIs), n = 28 (2.0 %), Noradrenaline Reuptake Inhibitors (NARIs), n = 3 (0.2 %); Monoamine Oxidase Inhibitors (MAO-Is), n = 5 (0.4 %); Vortioxetin, n = 6 (0.4 %), Tianeptin, n = 2 (0.1 %). With respect to the individual SNRIs, venlafaxine was administered in 63.7 % of the patients (n = 214) and followed by duloxetine in 30.7 % (n = 103) and milnacipran in 5.7 % (n = 19; Fig. 1). The mean daily dosage of venlafaxine was 190 mg, of duloxetine 83 mg and of milnacipran 126 mg. All significant socio-demographic and clinical differences between MDD patients receiving first-line SNRIs and those with other ADs that withstood the correction for multiple comparisons in our initial analyses (Table 1) and that remained robust in our *post-hoc* analyses (Supplementary Table) are summarized hereinafter.

MDD patients prescribed SNRIs as their first-line AD psychopharmacotherapy were more frequently treated as inpatients during the current MDE (43.2 % vs 31.9 %, p < .001) and spent generally more weeks in psychiatric inpatient-care during lifetime (mean 9.5 ± 35.0 vs 4.4 ± 12.9, p < .001) in relation to their counterparts receiving first-line AD agents other than SNRIs. Furthermore, patients prescribed first-line SNRIs experienced current suicidal risk more commonly than MDD patients with alternative first-line ADs (56.3 % vs 42.8 %, p < .001; Fig. 2), and showed higher severity of depressive symptoms measured with the MADRS at study entry (mean cMADRS total score 26.7 ± 10.5 vs 23.9 ± 11.5, p < .001), lower response rates (16.7 % vs 27.0 %) and experienced higher rates of TRD (45.5 % vs 39.0 %, p < .001; Fig. 3). In terms of the administered treatment strategies, a higher mean number of psychopharmacotherapeutics was detected in MDD patients with first-line SNRIs (2.4 ± 1.3 vs 2.1 ± 1.2, p < .001). In detail, they received augmentation and/or combination treatments in general (68.5 % vs 58.2 %, p < .001), and augmentation with at least one antipsychotic (AP) agent in particular (34.2 % vs 23.0 %, p < .001), more frequently as compared to their counterparts. In analogy, higher mean daily doses of the administered first-line AD agents were identified in patients treated with first-line SNRIs (51.5 ± 23.3 vs 37.5 ± 19.4, p < .001).

## 4. Discussion

In our naturalistic sample of 1410 patients with MDD as primary diagnosis, SNRIs were administered as first-line AD agents in almost one quarter of the cases. According to a systematic review comparing guidelines for the psychopharmacotherapy of MDD (Gabriel et al., 2020), only the Canadian CANMAT clinical practice guidelines (Kennedy et al., 2016) actually recommended a representative of SNRIs, namely milnacipran, for this indication. SNRI treatment in our investigation was significantly associated with a longer lifetime duration of psychiatric hospitalizations and higher severity of depressive symptoms at study entry reflected by the cMADRS total score. The current MDEs of patients with first-line SNRIs were characterized by the presence of suicidal risk, employment of higher daily doses of the administered ADs, and further add-on psychopharmacotherapeutic strategies in general and AP augmentation in particular, inpatient care, and treatment resistance.

The relatively high administration rate of first-line SNRIs in our sample (i.e., 23.8 %) coincides with previous reports from international pharmaco-epidemiological studies that pictured a steady increase in patients prescribed SNRIs throughout the last decades (Luo et al., 2020; Seifert et al., 2021). Indeed, the number of patients taking SNRIs increased from 17 % in the year 2001 to about 30 % in 2017 in German speaking European countries (Seifert et al., 2021), and from 3 % in 1996 to 16 % in 2015 in the United States (Luo et al., 2020). It is noteworthy in this context that the present results revealed a consistent relation of first-line SNRI psychopharmacotherapy to a rather worse socio-demographic status and more severe clinical profile. This also represents the most solid and clinically most relevant finding of our study that was evidenced by higher rates of TRD and the necessity of more complex treatment regimens including psychopharmacotherapeutic optimization strategies and psychiatric inpatient care in patients with primary SNRIs. Furthermore, the observed greater severity of depressive symptoms, the presence of suicidal risk, with a trend towards higher suicidality levels during the current MDEs, that were also trend-wise longer and accompanied by comorbid diabetes and unemployment, support the latter assumption.

Since the aforementioned patterns were repeatedly related to disease severity and chronicity and were further attributed to the so-called difficult-to-treat depression (McAllister-Williams et al., 2020), we assume that generally unfavorable disease and treatment outcome characteristics may have encouraged European clinicians to choose SNRIs over other AD substances. This might be supported by existing international evidence reporting advantageous effects of AD substances with dual reuptake of serotonin and noradrenaline over AD agents targeting the serotonergic system exclusively, which were evident especially in the case of additional melancholic features, suicidality, distinct psychiatric and somatic comorbidities, as well as higher severity of depressive symptoms in general (Montgomery et al., 2007; Dell'Osso et al., 2011; Bradley and Lenox-Smith, 2013; Bauer et al., 2017; Fugger et al., 2019; Bandelow et al., 2022; Fugger et al., 2022a, 2022b). Looking at the specific clinical constellations in detail, some authors claimed that, in patients with melancholia, agents acting via the noradrenergic pathway

**Table 1**
Socio-demographic and clinical patterns of the GSRD patients (Bartova et al., 2019) with primary MDD receiving first-line AD treatment with SNRIs.

| MDD patients' characteristics | Total Sample (n = 1410) | SNRIs as first-line AD treatment (n = 336) | Other first-line AD treatment* (n = 1074) | $x^2$/F | p-value ($x^2$/ ANCOVA) |
|---|---|---|---|---|---|
| Sex, n (%) | | | | | |
| Female | 943 (66.9) | 239 (71.1) | 704 (65.5) | 3.600 | 0.058 |
| Male | 467 (33.1) | 97 (28.9) | 370 (34.5) | | |
| Age, mean (SD), years (n = 1404) | 50.3 (14.1) | 50.7 (13.0) | 50.2 (14.5) | 3.364 | 0.546 |
| Bodyweight, mean (SD), kilograms (n = 1387) | 73.2 (16.8) | 73.1 (14.4) | 73.3 (17.5) | 0.034 | 0.854 |
| Ethnicity, n (%) | | | | | |
| Caucasian origin | 1356 (96.2) | 321 (95.5) | 1035 (96.4) | 0.482 | 0.487 |
| Education, n (%) (n = 1395) | | | | | |
| University education/non-university high education/high level general education | 755 (54.1) | 163 (49.5) | 592 (55.5) | 3.634 | 0.057 |
| General secondary/technical education/elementary school/none | 640 (45.9) | 166 (50.5) | 474 (44.5) | | |
| Occupation, n (%) (n = 1408) | | | | | |
| Employed | 659 (46.8) | 136 (40.6) | 523 (48.7) | 6.802 | 0.009 |
| Unemployed | 749 (53.2) | 199 (59.4) | 550 (51.3) | | |
| Relationship, n (%) | | | | | |
| Ongoing relationship | 703 (49.9) | 158 (47.0) | 545 (50.7) | 1.418 | 0.234 |
| No ongoing relationship | 707 (50.1) | 178 (53.0) | 529 (49.3) | | |
| Disease course, n (%) | | | | | |
| Single MDE | 127 (9.0) | 34 (10.1) | 93 (8.7) | 0.665 | 0.415 |
| Recurrent MDD | 1283 (91.0) | 302 (89.9) | 981 (91.3) | | |
| Additional features during the current MDE, n (%) | | | | | |
| Psychotic features | 154 (10.9) | 42 (12.5) | 112 (10.4) | 1.129 | 0.288 |
| Melancholic features | 856 (60.7) | 207 (61.6) | 649 (60.4) | 0.149 | 0.699 |
| Atypical features | 33 (2.3) | 9 (2.7) | 24 (2.2) | 0.221 | 0.639 |
| Catatonic features | 7 (0.5) | 3 (0.9) | 4 (0.4) | 1.403 | 0.236 |
| Suicidality[a] | | | | | |
| Current suicidal risk (dichotomous) | 649 (46.0) | 189 (56.3) | 460 (42.8) | 18.553 | **<0.001** |
| High/moderate level of suicidality | 377 (58.1) | 123 (65.1) | 254 (55.2) | 5.352 | 0.021 |
| Low level of suicidality | 272 (41.9) | 66 (34.9) | 206 (44.8) | | |
| Treatment setting, n (%) | | | | | |
| Inpatient | 488 (34.6) | 145 (43.2) | 343 (31.9) | 14.231 | **<0.001** |
| Outpatient | 922 (65.4) | 191 (56.8) | 731 (68.1) | | |
| Duration of the current MDE, mean (SD), days (n = 1114) | 204.7 (164.6) | 221.8 (190.4) | 199.1 (154.9) | 3.943 | 0.047 |
| Number of MDEs during lifetime, mean (SD) (n = 1044) | 3.3 (2.5) | 3.5 (2.3) | 3.3 (2.5) | 0.938 | 0.333 |
| Age of disease onset, mean (SD), years (n = 1329) | 37.2 (15.4) | 36.6 (14.5) | 37.4 (15.7) | 0.767 | 0.381 |
| Duration of psychiatric hospitalizations during lifetime, mean (SD), weeks (n = 1328) | 5.6 (20.5) | 9.5 (35.0) | 4.4 (12.9) | 14.455 | **<0.001** |
| Psychiatric comorbidities, n (%) | | | | | |
| Any anxiety disorder | 294 (20.9) | 71 (21.1) | 223 (20.8) | 0.021 | 0.885 |
| Generalized anxiety disorder | 151 (10.7) | 37 (11.0) | 114 (10.6) | 0.042 | 0.837 |
| Panic disorder | 114 (8.1) | 28 (8.3) | 86 (8.0) | 0.037 | 0.848 |
| Agoraphobia | 113 (8.0) | 34 (10.1) | 79 (7.4) | 2.651 | 0.103 |
| Social phobia | 45 (3.2) | 13 (3.9) | 32 (3.0) | 0.655 | 0.418 |
| Obsessive-compulsive disorder (n = 1397) | 22 (1.6) | 5 (1.5) | 17 (1.6) | 0.012 | 0.914 |
| Posttraumatic stress disorder | 20 (1.4) | 7 (2.1) | 13 (1.2) | 1.395 | 0.238 |
| Somatic comorbidities, n (%) | | | | | |
| Any somatic comorbidity | 653 (46.3) | 163 (48.5) | 490 (45.6) | 0.859 | 0.354 |
| Hypertension | 267 (18.9) | 64 (19.0) | 203 (18.9) | 0.004 | 0.952 |
| Thyroid dysfunction | 204 (14.5) | 52 (15.5) | 152 (14.2) | 0.362 | 0.547 |
| Migraine | 156 (11.1) | 39 (11.6) | 117 (10.9) | 0.132 | 0.716 |
| Diabetes | 84 (6.0) | 30 (8.9) | 54 (5.0) | 6.950 | 0.008 |
| Heart disease | 72 (5.1) | 18 (5.4) | 54 (5.0) | 0.057 | 0.811 |
| Arthritis | 65 (4.6) | 16 (4.8) | 49 (4.6) | 0.023 | 0.879 |
| Asthma | 48 (3.4) | 9 (2.7) | 39 (3.6) | 0.706 | 0.401 |
| Pain | 8 (0.6) | 1 (0.3) | 7 (0.7) | 0.569 | 0.451 |
| Severity of depressive symptoms, mean (SD) | | | | | |
| HAM-D total 21-item at study entry (n = 1407) | 19.8 (9.1) | 20.5 (8.8) | 19.6 (9.1) | 2.694 | 0.101 |
| MADRS total at study entry (cMADRS) (n = 1409) | 24.6 (11.3) | 26.7 (10.5) | 23.9 (11.5) | 16.389 | **<0.001** |
| MADRS total at onset of the current MDE (rMADRS) (n = 1395) | 34.1 (7.7) | 34.9 (7.7) | 33.8 (7.7) | 4.953 | 0.026 |
| Treatment outcome, n (%)[b] | | | | | |
| Response | 346 (24.5) | 56 (16.7) | 290 (27.0) | 14.891 | **<0.001** |
| Non-response | 492 (34.9) | 127 (37.8) | 365 (34.0) | | |
| Resistance | 572 (40.6) | 153 (45.5) | 419 (39.0) | | |
| MADRS total score change (rMADRS - cMADRS), mean (SD) (n = 1394) | −9.4 (10.8) | −8.0 (10.0) | −9.8 (11.0) | 7.206 | 0.007 |
| Ongoing additional psychotherapy, n (%) (n = 1279) | 399 (31.2) | 88 (30.3) | 311 (31.4) | 0.127 | 0.722 |
| Ongoing psychopharmacotherapy | | | | | |
| Number of concurrently administered psychopharmacotherapeutics, mean (SD) | 2.2 (1.2) | 2.4 (1.3) | 2.1 (1.2) | 15.748 | **<0.001** |
| Daily doses of the first-line AD treatment given in fluoxetine equivalents[c], mean (SD), mg/day (n = 1247) | 39.9 (20.8) | 51.5 (23.3) | 37.5 (19.4) | 87.943 | **<0.001** |
| Employed psychopharmacotherapeutic combination and augmentation strategies (in addition to the ongoing AD treatment), n (%) | | | | | |
| Any combination and augmentation treatment | 855 (60.6) | 230 (68.5) | 625 (58.2) | 11.285 | **<0.001** |

(*continued on next page*)

**Table 1** (*continued*)

| MDD patients' characteristics | Total Sample (n = 1410) | SNRIs as first-line AD treatment (n = 336) | Other first-line AD treatment* (n = 1074) | $x^2$/F | p-value ($x^2$/ ANCOVA) |
|---|---|---|---|---|---|
| Combination with at least 1 additional AD | 416 (29.5) | 115 (34.2) | 301 (28.0) | 4.730 | 0.030 |
| Augmentation with at least 1 AP | 362 (25.7) | 115 (34.2) | 247 (23.0) | 16.908 | **<0.001** |
| Augmentation with at least 1 MS | 159 (11.3) | 42 (12.5) | 117 (10.9) | 0.660 | 0.417 |
| Augmentation with pregabalin | 102 (7.2) | 28 (8.3) | 74 (6.9) | 0.794 | 0.373 |
| Augmentation with at least 1 low-potency AP[d] | 91 (6.5) | 34 (10.1) | 57 (5.3) | 9.815 | 0.002 |
| Augmentation with benzodiazepines including zolpidem and zopiclone | 466 (33.0) | 124 (36.9) | 342 (31.8) | 2.963 | 0.085 |

The p-values displayed in bold were significant after Bonferroni correction for multiple comparisons. *Selective Serotonin Reuptake Inhibitors (SSRIs), n = 734; Noradrenaline and Specific Serotonergic Antidepressants (NaSSAs), n = 121; Tricyclic Antidepressants (TCAs), n = 74; Norepinephrine Dopamine Reuptake Inhibitors (NDRIs), n = 32; Agomelatine, n = 69; Serotonin Antagonist/Reuptake Inhibitors (SARIs), n = 28, Noradrenaline Reuptake Inhibitor (NARIs), n = 3; Monoamine Oxidase Inhibitors (MAO-Is), n = 5; Vortioxetin, n = 6, Tianeptin, n = 2.

Abbreviations (alphabetical order): ADs = antidepressants; ANCOVA = analysis of covariance; APs = antipsychotics; GSRD = The European Group for the Study of Resistant Depression; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale (cMADRS = current MADRS; rMADRS = retrospective MADRS); MDD = major depressive disorder; MDE = major depressive episode; MS = mood stabilizer; n = number of participants; SD = standard deviation; SNRIs = serotonin-norepinephrine reuptake inhibitors.

[a] The presence of the current suicidal risk was measured based on the HAM-D item 3 (suicidality) ratings, whereby item-score 1 (feels life is not worth living) reflected low- and item-scores 2 (wishes to be dead or any thoughts of possible death to self), 3 (suicide ideas or gestures) and 4 (suicide attempts) moderate to high levels of suicidality (Dold et al., 2018).

[b] Non-response was defined by a previous single failed AD trial and resistance by two or more failed AD trials (Bartova et al., 2019).

[c] Fluoxetine dose equivalents were calculated according to Hayasaka and colleagues (Hayasaka et al., 2015; Bartova et al., 2019).

[d] Low-potency APs comprise the so-called low-potency first-generation APs and the second-generation AP quetiapine <100 mg/day (Bartova et al., 2019).

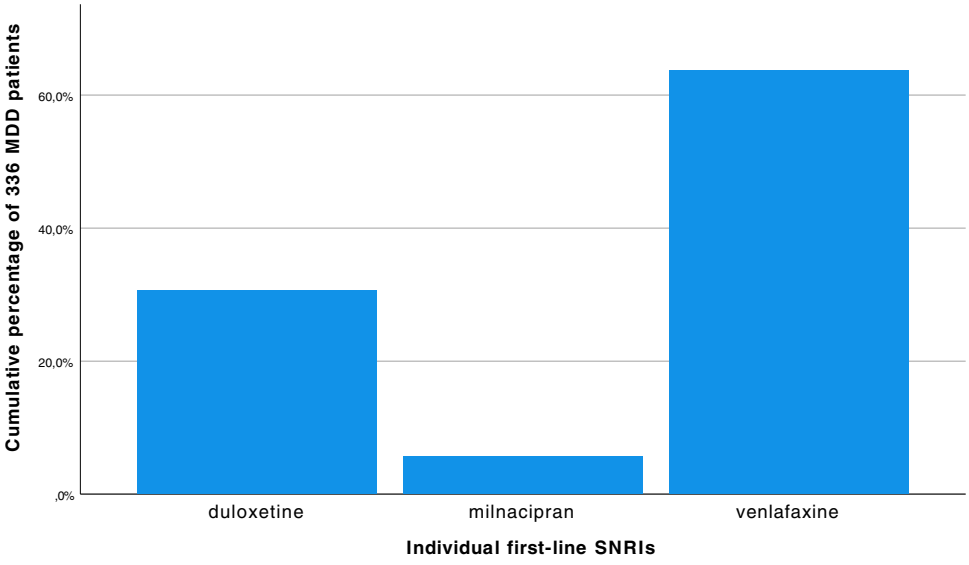


**Fig. 1.** Individual substances administered in 336 MDD patients treated with SNRIs as their first-line AD treatment.
Displayed cumulative percentages refer to the individual SNRIs administered as first-line AD treatment in 336 MDD patients. The mean dosage of venlafaxine was 190 mg, of duloxetine 83 mg and of milnacipran 126 mg. Abbreviations: AD = antidepressant; MDD = major depressive disorder; SNRIs = serotonin-norepinephrine reuptake inhibitors.

may exert superior effects by their potency to reduce psychomotor retardation more efficiently than other AD classes as SSRIs for instance (Eriksson, 2000; Brunello et al., 2002). These observations are, however, in contrast with results of a recent meta-analytic evidence based on 25 trials that found no difference in response rates of various ADs between MDD patients with and without melancholia (Undurraga et al., 2020). The latter finding together with the lacking association between the presence of additional melancholic features and the first-line AD treatment with SNRIs in our data, tend to question whether this clinical phenomenon should be regarded as a relevant indicator for the choice of SNRIs as first-line AD treatment for this indication.

With respect to co-occurring diseases, it might appear surprising that no significant between-group differences were found regarding psychiatric comorbidities, especially when the known beneficial effects of SNRIs in anxiety disorders are considered (Bandelow et al., 2015; Bandelow et al., 2022a, 2022b). On the other hand, the fact that the efficacy of SNRIs in anxiety syndromes was shown to be comparable with SSRIs (Bandelow et al., 2022), which represent the recommended first-line psychopharmacotherapy for both, MDD and anxiety disorders (Bauer et al., 2017; Bandelow et al., 2022; Bartova et al., 2023) and which were administered in the majority of our MDD patients (Fugger et al., 2022a, 2022b), puts the latter assumption into perspective. However, the detected trend towards higher prescription rates of first-line SNRIs in MDD patients with comorbid diabetes corresponds with international evidence and current therapeutic guidelines recommending especially duloxetine for the treatment of MDD and comorbid diabetic polyneuropathy (Bauer et al., 2017).

When the severity of depressive symptoms is considered, there is previous evidence for an advantageous role and efficacy of SNRIs, especially duloxetine and venlafaxine (Dell'Osso et al., 2011; Bradley and Lenox-Smith, 2013), and for higher response rates achieved with SNRIs in general compared to SSRIs, albeit with high numbers needed to treat (Papakostas et al., 2007). While higher severity of depressive symptoms was associated with first-line AD treatment with SNRIs in our analyses, we did not observe better outcomes in this patient population. Correspondingly, a recent network meta-analysis did not confirm the superior role of SNRIs regarding efficacy in the context of multiple agents with different modes of action beyond serotonin-reuptake, even

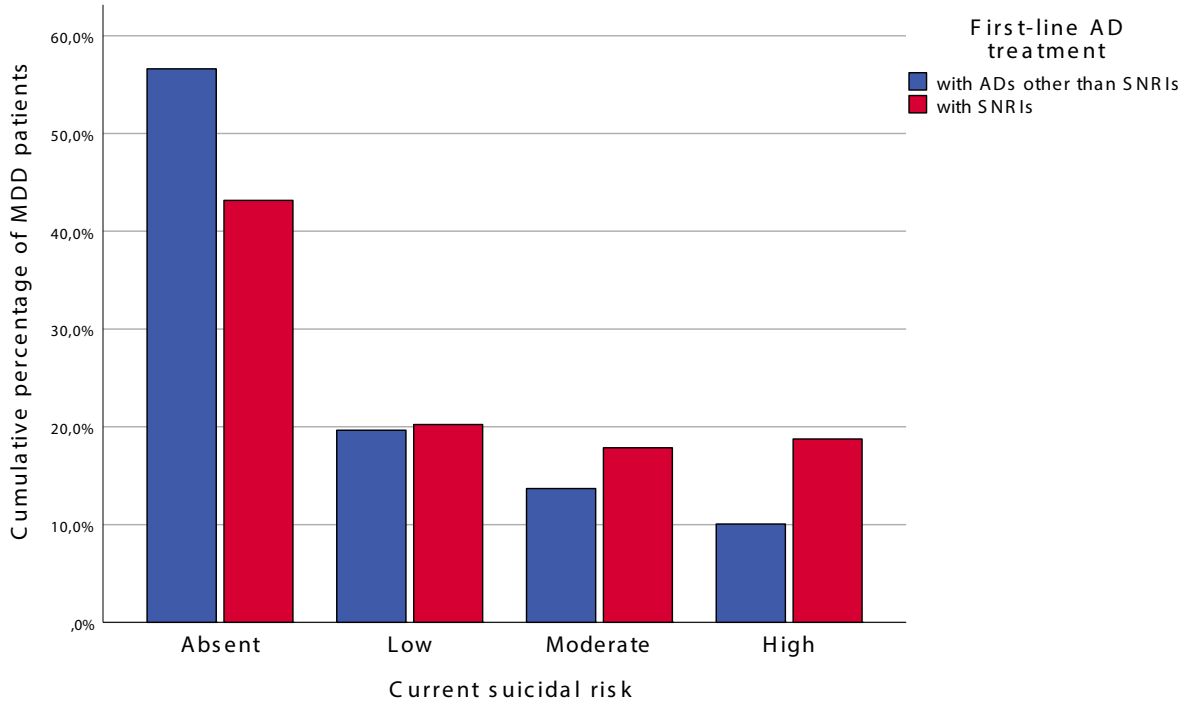


**Fig. 2.** The current suicidal risk of MDD patients receiving either SNRIs or other substances as their first-line AD treatment.
Displayed cumulative percentages refer to the proportion of MDD patients receiving either SNRIs ($n$ = 336; red colored) or alternative substances (n = 1074; blue colored) as their first-line AD treatment itemized according to the current suicidal risk that was assessed based on the HAM-D item 3 focusing exclusively on suicidality (Dold et al., 2018). While the absence of the current suicidal risk was reflected by the item-score 0 (absent), its presence was represented by item-score 1 (feels life is not worth living) reflecting low- and item-scores 2 (wishes to be dead or any thoughts of possible death to self), 3 (suicide ideas or gestures) and 4 (suicide attempts) portraying moderate to high levels of suicidality (Dold et al., 2018).
Abbreviations: AD = antidepressant; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; SNRIs = serotonin-norepinephrine reuptake inhibitors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

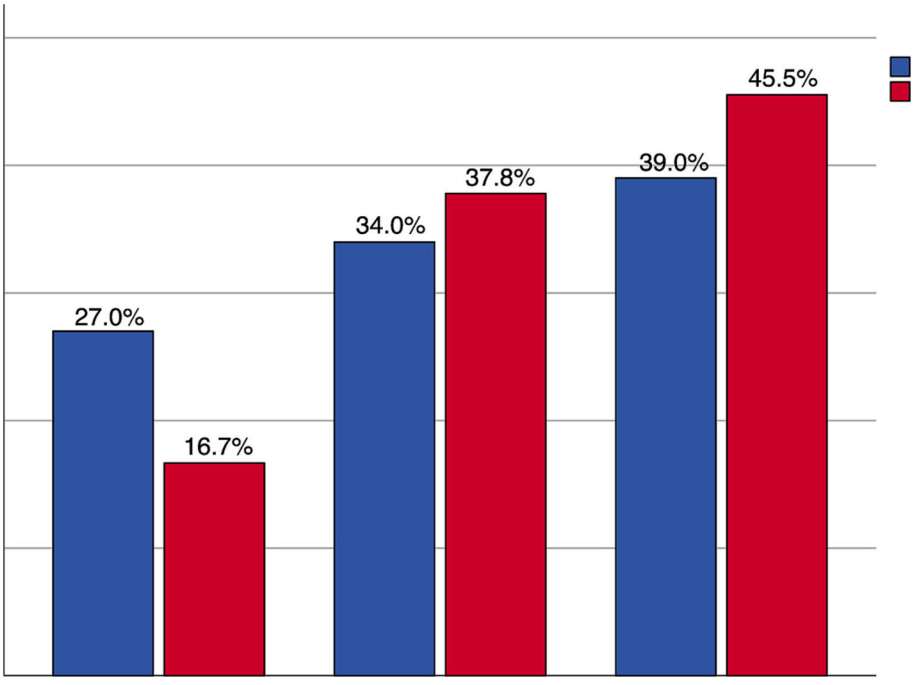


**Fig. 3.** Treatment outcome patterns in MDD patients receiving either SNRIs or other substances as their first-line AD treatment.
Displayed cumulative percentages refer to the proportion of MDD patients receiving either SNRIs (n = 336; red colored) or alternative substances (n = 1074; blue colored) as their first-line AD treatment itemized according to their treatment outcome patterns reflecting response, non-response and TRD. While non-response was defined by a previous single failed AD trial, at least two failed AD trials were mandatory for TRD (Bartova et al., 2019).
Abbreviations: AD = antidepressant; MDD = major depressive disorder; SNRIs = serotonin-norepinephrine reuptake inhibitors; TRD = treatment resistant depression. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

though venlafaxine was shown to rank among the most efficacious compounds in head-to-head comparisons (Cipriani et al., 2018).

While discussing disease severity and its AD psychopharmacotherapeutic management, it is noteworthy that the presence of current suicidal risk and trend-wise higher suicidality levels were detected in our MDD patients receiving first-line SNRIs. According to a recent network-based approach of genetic association data, SNRIs were shown to be more effective in this indication than SSRIs, bupropion or

reboxetine (Bozorgmehr et al., 2018), supporting the prescription of AD substances with dual reuptake of serotonin and noradrenaline particularly in depressed patients suffering from suicidality. However, the rationale for the internationally observed prescription practice related to this clinical phenomenon appears to be based on inconsistent evidence and still represents a matter of controverse discussion. Hereby, especially SSRIs have been accused of potentially increasing suicide risk in some patients due to their activating properties, which may, hence, reinforce suicidal intentions (Haussmann et al., 2016), and which may be even more pronounced in case of treatment with substances targeting both serotonergic and noradrenergic neurotransmission, which may bear a stronger potential to cause agitation or restlessness after their initiation (Bauer et al., 2017). However, a drug surveillance program investigating >219,000 patients treated with ADs showed that suicidal adverse events were rare in general, affecting 0.05 % of the investigated cases under SSRI and 0.03 % under SNRI first-line psychopharmacotherapy (Stubner et al., 2018). Similarly, a Danish cohort study found no difference regarding the frequency of suicidal behaviour between SSRIs, SNRIs and TCAs (Osler et al., 2019). Taken together, the existing overall international evidence suggests that suicidality represents a common and serious symptom occurring in the course of MDEs per se rather than a treatment-related consequence (Fugger et al., 2022a, 2022b). Currently, there is only indirect evidence that SNRIs may represent a favored choice in this special patient population (Bozorgmehr et al., 2018), while there are no confirming head-to-head comparisons with other AD substances.

In terms of the employed therapeutic strategies, our MDD patients undergoing first-line AD treatment with SNRIs received further augmentation and combination strategies more frequently than their counterparts with other first-line ADs. This seems to be in line with international evidence and is considered justified in international guidelines (Rhee and Rosenheck, 2019; Rothschild, 2021), especially considering the higher disease severity in the group of patients treated with first-line SNRIs, which generally requires further treatment optimization (Dold et al., 2016a, 2016b; Dold and Kasper, 2017; Kraus, Kadriu et al. 2019). Our results revealing higher rates of AP augmentation are in line with a recent study comparing the profile of MDD patients either treated with a combination of ADs or augmented with an AP. This study found that the latter strategy was more frequently applied in depressed patients with higher symptom severity, suicidality and comorbidities (Kern et al., 2021), representing characteristics that were also more common in our MDD patients with first-line SNRI treatment. The fact that the daily doses of the administered ADs were higher in the group of patients treated with first-line SNRIs may support the latter assumption, though the current international evidence failed to demonstrate a dose-response effect for individual SNRIs as well as for the whole SNRI class (Rink et al., 2021). Although existing literature and international guidelines generally advise against administering high dosages of SNRIs (Rink et al., 2021), European clinicians seemed to tend to max out the prescribed dosages as a result of the severe clinical picture.

While interpreting our results it is noteworthy that the most valuable strength derives from the real-world character of the sample allowing insights into a group of patients beyond randomized-controlled trials that are often reliant on very selected populations. In detail, our patients were recruited in different treatment settings in eight different countries including in- and outpatient units of university- as well as non-academic centers. They experienced heterogeneous clinical manifestations of MDD encompassing suicidality, melancholic- and/or psychotic features, psychiatric- and/or somatic comorbidities, and varied in terms of disease course and severity (Bartova et al., 2019; Fugger et al., 2022a, 2022b). Accordingly, the broad clinical routine might be reflected by the investigated patient population in the best possible way. Concurrently, potentially limiting factors inherent to the employed study design should be considered (Bartova et al., 2019). First, retrospective evaluation of treatment response is less accurate than a prospective one in spite of the fact that MDD patients were shown to be able to recall their symptoms very consistently across time spans of months (Dunlop et al., 2019). Second, findings from cross-sectional trials are not suitable to ascertain any causality, especially as the present analyses were performed *post-hoc*, representing an additional investigation of a large multi-site project (Bartova et al., 2019). Furthermore, the open treatment design bearing the risk of bias regarding selection and allocation in the individual recruitment centers should be taken into account. Potential cross-site differences in the prescription practices, inconsistent recommendations of clinical practice guidelines (Gabriel et al., 2020) as well as the varying adherence to those guidelines across countries, varying insurance situations and availabilities and/or approvals of the individual SNRIs and AD therapies in general including the heterogeneous treatment stages of the individual patients have to be mentioned in this regard. Moreover, the potentially varying clinician-related factors in terms of the individual experience should be mentioned in this context. In order to account for these shortcomings, exclusively experienced psychiatrists undergoing specific rater training performed the comprehensive clinical assessments of the enrolled MDD patients who were treated by senior consultants for psychiatry and psychotherapeutic medicine in all research centers. The variable "research center" was considered as covariate in our analyses, where the very conservative method of Bonferroni was used to correct for multiple comparisons in order to avoid any type two errors. Although the presence of potential comorbid personality disorders, representing an exclusion criterion, was established in the course of a thorough and structured clinical examination performed by experienced and well-trained psychiatrists, it might be of note in this regard that the SCID II questionnaire for a systematic evaluation of personality disorders was not routinely applied. Further, we did not consider plasma levels of the administered ADs, which have may modulated treatment outcomes. However, this potential bias has been suggested to be randomly distributed across groups (Cellini et al., 2022). Additionally, it should be mentioned that exclusively conventional on-label psychopharmacotherapeutics were investigated in the present study, as the use of other less common treatments has not been as well investigated (Brin et al., 2020; Fagiolini et al., 2020; Papakostas et al., 2020; Rancans et al., 2020). This might be of particular importance, when the advantages of novel substances that have recently been approved for MDD and/or TRD, as esketamine for instance (Kraus, Wasserman et al. 2019; Dold et al., 2020; Ionescu et al., 2021; Kasper et al., 2021) are taken into account. It is also of note that we adhered to the traditional indication-based nomenclature to ensure unhampered interpretability and comparison to available international evidence that, however, has increasingly been replaced by the so-called Neuroscience-based Nomenclature (NbN). The NbN is based on the pharmacological profiles of the individual substances and is, hence, thought to destigmatize prescribing practices and to improve therapeutic adherence (Zohar et al., 2015; Frazer and Blier, 2016). In general, since the present study represents a secondary analysis based on a project that was primarily designed to elucidate TRD and since the participating research centers include both, general psychiatric practices as well as academic institutions specialized for the treatment of patients non-responding to first-line AD therapies, the majority of our sample includes patients with recurrent and rather complex major depressive episodes requiring polypharmacy in the most cases. The fact that the present results may, hence, not be fully representative for patients who are frequently treated in primary care settings, should be considered when interpreting our findings.

## 5. Conclusion

In light of potential limitations inherent to the cross-sectional study design and the retrospective assessment of treatment response, our results point towards a preferred use of first-line SNRIs in generally more severely ill MDD patients. This was reflected by the observed greater severity of depressive symptoms, especially suicidality, and the

necessity of more complex treatment regimens during the current MDE, that lasted longer and was accompanied by higher rates of comorbid diabetes, unemployment and, most importantly, TRD. The fact that these clinical phenomena were repeatedly related to disease severity and chronicity in MDD and that the employment of first-line SNRIs did not result in superior treatment outcomes may lead to important clinical implications for optimal exploitation of diagnostic and therapeutic options. These will ideally follow the currently recommended treatment algorithms in the course of precision medicine, leading to faster responses and better outcomes, particularly in the so-called difficult-to-treat conditions including TRD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.03.068.

## Statement of ethics

Our research complies with internationally-accepted standards for research practice and reporting. The present investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed by appropriate ethical committees. The informed consent of the participants was obtained after the nature of the procedures had been fully explained.

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## CRediT authorship contribution statement

Dr. Bartova, Dr. Fugger and Dr. Kasper were significantly involved in designing the study and implementation of the research. Dr. Bartova and Dr. Fugger performed the statistical analyses and wrote the report including the first draft of the manuscript that was further elaborated and critically revised by Dr. Kasper. All authors substantially contributed to implementation of the research and have critically revised and approved the final manuscript.

## Conflict of interest

Within the last three years, Dr. Bartova has received travel grants and consultant/speaker honoraria from Alpine Market Research, Angelini, Biogen, Diagnosia, Dialectica, Janssen, Lundbeck, Market Access Transformation, Medizin Medien Austria, Novartis, Schwabe and Universimed. Dr. Fugger has received consultant/speaker honoraria from Janssen and Angelini. Dr. Dold has received travel grants and consultant/speaker honoraria from Medizin Medien Austria, Janssen and Universimed. Dr. Rujescu has received grant/research support from Janssen and Lundbeck; he has served as a consultant or on advisory boards for Janssen and Rovi and he has served on speakers bureaus of Janssen and Pharmagenetix. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr. Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr. Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GlaxoSmithKline, Jazz, and Solvay. Dr. Montgomery has served as a consultant or on advisory boards for Lundbeck. Dr. Fabbri has served as speaker for Janssen. Dr. Serretti has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier and Taliaz. Dr. Kasper has received grant/research support from Lundbeck; he has served as a consultant or on advisory boards for Angelini, Biogen, Esai, Janssen, IQVIA, Lundbeck, Mylan, Recordati, Sage and Schwabe; and he has served on speakers bureaus for Abbott, Angelini, Aspen Farmaceutica S.A., Biogen, Janssen, Lundbeck, Recordati, Sage, Sanofi, Schwabe, Servier, Sun Pharma and Vifor.

## Data availability statement

The data supporting the present study findings are available from the corresponding author upon reasonable request.

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