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Research paper

The sociodemographic and clinical phenotype of European patients with major depressive disorder undergoing first-line antidepressant treatment with NaSSAs

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ABSTRACT

Since selective serotonin reuptake inhibitors, that are recommended as first-line antidepressant psychopharmacotherapy for major depressive disorder (MDD), may not be the optimal choice for every patient, antidepressants with different modes of action exerting a distinct set of expectant effects, represent a valuable alternative. Despite the previously observed increased prescription rates of noradrenergic and specific serotonergic antidepressants (NaSSAs) - particularly mirtazapine - in Europe, the individual profiles of patients primarily prescribed NaSSAs in real-world settings have not been systematically investigated yet. In this secondary analysis based on a European, cross-sectional, naturalistic, multicenter study involving 1410 adult males and females with primary MDD, sociodemographic and clinical variables were compared between patients dispensed NaSSAs and those with alternative first-line antidepressants. Hereby, NaSSAs were administered in 8.6 % of the sample (mirtazapine: $n = 114$, mianserin: $n = 7$). We detected associations with older mean age, male sex, unemployment, as well as additional melancholic and catatonic features, inpatient treatment, lower mean daily-dosages of the administered antidepressants but higher rates of augmentation with low-potency antipsychotics, and greater mean reductions of depressive symptoms during their current major depressive episodes. Although the study design is unsuitable to draw any causal conclusions, our findings provide a realistic picture of patients eligible for first-line antidepressant treatment with NaSSAs, especially mirtazapine, and underscore the role of this AD substance class in severe MDD. Further, they may represent a promising basis for future systematic research focusing on precision diagnostics and treatment in MDD, that would ideally result in faster responses and better outcomes, especially in the so-called difficult-to-treat conditions including treatment resistant depression.

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1. Introduction

Major depressive disorder (MDD) represents one of the most frequent and burdensome diseases on a global scale (Vos et al., 2016). In the course of the broad armamentarium of effective psychopharmacotherapeutic options, the choice of the first-line antidepressant (AD) agent is usually dependent on multiple factors (Bartova et al., 2021b; Bauer et al., 2017; Winkler et al., 2019). These include the clinical picture of the current major depressive episode (MDE), the presence of somatic and/or psychiatric comorbidities, previous experiences of the individual patients and the eligible drugs themselves (Dold et al., 2017b). Hereby potential side effects and interactions with other co-administered compounds have to be considered (Bayes and Parker, 2019). Furthermore, the availability of the respective ADs as well as the expertise and/or experience of the prescribing clinicians may affect the treatment choice (Dold and Kasper, 2017).

Due to the generally favorable safety and tolerability profile (Dupuy et al., 2011), selective serotonin reuptake inhibitors (SSRIs) represent the recommended first-line AD treatment of MDD (Gabriel et al., 2020). However, they may not be suitable for every MDD patient (Bauer et al., 2017). Unlike the most second-generation ADs such as SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenaline-dopamine reuptake inhibitors (NDRIs) and the reversible monoamine oxidase inhibitor (MAOI) moclobemide, mirtazapine and mianserin neither inhibit the reuptake of monoamines nor impact the activity of the monoamine oxidase. Acting as antagonists of presynaptic α2-adrenoceptors and postsynaptic serotonin 5-HT2 and 5-HT3 receptors, they are referred to as noradrenergic and specific serotonergic antidepressants (NaSSA) (Haddjeri et al., 1995). Furthermore, they are known to be potent antagonists on histamine receptors and moderate antagonists on muscarinic receptors (Croom et al., 2009). Accordingly, a distinct set of expectant desirable- as well as side effects differentiates them from other AD agents and may outweigh minor discrepancies regarding efficacy (Cipriani et al., 2018) as a moderator of treatment decision and preference over other available ADs (Kasper et al., 1997).

Even though not undisputed, evidence for particular effectiveness of mirtazapine and hints for a somewhat faster onset of AD effect compared to other ADs was postulated already two decades ago (Gartlehner et al., 2011; Kasper, 1997; Watanabe et al., 2011). A recent large network meta-analysis found mirtazapine to be among the most efficacious of 21 investigated ADs, but tolerability quantified as drop-out rates appeared less favorable (Cipriani et al., 2018). Despite indications that the frequency of mirtazapine prescriptions has increased in some European countries (Hafferty et al., 2019), little is known about the sociodemographic and clinical phenotype of MDD patients who are prescribed NaSSAs as first-line ADs in real-world settings. Since this information would serve as a valuable proxy of moderators in clinical decision making, we aimed 1) to determine the proportion of patients receiving mirtazapine and mianserin as first-line AD treatment in a large naturalistic sample of MDD patients, and 2) to compare the sociodemographic and clinical variables including treatment regimen and outcome of patients receiving NaSSAs to those with alternative first-line ADs.

2. Material and methods

2.1. Study population investigated and methods used

This is a secondary analysis of an international, multicenter, cross-sectional, observational and non-interventional study conducted by the "European Group for the Study of Resistant Depression (GSRD)" (Bartova et al., 2019). The present work refers to the project "Clinical and biological correlates of resistant depression and related phenotypes" performed between 2011 and 2016 in Austria, Belgium, France (Elancourt, Toulouse), Germany, Greece, Israel, Italy (Bologna, Siena), and Switzerland (Bartova et al., 2019; Dold et al., 2018c). The ethics committees of the aforementioned research centers approved the study design and all related procedures that were comprehensively explained to all patients eligible to study participation before they signed the written informed consent.

In summary, adult male and female MDD patients were recruited in out- and inpatient units of both, university and non-academic centers. The presence of a single or recurrent MDE in the course of MDD established according to the DSM-IV-TR (Wittchen et al., 1997) as primary psychiatric diagnosis represented our main inclusion criterion. Furthermore, ongoing psychopharmacotherapy with AD agents administered in sufficient daily doses for at least four weeks during the current MDE was mandatory for study inclusion. Patients exhibiting primary psychiatric diagnoses other than MDD, any severe personality disorders and/or comorbid substance use disorders (with exception of caffeine and nicotine) that were present in the six months prior to study participation were excluded. Other psychiatric- and somatic comorbidities and specific disease manifestations including psychotic and/or melancholic features, and/or suicidality occurring during the current MDE were allowed due to the naturalistic study design (Bartova et al., 2019).

The socio-demographic and clinical variables of the included MDD patients were evaluated by experienced and specifically trained psychiatrists to assure a high standard of inter-rater reliability. To establish the current primary psychiatric diagnosis, the presence of potential additional features and/or psychiatric comorbidities the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was applied. The presence of potential somatic comorbidities and treatment strategies employed during the current MDE were rigorously assessed. The severity of depressive symptoms including the presence of suicidal risk at study entry was evaluated according to the 21-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). In line with previous evidence (Dold et al., 2018a; Kasper et al., 2010), the extent of the current suicidal risk was measured according to the item 3 of the HAM-D focusing exclusively on suicidality. Furthermore, the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) was applied to assess severity of depressive symptoms at study entry (current MADRS, cMADRS), as well as at the onset of the current MDE, when the first-line AD treatment was initiated, which was minimally four weeks before study enrollment (retrospective MADRS, rMADRS). The cMADRS and rMADRS total scores were calculated according to the MDD patients' assertions together with clinical data derived from their medical records.

In analogy with the staging model of the GSRD, treatment outcome during the current MDE was measured according to the MADRS total score change (rMADRS – cMADRS) after at least one AD trial of adequate daily dosing and duration of at least four weeks (Bartova et al., 2019). Accordingly, response was defined as a MADRS total score of <22 and a ≥ 50 % reduction of the MADRS total score after an adequate AD trial. The so-called non-response was characterized by a MADRS total score of ≥ 22 and a <50 % MADRS total score reduction after one adequate AD trial, while treatment resistant depression (TRD) was defined as non-response to two or more consecutive AD trials (Bartova et al., 2019).

2.2. Statistical procedures

All eligible MDD patients derived from a patient pool of the GSRD (Bartova et al., 2019) were subdivided into two groups based on whether they underwent first-line AD psychopharmacotherapy with NaSSAs or other ADs. Their sociodemographic, clinical, and psychopharmacotherapeutic characteristics were described as mean, standard deviation (SD), or percentages as appropriate. Chi-squared tests were performed to compare the distribution of categorical variables. Analyses of covariance (ANCOVAs) were employed for continuous variables, whereby the respective AD first-line treatment served as fixed effect and the recruitment center as covariate. The Bonferroni-Holm correction for multiple comparisons was applied and in case of statistical significance ($p \leq .05$), binary logistic regression with the relevant independent

variables were conducted *post-hoc* to analyze their relation to the respective first-line AD treatment that represented the dichotomous dependent variable. Hereby recruitment center, sex and age served as covariates. The analyses were performed employing the version 27 of IBM SPSS Statistics.

3. Results

The total sample gathered by the GSRD included 1410 MDD patients (Bartova et al., 2019) who were treated with either NaSSAs ($N = 121$, 8.6 %) or with other AD substances ($N = 1289$, 91.4 %) including SSRIs ($N = 734$; 56.9 % (Fugger et al., 2022)), SNRIs ($N = 336$; 26.1 %), tricyclic ADs (TCAs, $N = 74$; 5.7 %), agomelatine ($N = 69$; 5.4 %), NDRIs ($N = 32$; 2.5 %), serotonin antagonist and reuptake inhibitors (SARIs $N = 28$; 2.2 %), vortioxetine (N = 6; 0.5 %), MAOIs ($N = 5$; 0.4 %), noradrenaline reuptake inhibitors (NARIs, N = 3; 0.2 %) and tianeptine (N = 2; 0.2 %) as their first-line AD psychopharmacotherapy during the current MDE. In the NaSSA subgroup, mirtazapine was dispensed in 114 (94.2 %) and mianserin in 7 (5.8 %) patients.

The socio-demographic, clinical and treatment patterns of the whole GSRD sample (Bartova et al., 2019) and both patient groups split according to their first-line AD treatment with either NaSSAs or alternative substances are shown in Table 1, which also shows the identified differences between the two patient groups. Results of our *post-hoc* binary logistic regression analyses are depicted in Table 2. Significant and clinically meaningful findings are summarized below.

Our initial analyses (Table 1) revealed that NaSSAs were administered in MDD patients who were more often males (47.1 % vs 31.8 %, $p < .001$), older (mean age 53.4 ± 16.5 vs 50.0 ± 13.8 years, $p = .003$), unemployed (66.1 % vs 52.0 %, p = .003), and who experienced their first MDE in later age (mean age of MDD onset 40.9 ± 17.9 vs 36.9 ± 15.2, $p = .001$) compared to patients receiving other ADs prescribed as first-line psychopharmacotherapy. Furthermore, they were rather treated as inpatients during their current MDE (57.9 % vs 32.4 %, $p < .001$), that was more frequently accompanied by additional melancholic (78.5 % vs 59.0 %, p < .001) and/or catatonic (2.5 % vs 0.3 %, p = .001) features. A higher proportion of patients receiving NaSSAs suffered from comorbid hypertension as compared to those patients treated with other first-line ADs (28.9 % vs 18.0 %, $p = .003$). The severity of depressive symptoms at study entry, reflecting a time period after at least four weeks of adequate AD psychopharmacotherapy, was lower in comparison to patients taking alternative substances (mean HAM-D total score 19.1 ± 10.5 vs 19.8 ± 8.9, $p = .005$). The change in the MADRS total scores, reflecting the time span between the onset of the current MDE (rMADRS) and study entry (cMADRS) lasting at least four weeks, was higher in MDD patients receiving first-line NaSSAs (mean MADRS total score change −12.2 ± 12.9 vs −9.1 ± 10.6, $p < .001$). In terms of therapeutic strategies, lower mean daily doses of the first-line AD agents, that were calculated as fluoxetine dose equivalents (Hayasaka et al., 2015), were identified in patients treated with NaSSAs (32.8 ± 15.0 vs 40.6 ± 21.2, p < .001). However, they received combination with additional AD agents (42.1 % vs 28.3 %, $p = .001$) and/or augmentation with at least one low-potency antipsychotic (AP) drug (12.4 % vs 5.9 %, $p = .005$) more frequently than MDD patients medicated with other first-line AD substances.

The aforementioned between-group differences remained significant in our *post-hoc* binary logistic regression analyses considering age, sex and research center as covariates (Figs. 1 and 2), with the exception of the associations between first-line AD treatment with NaSSAs and older age of MDD onset ($p = .078$), comorbid hypertension ($p = .371$) and the administration of AD combinations ($p = .364$; Table 2).

4. Discussion

In the present naturalistic, European multicenter study, 8.6 % of our MDD patients received NaSSAs as their first-line AD treatment, whereby mirtazapine was dispensed in 94.2 %. As compared to other ADs, the administration of first-line NaSSAs was significantly associated with older age, male sex, unemployment, additional melancholic and/or catatonic features occurring during the current MDE, as well as higher reduction of depressive symptoms measured with the MADRS and a lower extent of depressive symptoms assessed with the HAM-D after at least four weeks of adequate psychopharmacotherapy. Furthermore, lower overall daily doses of the prescribed ADs but higher rates of augmentation treatment with low-potency APs and inpatient treatment settings were significantly related to the first-line AD treatment with NaSSAs.

Our real-world data point towards an administration of first-line NaSSAs in more severely ill MDD patients, which is in line with previous international evidence (Kasper, 1997). Especially the more frequent necessity of inpatient treatment was repeatedly observed in patients receiving first-line AD psychopharmacotherapy with NaSSA, particularly mirtazapine, that was administered per os as well as intravenously in previous studies (Bailer et al., 1998; Konstantinidis et al., 2002; Muhlbacher et al., 2006). The particular role of NaSSAs in the treatment of severe depression is further underscored by the specific clinical manifestation observed in patients receiving this AD class. This was characterized by a higher occurrence of melancholic, catatonic, and trend-wise atypical features as well as comorbid hypertension, representing challenging clinical phenomena which were frequently associated with severe conditions in MDD (Bartova et al., 2019; Kasper, 1997). With respect to comparable literature in this regard, most data is available for melancholia and comorbid hypertension which we focused on in our previous studies (Dold et al., 2021; Fugger et al., 2019). In melancholic depression, a previous randomized controlled trial (RCT) comparing mirtazapine and venlafaxine detected beneficial remission and response rates and fewer dropouts for mirtazapine. The latter results, however, failed to achieve statistical significance (Guelfi et al., 2001). As compared to venlafaxine and SSRIs, TCAs performed best in terms of remission rates in a more recent study in melancholic depression (Valerio et al., 2018). Since existing evidence for the effect of mirtazapine in catatonic depression is limited to positive findings in case reports (Patel et al., 2020), the exact mode of action in this special MDD sub-population is still to be disentangled in future systematic research. The observed association of first-line NaSSAs prescription and comorbid hypertension in our primary statistical analyses may appear counterintuitive at first glance because of the known noradrenergic properties of these compounds and the related potential to increase blood pressure (Haddjeri et al., 1995). However, it is noteworthy in this regard that this observation was not confirmed in our *post-hoc* regression analyses considering sex, age and research center as covariates and is, hence, likely attributable to these factors rather than the first-line AD treatment with NaSSAs per se. Especially the fact that patients prescribed NaSSAs were significantly older than patients receiving other ADs as their first-line psychopharmacotherapy seems to be of relevance, since the risk for hypertension and other chronic somatic comorbidities was repeatedly shown to increase with age (Fugger et al., 2019). The latter assumption might be further underlined by international evidence revealing that blood pressure or electrocardiogram of patients treated with NaSSAs was largely unaltered at least in low to moderate dosages (Behlke et al., 2020; Blier et al., 2009, 2010; Kasper et al., 1997).

Our observation of more severe clinical manifestations going along with greater requirement for inpatient treatment in MDD patients receiving first-line NaSSAs is further complemented by higher prescription rates of additional psychopharmacotherapeutic strategies comprising augmentation with low-potency AP agents and AD combinations detected in this patient population. In detail, the significantly higher proportion of co-prescribed low-potency APs may be an indirect indication of higher rates of sleep disturbances and a greater need for calming and tranquilization in patients receiving first-line NaSSAs (Dold et al., 2020, 2018b, 2018c; Dold and Kasper, 2017; Dold et al., 2016). Correspondingly, a recent European pharmaco-epidemiological study of

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

MDD patients' characteristics	Total sample ($n = 1410$)	NaSSAs as first-line AD treatment ($n = 121$)	Other first-line AD treatment ($n = 1289$)	x^2/F	p-Value (x^2/ ANCOVA)
Sex, n (%)					
Female	943 (66.9)	64 (52.9)	879 (68.2)	11.690	**<0.001**
Male	467 (33.1)	57 (47.1)	410 (31.8)		
Age, mean (SD), years ($n = 1404$)	50.3 (14.1)	53.4 (16.5)	50.0 (13.8)	8.563	**0.003**
Bodyweight, mean (SD), kilograms ($n = 1387$)	73.2 (16.8)	75.4 (17.0)	73.0 (16.8)	0.358	0.550
Ethnicity, n (%)					
Caucasian origin	1356 (96.2)	118 (97.5)	1238 (96.0)	0.655	0.418
Education, n (%) ($n = 1395$)					
University education/non-university high education/high level general education	755 (54.1)	68 (56.2)	687 (53.9)	0.230	0.631
General secondary/technical education/elementary school/none	640 (45.9)	53 (43.8)	587 (46.1)		
Occupation, n (%) ($n = 1408$)					
Employed	659 (46.8)	41 (33.9)	618 (48.0)	8.875	**0.003**
Unemployed	749 (53.2)	80 (66.1)	669 (52.0)		
Relationship, n (%)					
Ongoing relationship	703 (49.9)	61 (50.4)	642 (49.8)	0.016	0.898
No ongoing relationship	707 (50.1)	60 (49.6)	647 (50.2)		
Disease course, n (%)					
Single MDE	127 (9.0)	10 (8.3)	117 (9.1)	0.089	0.765
Recurrent MDD	1283 (91.0)	111 (91.7)	1172 (90.9)		
Additional features during the current MDE, n (%)					
Psychotic features	154 (10.9)	15 (12.4)	139 (10.8)	0.296	0.586
Melancholic features	856 (60.7)	95 (78.5)	761 (59.0)	17.587	**<0.001**
Atypical features	33 (2.3)	6 (5.0)	27 (2.1)	3.970	0.046
Catatonic features	7 (0.5)	3 (2.5)	4 (0.3)	10.535	**0.001**
Suicidality[a]					
Current suicidal risk (dichotomous)	649 (46.0)	61 (50.4)	588 (45.6)	1.024	0.311
High/moderate level of suicidality	377 (58.1)	32 (52.5)	345 (58.7)	0.877	0.349
Low level of suicidality	272 (41.9)	29 (47.5)	243 (41.3)		
Treatment setting, n (%)					
Inpatient	488 (34.6)	70 (57.9)	418 (32.4)	31.591	**<0.001**
Outpatient	922 (65.4)	51 (42.1)	871 (67.6)		
Duration of the current MDE, mean (SD), days ($n = 1114$)	204.7 (164.6)	180.3 (174.3)	207.2 (163.5)	1.153	0.283
Number of MDEs during lifetime, mean (SD) ($n = 1044$)	3.3 (2.5)	3.1 (2.5)	3.4 (2.5)	2.777	0.096
Age of disease onset, mean (SD), years ($n = 1329$)	37.2 (15.4)	40.9 (17.9)	36.9 (15.2)	10.872	**0.001**
Duration of psychiatric hospitalizations during lifetime, mean (SD), weeks ($n = 1328$)	5.6 (20.5)	6.8 (12.0)	5.5 (21.1)	0.091	0.763
Psychiatric comorbidities, n (%)					
Any anxiety disorder	294 (20.9)	22 (18.2)	272 (21.1)	0.571	0.450
Generalized anxiety disorder	151 (10.7)	11 (9.1)	140 (10.9)	0.363	0.547
Panic disorder	114 (8.1)	7 (5.8)	107 (8.3)	0.942	0.332
Agoraphobia	113 (8.0)	12 (9.9)	101 (7.8)	0.650	0.420
Social phobia	45 (3.2)	2 (1.7)	43 (3.3)	1.014	0.314
Obsessive-compulsive disorder ($n = 1397$)	22 (1.6)	0 (0.0)	22 (1.7)	2.120	0.145
Posttraumatic stress disorder	20 (1.4)	2 (1.7)	18 (1.4)	0.052	0.820
Somatic comorbidities, n (%)					
Any somatic comorbidity	653 (46.3)	66 (54.5)	587 (45.5)	3.609	0.057
Hypertension	267 (18.9)	35 (28.9)	232 (18.0)	8.604	**0.003**
Thyroid dysfunction	204 (14.5)	19 (15.7)	185 (14.4)	0.163	0.686
Migraine	156 (11.1)	9 (7.4)	147 (11.4)	1.768	0.184
Diabetes	84 (6.0)	8 (6.6)	76 (5.9)	0.101	0.751
Heart disease	72 (5.1)	10 (8.3)	62 (4.8)	2.724	0.099
Arthritis	65 (4.6)	7 (5.8)	58 (4.5)	0.416	0.519
Asthma	48 (3.4)	5 (4.1)	43 (3.3)	0.213	0.644
Pain	8 (0.6)	2 (1.7)	6 (0.5)	2.765	0.096
Severity of depressive symptoms, mean (SD)					
HAM-D total 21-item at study entry ($n = 1407$)	19.8 (9.1)	19.1 (10.5)	19.8 (8.9)	7.933	**0.005**
MADRS total at study entry (cMADRS) ($n = 1409$)	24.6 (11.3)	24.1 (12.6)	24.7 (11.2)	2.801	0.094
MADRS total at onset of the current MDE (rMADRS) (n = 1395)	34.1 (7.7)	36.2 (7.6)	33.9 (7.7)	4.876	0.027
Treatment outcome, n (%)[b]					
Response	346 (24.5)	37 (30.6)	309 (24.0)	8.272	0.016
Non-response	492 (34.9)	28 (23.1)	464 (36.0)		
Resistance	572 (40.6)	56 (46.3)	516 (40.0)		
MADRS total score change (rMADRS - cMADRS), mean (SD) ($n = 1394$)	−9.4 (10.8)	−12.2 (12.9)	−9.1 (10.6)	11.381	**<0.001**
Ongoing additional psychotherapy, n (%) ($n = 1279$)	399 (31.2)	39 (34.2)	360 (30.9)	0.530	0.467

(continued on next page)

Table 1 (*continued*)

MDD patients' characteristics	Total sample ($n = 1410$)	NaSSAs as first-line AD treatment ($n = 121$)	Other first-line AD treatment ($n = 1289$)	x^2/F	p-Value (x^2/ ANCOVA)
Ongoing psychopharmacotherapy					
Number of concurrently administered psychopharmacotherapeutics, mean (SD)	2.2 (1.2)	2.5 (1.3)	2.2 (1.2)	4.207	0.040
Daily doses of the first-line AD treatment given in fluoxetine equivalents[c], mean (SD), mg/day ($n = 1247$)	39.9 (20.8)	32.8 (15.0)	40.6 (21.2)	22.175	**<0.001**
Employed psychopharmacotherapeutic combination and augmentation strategies (in addition to the ongoing AD treatment), n (%)					
Any combination and augmentation treatment	855 (60.6)	86 (71.1)	769 (59.7)	6.040	0.014
Combination with at least 1 additional AD	416 (29.5)	51 (42.1)	365 (28.3)	10.176	**0.001**
Augmentation with at least 1 AP	362 (25.7)	39 (32.2)	323 (25.1)	2.983	0.084
Augmentation with at least 1 MS	159 (11.3)	12 (9.9)	147 (11.4)	0.244	0.621
Augmentation with pregabalin	102 (7.2)	12 (9.9)	90 (7.0)	1.420	0.233
Augmentation with at least 1 low-potency AP[d]	91 (6.5)	15 (12.4)	76 (5.9)	7.743	**0.005**
Augmentation with benzodiazepines including zolpidem and zopiclone	466 (33.0)	45 (37.2)	421 (32.7)	1.025	0.311

The p-values given in bold remained significant after Bonferroni-Holm correction for multiple comparisons.
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; NaSSAs = noradrenergic and specific serotonergic antidepressants.
[a] The presence of the current suicidal risk including its extent were evaluated according to the HAM-D item 3 ratings focusing exclusively on suicidality, whereby the item-score 1 reflected low- and the item-scores 2–4 moderate to high level of the current suicidal risk (Dold et al., 2018a).
[b] Treatment non-response was characterized by a previous single failed AD trial and treatment resistance by at least two failed AD trials during the current MDE (Bartova et al., 2019).
[c] Fluoxetine dose equivalents were calculated based on Hayasaka and colleagues (Bartova et al., 2019; Hayasaka et al., 2015).
[d] Low-potency APs included the so-called low-potency first-generation APs and the second-generation AP quetiapine administered at daily doses <100 mg (Bartova et al., 2019).

Table 2
Post-hoc binary logistic regression analyses investigating the association between the administered first-line AD treatment with NaSSAs and variables identified as significant in our primary analyses in 1410 MDD patients.

MDD patients' characteristics	adjusted OR (95 % CI)/ B ± SE	*p*-Value
Sex	0.545 (0.372–0.800)	**0.002**
Age	0.018 ± 0.007	**0.009**
Occupation	1.554 (1.016–2.377)	**0.042**
Melancholic features	0.599 (0.370–0.970)	**0.037**
Catatonic features	0.113 (0.023–0.556)	**0.007**
Treatment setting	0.549 (0.358–0.842)	**0.006**
Age of disease onset	0.015 ± 0.008	0.078
Comorbid hypertension	0.806 (0.503–1.293)	0.371
HAM-D total 21-item at study entry	−0.029 ± 0.011	**0.008**
MADRS total score change (rMADRS - cMADRS)	−0.026 ± 0.008	**0.002**
Daily doses of the first-line AD treatment given in fluoxetine equivalents[a]	−0.032 ± 0.006	**<0.001**
Combination with at least 1 additional AD	0.826 (0.546–1.248)	0.364
Augmentation with at least 1 low-potency antipsychotic agent[b]	0.534 (0.290–0.983)	**0.044**

This table displays results of our post-hoc binary logistic regression analyses on the association between the administered first-line AD treatment with NaSSAs and variables identified as significant in our primary analyses in 1410 MDD patients. The present analyses were adjusted for the variables research center, sex and age. Adjusted ORs with 95 % CIs are presented for dichotomous independent variables, while Bs with SEs are presented for continuous independent variables. The *p*-values that remained significant are displayed in bold.
Abbreviations (alphabetical order): AD = antidepressant; B = regression coefficient; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale (cMADRS = current MADRS; rMADRS = retrospective MADRS); MDD = major depressive disorder; OR = odds ratio; SE = standard error; NaSSAs = noradrenergic and specific serotonergic antidepressants.
[a] Fluoxetine dose equivalents were calculated based on Hayasaka and colleagues (Bartova et al., 2019; Hayasaka et al., 2015).
[b] Low-potency APs included the so-called low-potency first-generation APs and the second-generation AP quetiapine administered at daily doses <100 mg (Bartova et al., 2019).

MDD inpatients revealed a considerable demand for sedation in general and found that a primary treatment with NaSSAs was linked to a higher co-administration of other drugs with tranquilizing properties than in the case of primary SSRI or SNRI psychopharmacotherapy for instance (Seifert et al., 2021).

The higher proportion of AD combination treatment observed in our MDD patients prescribed NaSSAs in the primary analyses lost statistical robustness when age, sex and research center were included in the *post-hoc* regression analyses. Although the strategy of combining ADs to overcome non-response or even TRD is still understudied compared to other psychopharmacotherapeutic options such as augmentation with second-generation APs (Papakostas, 2009), it is widely used in clinical practice, especially involving a combination of SSRIs or SNRIs with mirtazapine or trazodone (Bauer et al., 2017; de la Gandara et al., 2005; Dold et al., 2018c; Dold and Kasper, 2017; Dold et al., 2016). A very recent report compared the efficacy of either a combination of paroxetine and mirtazapine or mirtazapine monotherapy as consecutive step following insufficient response to paroxetine monotherapy, but found no evidence for better outcome in either group of patients (Xiao et al., 2021). However, studies comparing SSRI monotherapy to a combination of ADs of different classes with mirtazapine from treatment initiation of the MDE onwards reported higher rates of response and largely equal side effect profiles in the combination group (Blier et al., 2009, 2010; Rocha et al., 2012). Importantly, the unique receptor profile of NaSSAs is thought to play a role in the aforementioned findings, as antagonism on 5-HT2 receptors together with serotonin reuptake inhibition may result in beneficial AD effects (Marek et al., 2003), while the blockage of 5-HT3 receptors may be useful to neutralize common side effects of early SSRI treatment such as nausea (Bergeron and Blier, 1994).

Considering the rather unfavorable disease profile and largely increased therapeutic efforts in our MDD patients undergoing first-line AD treatment with NaSSAs, it might be surprising that exactly this patient population was prescribed significantly lower daily dosages quantified in fluoxetine equivalents (Hayasaka et al., 2015). The latter observation might be explained by the more frequently established combination and augmentation strategies and, hence, less need for further treatment optimization. Concurrently, it might support the assumption that NaSSAs administered in daily doses not exceeding 45

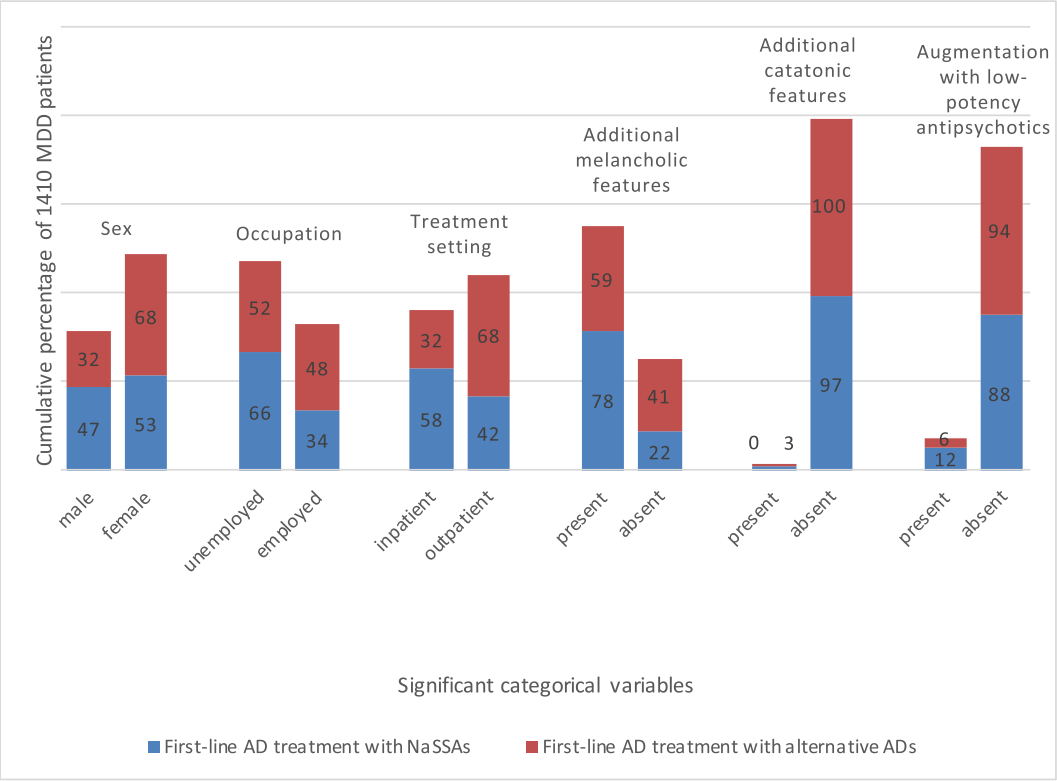

Fig. 1. Overview of significantly different categorical variables of MDD patients receiving either NaSSAs or a different first-line AD treatment.
Displayed are cumulative percentages referring to the proportion of MDD patients ($N = 1410$) receiving either NaSSAs ($N = 121$; 8.6 %; blue colored) or alternative substances ($N = 1289$; 91.4 %; red colored) as their first-line AD treatment itemized according to the categorical variables which remained significant in our initial analyses and *post-hoc* regression analyses considering age, sex and research center as covariates.
Low-potency APs included the so-called low-potency first-generation APs and the second-generation AP quetiapine administered at daily doses <100 mg.
Abbreviations (alphabetical order): AD = antidepressant; AP = antipsychotic; MDD = major depressive disorder; NaSSAs = noradrenergic and specific serotonergic antidepressants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mg may suffice to achieve adequate treatment outcome. The latter assumption might be highlighted by international reports that failed to confirm superior efficacy of AD dose escalation in MDD (Bruijn et al., 1996; Dold et al., 2017a) as well as international recommendations for evidence-based MDD treatment (Bauer et al., 2017; Dold and Kasper, 2017).

In terms of treatment outcome, it is noteworthy that patients dispensed first-line NaSSAs showed higher reductions of depressive symptoms after at least four weeks of adequate psychopharmacotherapy. This was evidenced by a more than three-point difference on the MADRS total score and lower HAM-D total scores at study entry and might gain on relevance, when the trend towards higher rMADRS scores at onset of the current MDE detected in patients receiving first-line NaSSAs is considered. Even though our significant results regarding treatment outcome per se did not withstand the Bonferroni-Holm correction for multiple testing, the observed higher reduction of depressive symptoms under NaSSAs may strengthen the considerable body of evidence supporting the role of these compounds, especially mirtazapine, among the most efficacious ADs available for MDD treatment (Cipriani et al., 2018, 2009). In detail, a superior efficacy of mirtazapine compared to SSRIs was postulated in a meta-analysis published a decade ago (Thase et al., 2010), which seems to be of importance, since SSRIs were administered as first-line AD treatment in the majority of our MDD patient population (Fugger et al., 2022). One of the most interesting and distinct properties of mirtazapine, that was dispensed in 94.2 % of our patients receiving first-line NaSSAs, is the proposed more rapid onset of AD effects in clinical trials (Gartlehner et al., 2008; Kasper et al., 1997). In direct comparison to SSRIs, the aforementioned effects of faster onset were shown to be robust (Quitkin et al., 2001; Watanabe et al., 2008). Such early differences in efficacy, however, appeared to level out after six to twelve weeks of treatment (Watanabe et al., 2011, 2008). The more pronounced reduction of depressive symptoms during the current MDE under NaSSAs in our investigation might, hence, be linked to the evaluation of depressive symptoms after a minimum of four weeks of adequate AD treatment already, and may thus be related to the faster onset of NaSSAs' action compared to other first-line ADs, and not a factual difference in efficacy.

With respect to the socio-demographic aspects it is noteworthy that unemployment was more common in patients receiving first-line NaSSAs. Unemployment was generally shown to be closely tied to MDD as a risk factor (Zuelke et al., 2018), particularly among inpatients (Fortney et al., 2007), and our MDD patients receiving NaSSAs were also more often treated in inpatient settings. The higher proportion of males among those patients receiving NaSSAs might be related to the profile of side effects of this AD substance class, especially regarding the potential of inducing weight gain (Blier et al., 2009, 2010) that seems to be preferably feared by women (Bartova et al., 2021a). With respect to sexual dysfunction representing a common side effect going along with AD treatment, it is noteworthy that NaSSAs seem to be advantageous compared to many other classes of ADs (Benjamin and Doraiswamy, 2011; Kasper et al., 1997; Watanabe et al., 2011), particularly in head-to-head comparison with some SSRIs (Reichenpfader et al., 2014). According to a previous meta-analysis, the risk of sexual dysfunction under mirtazapine was shown to be insignificantly different from placebo (Serretti and Chiesa, 2009), which makes it a valuable treatment option in this regard (Clayton and Montejo, 2006; Kasper et al., 1997; Montgomery, 1995). Our finding of significantly older age observed in the group of our patients receiving first-line NaSSAs is in line with existing

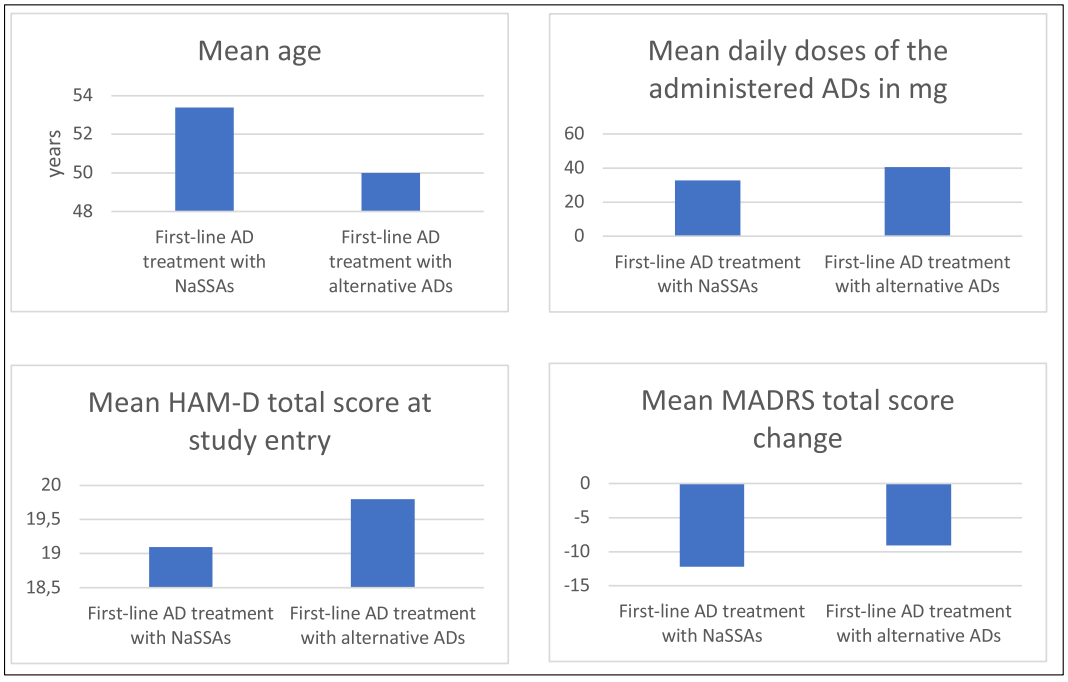

Fig. 2. Overview of significantly different continuous variables of MDD patients receiving either NaSSAs or other first-line AD treatment.
Displayed are significant differences in continuous variables remaining significant in our initial analyses and *post-hoc* regression analyses considering age, sex and research center as covariates between MDD patients receiving NaSSAs ($N = 121$; 8.6 %) and alternative ADs ($N = 1289$; 91.4 %) as their first-line AD treatment. Mean age is given in years. Mean daily doses of the administered ADs were calculated as fluoxetine dose equivalents in mg based on Hayasaka and colleagues (Bartova et al., 2019; Hayasaka et al., 2015). The severity of depressive symptoms at study entry is reflected by the mean total score on the 21-item HAM-D rating scale (Hamilton, 1960). The improvement of depressive symptoms during the current MDE is represented by the mean total score change on the MADRS (Montgomery and Asberg, 1979) that was gathered after at least one AD trial of adequate daily dosing and duration of at least four weeks (Bartova et al., 2019).
Abbreviations (alphabetical order): AD = antidepressant; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; MDE = major depressive episode; NaSSAs = noradrenergic and specific serotonergic antidepressants.

evidence postulating that this AD class is well tolerated in the elderly (Montgomery, 1995), also in case of somatic comorbidities or cognitive impairment (Roose et al., 2003). The anticholinergic side effects caused by standard dosages of NaSSAs, especially mirtazapine, were found to be limited (Kasper et al., 1997) and comparable to SSRIs, with the exception of paroxetine that was shown to exhibit stronger anticholinergic properties (Chew et al., 2008). Importantly, a lower need for anxiolytic co-medication including benzodiazepines was evidenced in older patients treated with mirtazapine (Gardner et al., 2004), which corresponds with our findings that did not reveal any significant difference in prescription rates of benzodiazepines and/or pregabalin. This may represent a general advantage in this patient population. Although evidence regarding efficacy and tolerability in older patients is scarce, it is noteworthy that a previous RCT comparing paroxetine and mirtazapine found data in favor of the latter substance for both (Schatzberg et al., 2002), which were further shown to be modified by genetic variants related to the brain-derived neurotrophic factor (BDNF), cyclic AMP responsive element binding protein (CREB) (Murphy et al., 2013), ATP-binding cassette, subfamily B, member 1 transporter (ABCB1) multidrug-resistance gene (Sarginson et al., 2010a), apolipoprotein E (APOE) epsilon4 (Murphy et al., 2003), the promoter of the serotonin transporter gene (SLC6A4) to a lesser degree (Murphy et al., 2004), while contrary results were suggested in terms of the FK506-binding protein 5 (FKBP5) polymorphisms (Sarginson et al., 2010b).

4.1. Study limitations

Despite the fact that our data provide a real-world perspective on the factors and traits associated with first-line treatment with NaSSAs in a large naturalistic European sample of MDD patients gathered in university and non-academic in- and outpatient settings, and thus reflecting broad everyday practice of care, several limitations have to be emphasized. The current analyses were carried out *post-hoc* as the study was not originally designed to test the present hypothesis. Due to the given study design, allocation- and assessment bias cannot be fully ruled out, as well as possible heterogeneity in evaluation across research centers, even though we adjusted for this variable in our statistical analyses. Furthermore, the cross-sectional design does not allow to draw any causal conclusions. The only variable with longitudinal character was the rMADRS that was retrospectively assessed at study entry. Even though MDD patients were previously shown to adequately recall their MDD symptoms for considerable time periods exceeding several months (Dunlop et al., 2019), this approach is inferior to prospective investigations. Being aware of indisputable advantages of the so-called Neuroscience based Nomenclature (NbN) (Frazer and Blier, 2016; Zohar et al., 2015), we decided to adhere mostly to traditional nomenclature because of the easier readability and comparability with existing international evidence.

5. Conclusion and implications for future work

MDD patients who were prescribed first-line NaSSAs were rather males, older, unemployed, and exhibited melancholic and/or catatonic features more commonly than patients receiving other ADs. They received lower AD dosages but more common augmentation with low-potency APs and were rather treated as inpatients. Higher reductions of depressive symptoms during the current MDE as well as lower extent of depressive symptoms after at least four weeks of adequate psychopharmacotherapy were revealed in patients undergoing first-line AD treatment with NaSSAs. The rationale for this particular prescription pattern can only be marginally considered evidence-based according to the literature. Despite the rather unfavorable socio-demographic and

clinical profile associated with this patient population, reductions of depressive symptoms under NaSSAs were greater compared to alternative first-line ADs, which emphasizes the role of this specific AD substance class in the treatment of severe MDD, and may hence lead to potential further implications for the treatment of challenging phenomena including TRD. This seems to be of relevance, as the sociodemographic and clinical characteristics related to the first-line AD treatment with NaSSAs in the present study were repeatedly observed in patients suffering from TRD (Bartova et al., 2019; Kraus et al., 2019). Even though the study design is unsuitable to draw any causal conclusions, our findings derived from real-world clinical settings may very well serve as a promising basis for future systematic research, with the aim to replace eventual trial-and-error prescription practice with tailored treatment approaches in MDD. This would ideally result in faster responses and better outcomes, especially in patients suffering from challenging clinical conditions.

Authorship contribution statement

Dr. Fugger and Dr. Bartova contributed equally to designing the study, implementation of the research, statistical analyses, and writing the report including the first draft of the manuscript. Dr. Kasper contributed to designing the study, implementation of the research, and writing the report. All authors substantially contributed to implementation of the research and have critically revised and approved the final manuscript.

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.

Declaration of competing interest

Dr. Fugger has received consultant/speaker honoraria from Janssen. Dr. Bartova has received travel grants and consultant/speaker honoraria from AOP Orphan, Medizin Medien Austria, Vertretungsnetz, Schwabe Austria, Janssen and Angelini. Dr. Fabbri has served as speaker for Janssen. Dr. Dold has received travel grants and consultant/speaker honoraria from Medizin Medien Austria and Janssen. 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 AstraZeneca, Bionevia, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis, and Wyeth. 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, and Servier. Within the last three years, 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 Aspen Farmaceutica S.A., Angelini, Biogen, Janssen, Lundbeck, Neuraxpharma, Recordati, Sage, Sanofi, Schwabe, Servier and Sun Pharma. Other authors declare that they have no potential conflicts of interest.

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