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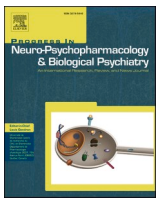

Evidence on sociodemographic and clinical correlates of antidepressant combination or augmentation with second-generation antipsychotics in major depressive disorder

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ABSTRACT

About two thirds of the patients with major depressive disorder (MDD) do not sufficiently respond to monotherapy with antidepressants (ADs) which makes them reliant on further treatment approaches. Hereby, combination of different ADs and augmentation with second-generation antipsychotics (SGAs) are widely used and recommended psychopharmacotherapeutic strategies.

The present secondary analyses are based on an international, naturalistic, cross-sectional multicenter study conducted by the European Group for the Study of Resistant Depression. Comparing socio-demographic and clinical characteristics of 436 adult MDD patients receiving either SGAs (N = 191, 43.8%) or ADs (N = 245, 56.2%), that were additionally administered to their first-line AD psychopharmacotherapy, we aimed to identify possible trajectories of decision-making for clinicians regarding which treatment option to prefer in individual patients.

Our most robust findings represent an association of SGA augmentation with the presence of psychotic symptoms, longer mean duration of lifetime psychiatric hospitalizations, employment of further augmentation strategies with mood-stabilizers and benzodiazepines, and a trend towards higher mean daily dosages of their first-line ADs and current suicidal risk. Treatment outcome was not significantly different between patients receiving either SGA augmentation or AD combination.

Being aware of limitations inherent to the cross-sectional study design and the lack of randomization, more severe and rather chronic conditions in MDD seemed to encourage clinicians to choose SGA augmentation over AD combination. The fact that mood-stabilizers and/or benzodiazepines were more frequently co-administered with SGAs may represent a requirement of an overall refined psychopharmacotherapy including additional fast-acting agents with potent AD, tranquilizing and anti-suicidal effects in MDD patients experiencing challenging clinical manifestations. New glutamatergic substances seem to be promising in this regard.

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1. Background

Major depressive disorder (MDD) ranks among the most frequent and most debilitating adult disorders on a global scale (Vos et al., 2016). The efficacy of a plethora of antidepressant (AD) agents for the first-line treatment has been confirmed by more than 500 randomized-controlled-trials (RCTs), and can, hence, be regarded as robust evidence (Cipriani et al., 2018). Despite the fact that most ADs are effective in the treatment of MDD, clinical practice relentlessly shows us that some agents may not work sufficiently in individual patients. In fact, more than two-thirds of MDD patients treated with an initial AD do not achieve remission (Kolovos et al., 2017) leaving them with residual symptoms, functional impairment, increased suicidal risk and mortality (Papakostas, 2016; Bachmann, 2018).

In clinical routine, frequently applied psychopharmacotherapeutic approaches following insufficient response to the first-line AD agent include its combination with an additional AD or its augmentation with second-generation antipsychotics (SGAs) (Ng et al., 2006; Thase, 2016; Bauer, Severus et al., 2017; Dold and Kasper, 2017; Kraus et al., 2019). The latter strategy has received approval by regulatory authorities in some countries (quetiapine extended release (XR) in Europe and aripiprazole, quetiapine XR, olanzapine plus fluoxetine combination and brexpiprazole in the United States (U.S.)) (Wang et al., 2016).

The efficacy of augmentation of the first-line AD therapy with selected SGAs was evidenced by numerous meta-analyses and RCTs (Nelson and Papakostas, 2009; Spielmans et al., 2013; Zhou et al., 2015; Mohamed, Johnson et al., 2017). Nonetheless, the role of potential side effects, including those affecting extrapyramidal motor functions and metabolic consequences (Ucok and Gaebel, 2008), have to be thoroughly kept in mind in patients with MDD (Dold and Kasper, 2017).

With respect to the AD combination treatment only a limited number of possible combinations, namely monoamine reuptake inhibitors with mianserine, mirtazapine, bupropion and desipramine, can be regarded as options with sufficient scientific evidence (Papakostas, 2009; Davies et al., 2019). A previous meta-analysis investigating the efficacy of AD combinations found benefits over monotherapy, but the results have to be cautiously considered due to a small number of included trials and the fact that two ADs were combined from the beginning of the treatment and not prescribed as potentiation of an established monotherapy in case of insufficient response (Rocha et al., 2012).

Recent reviews compared clinical guidelines for the management of insufficient response in MDD. They detected considerable inconsistencies with respect to the recommended subsequent steps when the first-line AD therapy is unsatisfactory, often failing to adequately underline the limitations of the existing evidence (MacQueen et al., 2017; Bayes and Parker, 2018). This brings up the clinically relevant question of identifying factors which may guide the clinicians' decisions regarding further treatment optimization steps. In order to elucidate the respective conditions potentially leading them to either augment the ongoing AD therapy with SGAs or to add another AD, the present cross-sectional multicenter European study investigating a naturalistic sample of medicated MDD patients sought 1) to identify the proportion of patients receiving either augmentation with SGAs or AD combination treatment, and 2) to investigate the respective associations with their socio-demographic, clinical and therapeutic characteristics.

2. Methodology

2.1. Study design

The present secondary analyses refer to an international, multicentric, observational, cross-sectional and non-interventional study with a retrospective evaluation of treatment response that was performed by the "European Group for the Study of Resistant Depression (GSRD)" (Bartova et al., 2019). They are based on the GSRD project "Clinical and biological correlates of resistant depression and related phenotypes" conducted between 2011 and 2016 by ten research centers located in Austria (Vienna), Belgium (Brussels), France (two sites in Elancourt and Toulouse), Germany (Halle), Greece (Athens), Israel (Tel Hashomer), Italy (two sites in Bologna and Siena) and Switzerland (Geneva) (Dold et al., 2016; Bartova et al., 2019). The local ethics committees in each participating research center approved the study as well as all related procedures that were comprehensively described in our recent publications (Dold et al., 2016; Bartova et al., 2019; Fugger et al., 2019; Dold et al., 2021) and are summarized below.

2.2. Study sample

Adult patients were recruited in universities as well as non-academic clinical centers including both in- and outpatient units. Interested patients eligible to study participation signed written informed consent after a thorough explanation of the study and all related procedures. Present single or recurrent major depressive episode (MDE) occurring in the course of MDD, that was diagnosed based on the DSM-IV-TR (Wittchen et al., 1997) and that represented the primary psychiatric diagnosis, was mandatory for study enrollment. An ongoing and adequate psychopharmacotherapy with an AD agent that was administered in sufficient daily doses for minimally four weeks during the current MDE was required for inclusion (Dold et al., 2016; Bartova et al., 2019). Furthermore, only MDD patients who were treated with a first-line AD agent that was either augmented with a SGA (first-line AD agent + augmentation with a SGA) or combined with an additional AD (first-line AD agent + combination with another AD agent) were included to the present secondary analysis. Exclusion criteria comprised the presence of a primary psychiatric diagnosis other than MDD, comorbid severe personality disorders as well as substance use disorders (with exception of caffeine and nicotine) that have co-occurred in the previous six months. The presence of other psychiatric- and/or somatic comorbidities and of specific clinical manifestations appearing during the current MDE including suicidality and/or additional features (e. g. psychotic symptoms, melancholia) were not exclusion criteria, in line with the naturalistic study design.

2.3. Patient evaluation

Experienced and specifically trained psychiatrists assessed the socio-demographic, clinical and treatment characteristics of the included MDD patients to guarantee a high standard of inter-rater reliability. Besides patients´ assertions, clinical data derived from their medical records were additionally considered. The primary psychiatric diagnosis, the presence of potential specific features occurring during the current MDE and/or psychiatric comorbidities were determined according to the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The presence of potential somatic comorbidities and the therapies employed during the current MDE were precisely established.

In accordance with the GSRD study protocol described in our previous reports (Bartova et al., 2019), the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) was used to measure depressive symptoms at two time-points during the current MDE. Furthermore, the MADRS was applied to estimate treatment outcome of the current MDE. Hereby, the current MADRS (cMADRS) was applied to assess the severity of depressive symptoms at study entry, representing a time-point when the included MDD patients have received an adequate psychopharmacotherapy for at least four weeks. To assess the severity of depressive symptoms at the onset of the current MDE, we used the retrospective MADRS (rMADRS), representing a time point of at least four weeks before study enrollment, respectively before the first-line AD treatment was initiated. The rMADRS was calculated based on patients' retrospective assertions and their medical records. In line with the GSRD staging model for treatment outcome (Bartova et al., 2019), the change of the MADRS total score (rMADRS – cMADRS) in the course of the current MDE was calculated. Accordingly,

treatment response was achieved with a cMADRS total score of <22 and its reduction of ≥50% after an AD trial of sufficient daily dosing and duration of at least four weeks. Non-response was characterized by a total score of ≥22 at the cMADRS and its reduction of <50% after one adequate AD trial. Treatment-resistant depression (TRD) was defined as a non-response to two or more consecutive and adequate AD trials. Importantly, exclusively psychopharmacotherapeutic strategies that were administered in the course of the current MDE were considered in the aforementioned staging model for treatment outcome.

Additionally, the 21-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) was employed to evaluate depressive symptoms at study enrollment. In this context and in line with the existing evidence (Kasper et al., 2010; Dold et al., 2018a), current suicidality was evaluated according to the item 3 of the HAM-D (1 = low degree of current suicidal risk, while scores 2, 3 and 4 characterized moderate to high levels of current suicidal risk (Dold et al., 2018b)).

2.4. Statistical analyses

Among included MDD patients (Bartova et al., 2019), for the present analyses we considered only those who underwent either augmentation with a SGAs or an AD combination treatment administered additionally to their ongoing first-line AD psychopharmacotherapy. Patients who were simultaneously treated with both additional psychopharmacotherapies (first-line AD + SGA+AD) were excluded from the present secondary analyses that were performed with version 27 of IBM SPSS Statistics.

Socio-demographic, clinical and psychopharmacotherapeutic characteristics were evaluated in the two patient groups using descriptive statistics (percentages for categorical variables; means and standard deviation (SD) for continuous variables). The distribution of categorical variables between groups was compared applying chi-squared tests, while analyses of covariance (ANCOVAs) were employed to evaluate continuous variables. The respective additional treatment strategy served as fixed effect and recruiting center as covariate in the ANCOVAs. The Bonferroni-Holm correction for multiple comparisons was applied. For all variables with $p \leq 0.05$ in the primary analyses, also after correction for multiple tests, we conducted binary logistic regression analyses *post-hoc* to determine their relation to the employment of either SGA augmentation or AD combination treatment. In the *post-hoc* binary logistic regression analyses, the significant variables derived from our initial analyses served as independent variables and the respective treatment optimization strategies as dichotomous dependent variables. Research center was included as covariate.

3. Results

In total, the analyzed sample of eligible patients with MDD included 436 subjects, of which 245 (56.2%) received combination treatment with additional AD agents and 191 (43.8%) augmentation with SGAs that were both administered together with the first-line AD psychopharmacotherapy. As patients receiving both SGAs and ADs additionally to their ongoing first-line AD therapy were excluded, the present investigation yielded a different number of patients receiving SGAs in contrast to a previous GSRD publication comparing augmentation treatments with either lithium or SGAs (Dold et al., 2018a). The socio-demographic, clinical and therapeutic characteristics of the whole sample and both patient groups as well as the between-group differences identified in our initial analyses are displayed in Table 1 in detail.

In summary, patients who received SGAs augmentation experienced a longer overall duration of psychiatric hospitalizations during their lifetime given in weeks (13.3 ± 41.2 vs. 6.7 ± 14.7, $p = 0.008$) and exhibited psychotic features (18.8% vs. 8.2%, $p < 0.001$) more often as compared to MDD patients receiving AD combination treatment. Further, patients with SGA augmentation were prescribed MSs (20.9% vs. 11.8%, $p = 0.01$) and BZDs (50.8% vs. 38%, $p = 0.007$) more often than those receiving AD combination. Elevated suicidal risk (59.2% vs. 48.2%, $p_{uncorrected} = 0.022$), an overall higher mean number of concurrent psychopharmacotherapeutics (3.0 ± 0.9 vs. 2.8 ± 0.8, $p_{uncorrected} = 0.027$) and higher mean daily dosages of the AD first-line therapy (46.3 ± 20 vs. 41.3 ± 29.4, $p_{uncorrected} = 0.038$) were also associated to SGA augmentation but significance was lost by correction after Bonferroni-Holm.

The aforementioned between-group differences withstanding the Bonferroni-Holm correction for multiple testing remained significant also in our *post-hoc* binary logistic regression analyses considering research center as covariate (Table 2).

We did not detect any significant between-group differences with respect to the socio-demographic parameters, the severity of depressive symptoms, the presence of psychiatric and/or somatic comorbidities, the administered first-line AD substances, and the treatment outcome patterns (response, non-response and TRD).

The administered first-line AD treatment of the whole MDD sample itemized according to the employed additional treatment is displayed in Fig. 1.

The most common substances administered as second ADs in MDD patients undergoing AD combination treatment were SARIs (29.4%), namely trazodone in all cases, followed by NaSSAs (25.7%) represented by mirtazapine in 62 MDD patients and mianserin in one case (Fig. 2).

The most frequent individual agent that was prescribed in the MDD patient group receiving SGA augmentation treatment was quetiapine (50.6%) followed by olanzapine (21.6%), risperidone (10.5%), aripiprazole (8%), amisulpride (8%) and ziprasidone (1.2%; Fig. 3).

4. Discussion

In the present naturalistic cross-sectional study comprising 436 patients with primary MDD, AD combination treatment was employed in 245 individuals, while additional SGAs were dispensed in 191 patients. With respect to the identified clinical characteristics, additional psychotic features occurred more frequently in MDD patients receiving SGA augmentation during their current MDE. In terms of treatment patterns, these patients spent a longer time duration in psychiatric hospitalizations over their lifetime and received additional augmentation strategies with MSs and BZDs during their current MDE more often than their counterparts with AD combination treatment. Furthermore, trends towards the presence of current suicidal risk, higher daily doses of the first-line ADs, as well as a higher number of concomitant psychotropic drugs were observed in the patient population receiving SGAs in the course of their current MDE. We did not detect any significant between-group differences in terms of socio-demographic characteristics, which differs from previous studies investigating various patient populations that found associations of older age and female sex with SGA augmentation (Lin et al., 2014).

The larger proportion of our MDD patients who received AD combination compared to SGA augmentation might reflect the current approval situation in Europe, where a plethora of ADs are approved for the treatment of MDD, while only one SGA - quetiapine XR - is officially licensed by the European Medicines Agency for augmentation in MDD (EMA; http://www.ema.europa.eu) (Bauer, Severus et al., 2017; Dold and Kasper, 2017). As the U.S. Food and Drug Administration (FDA) licensed also aripiprazole and the olanzapine/fluoxetine combination for this indication (Wang et al., 2016; Mohamed, Johnson et al., 2017), the prescription rates might, hence, differ from comparable patient samples collected in countries with different licensed SGAs (Gerhard et al., 2014).

Another plausible explanation for the observed prescription culture of higher rates of AD combination treatment, including trazodone and mirtazapine in the most cases, might be the necessity of treatment of individual depressive symptoms frequently occurring during MDEs, such as sleep disturbances, rather than the requirement of boosting antidepressant efficacy (Blier et al., 2010). The latter assumption might

Table 1
MDD patients' socio-demographic, clinical, and treatment profile itemized according to whether they received AD combination or SGA augmentation treatment.

Characteristics of MDD patients	Total sample (n = 436)	AD combination (n = 245)	SGA augmentation (n = 191)	x^2/F	p-value (x^2/ ANCOVA)
Sex, n (%)					
Female	267 (61.2)	148 (60.4)	119 (62.3)	0.2	0.687
Male	169 (38.8)	97 (39.6)	72 (37.7)		
Age, mean (SD), years (n = 435)	54 (14.5)	54.5 (15.2)	53.2 (13.6)	0.975	0.324
Bodyweight, mean (SD), kilograms (n = 431)	76.8 (17.6)	77.3 (17.4)	76.1 (17.9)	0.072	0.789
Ethnic origin, n (%)					
Caucasian	429 (98.4)	242 (98.8)	187 (97.9)	0.5	0.473
Educational status, n (%) (n = 431)					
University education/non-university high education/high level general education	224 (52.0)	133 (54.5)	91 (48.7)	1.5	0.229
General secondary/technical education/elementary school/none	207 (48.0)	111 (45.5)	96 (51.3)		
Occupational status, n (%)					
Employed	149 (34.2)	82 (33.5)	67 (35.1)	0.1	0.725
Unemployed	287 (65.8)	163 (66.5)	124 (64.9)		
Relationship status, n (%)					
With ongoing relationship	213 (48.9)	120 (49.0)	93 (48.7)	0.0	0.952
Without ongoing relationship	223 (51.1)	125 (51.0)	98 (51.3)		
Disease course, n (%)					
Single MDE	35 (8.0)	18 (7.3)	17 (8.9)	0.4	.0.554
Recurrent MDD	401 (92.0)	227 (92.7)	174 (91.1)		
Specific additional features, n (%)					
Psychotic features	56 (12.8)	20 (8.2)	36 (18.8)	11	**<0.001**
Melancholic features	330 (75.7)	190 (77.6)	140 (73.3)	1.1	0.304
Atypical features	17 (3.9)	10 (4.1)	7 (3.7)	0.1	0.824
Catatonic features	4 (0.9)	2 (0.8)	2 (1.0)	0.1	0.802
Suicidality[a]					
Current suicidal risk (dichotomous)	231 (53.0)	118 (48.2)	113 (59.2)	5.2	0.022
High/moderate	135 (58.4)	67 (56.8)	68 (60.2)	0.3	0.600
Low	96 (41.6)	51 (43.2)	45 (39.8)		
Treatment setting, n (%)					
Inpatient	237 (54.4)	126 (51.4)	111 (58.1)	1.9	0.164
Outpatient	199 (45.6)	119 (48.6)	80 (41.9)		
Duration of the current MDE, mean (SD), days (n = 340)	177.7 (148.7)	168.8 (139.1)	189.1 (160.0)	1.148	0.285
Number of MDEs during lifetime, mean (SD) (n = 362)	3.4 (2.6)	3.3 (2.3)	3.5 (2.8)	0.681	0.410
Age of MDD onset, mean (SD), years (n = 413)	38.2 (15.8)	38.6 (15.3)	37.6 (16.4)	0.643	0.423
Duration of psychiatric inpatient care during lifetime, mean (SD), weeks (n = 409)	9.5 (29.1)	6.7 (14.1)	13.3 (41.2)	7.141	**0.008**
Psychiatric comorbidities, n (%)					
Any anxiety disorder	89 (20.4)	42 (17.1)	47 (24.6)	3.7	0.055
Generalized anxiety disorder	41 (9.4)	18 (7.3)	23 (12.0)	2.8	0.096
Panic disorder	46 (10.6)	24 (9.8)	22 (11.5)	0.3	0.561
Agoraphobia	37 (8.5)	19 (7.8)	18 (9.4)	0.4	0.535
Social phobia	17 (3.9)	7 (2.9)	10 (5.2)	1.6	0.203
Obsessive-compulsive disorder (n = 429)	9 (2.1)	3 (1.2)	6 (3.2)	2.0	0.163
Posttraumatic stress disorder	7 (1.6)	3 (1.2)	4 (2.1)	0.5	0.473
Somatic comorbidities, n (%)					
Any somatic comorbidity	237 (54.4)	147 (60.0)	90 (47.1)	7.2	0.007
Hypertension	121 (27.8)	77 (31.4)	44 (23.0)	3.8	0.052
Thyroid dysfunction	78 (17.9)	36 (14.7)	42 (22.0)	3.9	0.049
Migraine	36 (8.3)	25 (10.2)	11 (5.8)	2.8	0.094
Diabetes	39 (8.9)	26 (10.6)	13 (6.8)	1.9	0.167
Heart disease	34 (7.8)	18 (7.3)	16 (8.4)	0.2	0.691
Arthritis	19 (4.4)	12 (4.9)	7 (3.7)	0.4	0.532
Asthma	17 (3.9)	10 (4.1)	7 (3.7)	0.1	0.824
Pain	3 (0.7)	2 (0.8)	1 (0.5)	0.1	0.714
Severity of depressive symptoms, mean (SD)					
HAM-D total 21-item at study entry (n = 435)	19.5 (9.2)	20.0 (8.9)	18.7 (9.7)	1.054	0.305
MADRS total at study entry (cMADRS)	25.1 (11.7)	25.2 (11.2)	25.0 (12.3)	0.011	0.916
MADRS total at onset of the current MDE (rMADRS)	35.8 (8.4)	35.6 (8.3)	36.1 (8.5)	1.021	0.313
Treatment response, n (%)[b]					
Response	110 (25.2)	55 (22.4)	55 (28.8)	4.6	0.099
Non-response	161 (36.9)	87 (35.5)	74 (38.7)		
Resistance	165 (37.8)	103 (42.0)	62 (32.5)		
MADRS total change (rMADRS -cMADRS), mean (SD)	−10.7 (11.9)	−10.4 (11.1)	−11.2 (12.8)	0.657	0.418
Ongoing psychotherapy, n (%) (n = 378)					
Any psychotherapy	114 (30.2)	58 (27.5)	56 (33.5)	1.6	0.203

(*continued on next page*)

Table 1 (*continued*)

Characteristics of MDD patients	Total sample (n = 436)	AD combination (n = 245)	SGA augmentation (n = 191)	x^2/F	p-value (x^2/ ANCOVA)
Cognitive behavioral therapy	74 (19.6)	39 (18.5)	35 (21.0)	4.1	0.398
Psychoanalytic psychotherapy	15 (4.0)	5 (2.4)	10 (6.0)		
Systemic psychotherapy	8 (2.1)	5 (2.4)	3 (1.8)		
Other psychotherapy	17 (4.5)	9 (4.3)	8 (4.8)		
Ongoing psychopharmacotherapy					
Number of concurrently administered psychopharmaco-therapeutics, mean (SD)	2.9 (0.8)	2.8 (0.8)	3.0 (0.9)	4.935	0.027
Administered first-line antidepressant treatment during the current MDE, n (%)					
Selective serotonin reuptake inhibitors	203 (46.6)	110 (44.9)	93 (48.7)	12.0	0.153
Serotonin-norepinephrine reuptake inhibitors	114 (26.1)	57 (23.3)	57 (29.8)		
Noradrenergic and specific serotonergic antidepressants	46 (10.6)	29 (11.8)	17 (8.9)		
Tricyclic antidepressants	30 (6.9)	17 (6.9)	13 (6.8)		
Agomelatine	8 (1.8)	7 (2.9)	1 (0.5)		
Noradrenaline-dopamine reuptake inhibitors	16 (3.7)	12 (4.9)	4 (2.1)		
Serotonin antagonist and reuptake inhibitors	17 (3.9)	12 (4.9)	5 (2.6)		
Monoamine oxidase inhibitors	1 (0.2)	0 (0.0)	1 (0.5)		
Noradrenaline reuptake inhibitors	1 (0.2)	1 (0.4)	0 (0.0)		
AD daily doses given in fluoxetine equivalents[c], mean (SD), mg/day (n = 386)	43.5 (25.8)	41.3 (29.4)	46.3 (20.0)	4.343	0.038
Further psychopharmacotherapeutic strategies administered together with the ongoing antidepressant treatment, n (%)					
Augmentation with at least 1 mood stabilizer	69 (15.8)	29 (11.8)	40 (20.9)	6.7	**0.010**
Augmentation with pregabalin	58 (13.3)	31 (12.7)	27 (14.1)	0.2	0.651
Augmentation with at least 1 low-potency antipsychotic agent[d]	40 (9.2)	29 (11.8)	11 (5.8)	4.8	0.029
Augmentation with benzodiazepines including zolpidem and zopiclone	190 (43.6)	93 (38.0)	97 (50.8)	7.2	**0.007**

The p-values displayed in bold were significant after Bonferroni-Holm correction.

[a] The presence of the current suicidal risk was measured based on the HAM-D item 3 (suicidality) ratings. While the absence of the current suicidal risk was based on an item-score of 0 (absent), the presence of the current suicidal risk was represented by item-scores of 1 (feels life is not worth living), 2 (wishes to be dead or any thoughts of possible death to self), 3 (suicide ideas or gestures) or 4 (suicide attempts) (Dold et al., 2018a).

[b] Non-response was defined by a previous single failed trial and treatment resistance by two or more failed trials.

[c] Fluoxetine dose equivalents were calculated according to Hayasaka et al. (2015).

[d] Low-potency antipsychotics comprise the so-called low-potency first-generation antipsychotics and the second-generation antipsychotic quetiapine <100 mg/day (Dold et al., 2016). Abbreviations (alphabetical order): ADs = antidepressants; ANCOVA = analysis of covariance; 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; MDE = major depressive episode; n = number of participants; SD = standard deviation; SGAs = second-generation antipsychotics.

Table 2
Posthoc binary logistic regression analyses investigating the association between the variables identified as significant in our primary analyses in 436 MDD patients and the respective additional psychopharmacotherapy.

Characteristics of MDD patients	Adjusted OR (95% CI)/ B ± SE	*p*-value
Additional psychotic features	2.5 (1.398–4.524)	**0.002**
Duration of psychiatric inpatient care during the lifetime in weeks	−0.016 ± 0.007	**0.020**
Augmentation with at least 1 mood stabilizer	1.9 (1.103–3.158)	**0.020**
Augmentation with benzodiazepines including zolpidem and zopiclone	1.7 (1.147–2.483)	**0.008**

Table 2 displays results of our *post-hoc* binary logistic regression analyses in 436 MDD patients. Only variables identified as statistically significant in our primary analyses (indicated in bold in Table 1) were considered. Adjusted ORs with 95% CIs are presented for categorical independent variables, while Bs with SEs are presented for continuous independent variables, quantifying the association between the eligible variables and the choice of SGA augmentation over AD combination serving as the dependent dichotomous variable. The present regression analysis was adjusted for the variable research center. Significant *p*-values are displayed in bold. Abbreviations (alphabetical order): B = regression coefficient; CI = confidence interval; MDD = major depressive disorder; OR = odds ratio, SE = standard error.

be supported by the fact that the severity of depressive symptoms and treatment outcome patterns during the current MDE did not significantly differ between patient groups, and that trazodone and mirtazapine represent frequently prescribed ADs, especially due to their potential to optimally target insomnia in MDD (Fagiolini et al., 2012; Dold et al., 2016; Bauer, Severus et al., 2017; Dold and Kasper, 2017). Also here, the adherence of European psychiatrists to the current clinical practice guidelines (CPGs) recommending the combination of ADs with complementary modes of action as SSRIs/SNRIs with SARIs/NaSSAs (Bauer, Severus et al., 2017, Dold and Kasper, 2017) might be further reflected. Some SGAs, especially lower dosages of quetiapine, are also frequently used to combat sleep disturbances (Riemann et al., 2017), however, our data indicate that AD combinations may be preferred over SGA augmentation, most likely for reasons of better tolerability and acceptability (Ucok and Gaebel, 2008).

With respect to clinical factors going along with chronicity, previous reports detected associations with SGA augmentation and the number of previous MDEs (Garcia-Toro et al., 2012) which was, however, not replicated in our study. Nevertheless, it is noteworthy that our MDD patients treated with SGAs spent twice as much time as inpatients in psychiatric wards compared to those receiving AD combination treatment. The longer duration of treatment as inpatients in the SGA add-on group suggests that SGAs were used in later phases of failure than AD combination. It might be surprising in this context that inpatient status during the current MDE was not related to either treatment optimization strategy, even though it might appear intuitive that current inpatient or outpatient status would influence the choice of AD combination versus SGA augmentation. Additionally, previous evidence repeatedly associated psychiatric and somatic comorbidities, especially personality disorders, substance abuse- and anxiety disorders with SGA augmentation in MDD (Lin et al., 2014; Gobbi et al., 2018). In fact, we observed a trend for higher rates of anxiety disorders in MDD patients receiving SGA augmentation, while higher rates for somatic comorbidities were associated with AD combination treatment. The latter findings, however, narrowly missed statistical significance. Since the presence of severe

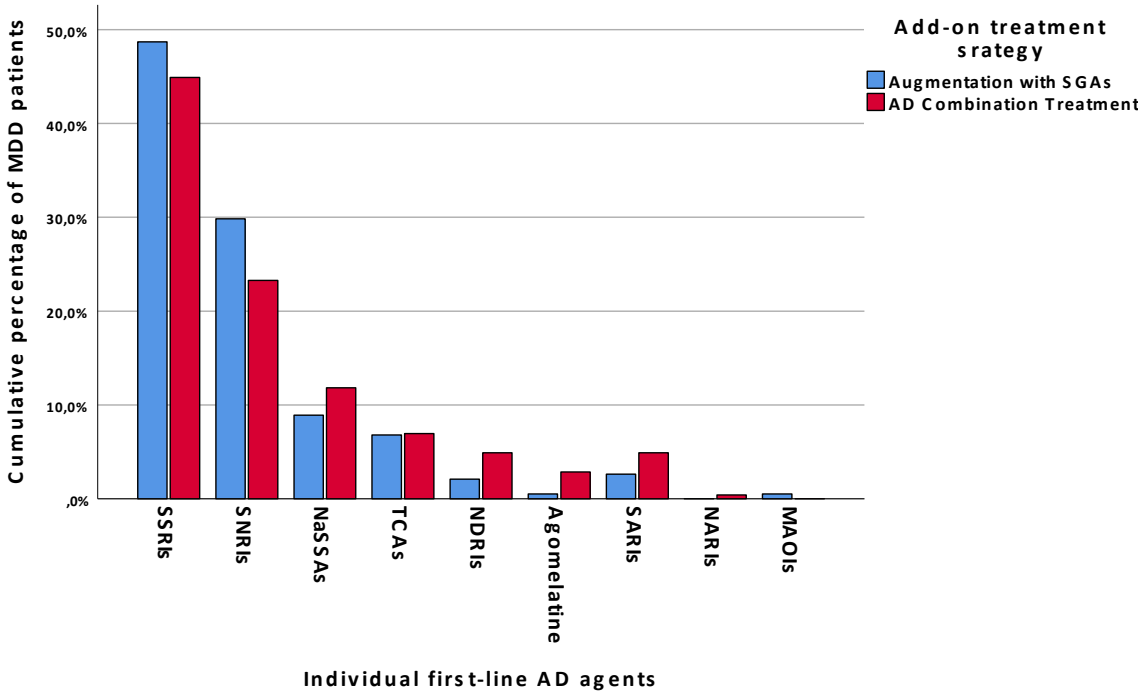

Fig. 1. First-line AD treatment administered in MDD patients receiving either SGA augmentation or AD combination treatment.
Displayed cumulative percentages refer to the first-line AD treatment administered in MDD patients receiving either augmentation with SGAs (n = 191) or AD combination (n = 245) as additional treatment strategy. Abbreviations: AD = antidepressant; ADs = antidepressants; MAOIs = monoamine oxidase inhibitors; MDD = major depressive disorder; NARIs = noradrenaline reuptake inhibitors; NaSSAs = noradrenergic and specific serotonergic ADs; NDRIs = noradrenergic-dopamine reuptake inhibitors; SARIs = serotonin antagonist and reuptake inhibitors; SGAs = second-generation antipsychotics; SNRIs = serotonin- norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic ADs.

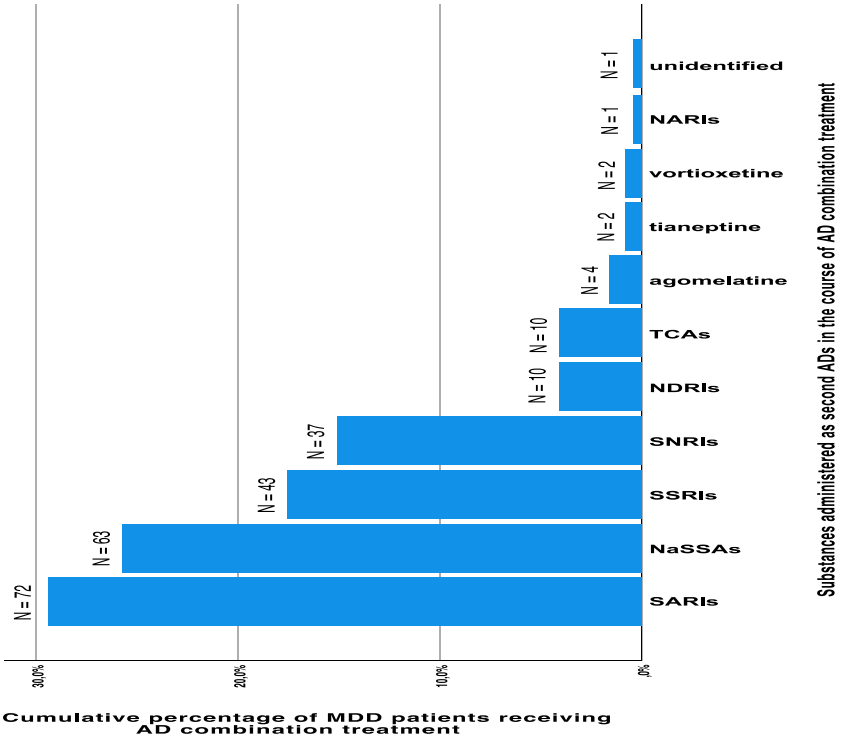

Fig. 2. Individual ADs administered as second AD treatment in MDD patients undergoing AD combination additionally to the ongoing first-line AD treatment.
Displayed cumulative percentages refer to the patient group receiving AD combination treatment additionally to their ongoing first-line AD treatment (n = 245) itemized according to the individual AD agents administered as the second AD treatment, whereby the respective number of MDD patients is provided for each second-line AD treatment. SARIs were administered in 29.4%, NaSSAs in 25.7%, SSRIs in 17.6%, SNRIs in 15.1%, NDRIs in 4.1%, TCAs in 4.1%, agomelatine in 1.6%, tianeptine in 0.8%, vortioxetine in 0.8% and NARIs in 0.4% of the patients. The exact AD agent administered in the course of combination treatment was not available for one patient. Abbreviations: AD = antidepressant; ADs = antidepressants; MDD = major depressive disorder; NARIs = noradrenaline reuptake inhibitors; NaSSAs = noradrenergic and specific serotonergic ADs; NDRIs = noradrenergic-dopamine reuptake inhibitors; SARIs = serotonin antagonist and reuptake inhibitors; SNRIs = serotonin- norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic ADs.

personality- and current substance abuse disorders represented predefined exclusion criteria for patient recruitment in our study to avoid any confounding of the findings, we cannot provide any supporting evidence in this regard.

In terms of individual symptoms, the identified association between SGA augmentation and the occurrence of psychotic features during the

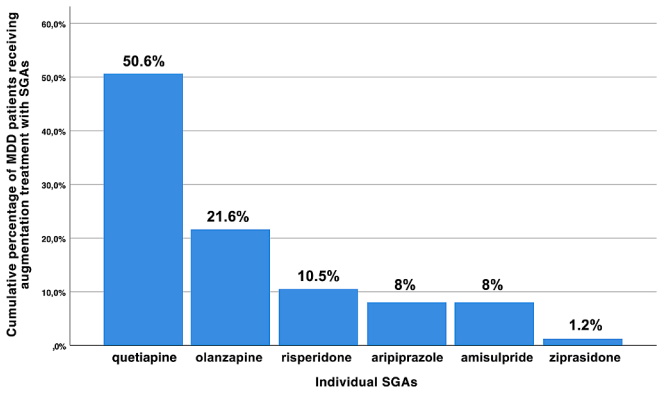

Fig. 3. Individual SGAs administered in MDD patients as augmentation treatment additionally to the ongoing first-line AD treatment.
Displayed cumulative percentages refer to the patient group receiving SGA augmentation treatment additionally to their ongoing first-line AD treatment (n = 191). Abbreviations: AD = antidepressant; ADs = antidepressants; MDD = major depressive disorder; SGAs = second-generation antipsychotics.

current MDE represents one of our most robust findings, as it is in line with previous international reports (Garcia-Toro et al., 2012; Keller et al., 2017; Dold et al., 2019). This circumstance might be explained by the fact that the treatment of psychotic depression is specifically addressed in the vast majority of CPGs worldwide and, secondly, the preference of SGA augmentation in this regard appears to be highly consistent (Bayes and Parker, 2018). A clear superiority of AD augmentation with a SGA in acute psychotic depression compared to monotherapy with either substance was evidenced meta-analytically (Farahani and Correll, 2012). However, clinicians tend to adhere to the guidelines in half of the cases according to previous findings (Craig et al., 2007). In our sample, 64% of the patients who exhibited psychotic symptoms were dispensed SGAs in addition to their first-line AD treatment, which represents a modest increase compared to the cited study, but still one third of the affected patients failed to be treated according to the current state-of-the-art, which could represent a potentially limiting factor that might have hindered them in achieving optimum treatment outcomes.

We also found higher odds of current suicidal risk in patients receiving SGA augmentation, even though this result did not reach statistical significance after correction for multiple comparisons. It is relevant to mention in this regard that augmentation of the ongoing AD with risperidone yielded promising results regarding anti-suicidal effects in one clinical trial that, however, needs to be confirmed in larger samples (Reeves et al., 2008). Clozapine represents the only modern antipsychotic substance that is approved for reducing suicidal risk albeit only in schizophrenia but this compound may also exert a certain anti-suicidal potential in affective disorders along with quetiapine, olanzapine or aripiprazole for instance (Pompili et al., 2016). Quetiapine and olanzapine have known and rapid calming effects, and they represented the most commonly dispensed SGAs in our sample, suggesting that these effects are usually preferred by clinicians when fast-acting agents with potent AD and tranquilizing effects are needed for challenging clinical manifestations such as suicidality. The latter assumption is in line with our finding of higher rates of BZD co-administration in MDD patients augmented with SGAs, since BZDs are frequently administered in suicidal patients due to their immediate sedating effects (Dold et al., 2020a). The fact that our MDD patients who received augmentation with SGAs were also prescribed MSs more frequently might represent additional important support in this regard, as lithium and, to a lesser extent, antiepileptic drugs with potent MS properties are known to be meaningful players to treat suicidality in MDD (Tondo and Baldessarini, 2016). In this context, it is noteworthy that the increasing implementation of novel add-on substances exhibiting rapid onset of AD and anti-suicidal effects like esketamine embodies a crucial progress in the treatment of MDD, especially when potential adverse effects may occur in the course of complex polypsychopharmacotherapies (Bauer, Severus et al., 2017; Dold and Kasper, 2017; Gunduz-Bruce et al., 2019; Kraus et al., 2019; Dold et al., 2020b; Kasper et al., 2020; Sanders Benjamin, 2021).

Our MDD patients undergoing SGA augmentation received a higher overall number of psychopharmacotherapeutics as compared to patients with AD combination treatment. Furthermore, the daily dosages of the administered first-line ADs were higher in case of SGA augmentation, which corresponds with previous evidence (Lin et al., 2014; Rhee and Rosenheck, 2019). It might be of interest that dose escalation beyond standard dosages does not rank among recommended psychopharmacotherapeutic strategies according to current CPGs due to the potentially increased risk of side-effects and missing evidence for a better outcome (Dold et al., 2017). Obviously, the simultaneous administration of SGAs, mostly quetiapine and olanzapine, BZDs and MSs together with the higher-dosed first-line AD treatment might reflect the more severe illness profile of the respective patients exhibiting psychotic symptoms, suicidality and/or comorbid anxiety disorders. This assumption is underlined by existing evidence that found loading of agents with sedative properties to be a marker for illness severity in MDD (Wang et al., 2019; Dold et al., 2020a). Taken together, the elevated AD daily dosages as well as the overall higher number of the administered psychopharmacotherapeutics together with the greater requirement for psychiatric inpatient care over the lifetime observed in our MDD patients augmented with SGA might reflect the generally increased therapeutic efforts undertaken by clinicians to overcome the severe symptomatology of these patients.

Although our MDD patients receiving SGA augmentation differed from those with AD combination treatment in terms of suicidality, psychotic symptoms and increased therapeutic efforts, representing phenomena that were repeatedly related to TRD (Gobbi et al., 2018; Bartova et al., 2019; Kraus et al., 2019) and difficult-to-treat depression (McAllister-Williams et al., 2020), the severity of depressive symptoms in general and the treatment outcome patterns differentiating between response, non-response and TRD in the course of the current MDE were comparable between both patient groups. A smaller Canadian study comparing the two treatment strategies in 86 patients with TRD observed a greater decrease in mean scores of the MADRS and the HAM-D in patients receiving SGA augmentation (Gobbi et al., 2018). Accordingly, the authors support the current international guidelines recommending SGA augmentation as a first-line additional treatment option in TRD. In our sample of MDD patients, not only comprising individuals with TRD, we observed an inverse prescription approach compared to Gobbi and colleagues with more patients receiving AD combination therapies. Consequently, we hypothesize that the treatment outcome rates observed in our study may have theoretically been affected by a selection bias, whereby we suppose a reluctance of SGA administration in patients with a more beneficial clinical profile by psychiatrists in charge.

The present secondary analyses were conducted in a real-world population of MDD patients derived from in- and outpatient units of academic as well as non-academic centers in eight European countries (Souery, Oswald et al., 2007; Schosser et al., 2012; Bartova et al., 2019). It differs from most RCTs in terms of the heterogeneous clinical manifestations of MDD, including suicidality and/or additional psychotic, atypical, catatonic and/or melancholic features, psychiatric and somatic comorbidities, and the varying disease severity and course, ranging from single to recurrent MDEs, with mild to severe extent of the current depressive symptoms. Such a varying clinical picture may best reflect the everyday routine in different countries and may, hence, represent a relevant strength. On the other hand, the potentially related cross-site differences cannot be fully ruled out, even though the variable "research center" was included in the present statistical analyses.

This study represents a part of a large multi-site GSRD project

(Souery, Oswald et al., 2007, Schosser et al., 2012, Bartova et al., 2019) that was not originally designed to compare augmentation and combination therapies in MDD. A possible selection bias inherent to the open treatment design and the lack of a control group and randomization has to be carefully considered when interpreting the aforementioned results. Generally, the fact that the psychiatrists´ choice to administer either AD combination or SGA augmentation may rely on different clinical conditions *per se* may represent a generally limiting factor in this regard. Since current international treatment guidelines recommend both, AD combination and SGA augmentation, as evidence-based optimization strategies in case of insufficient response to the initial AD psychopharmacotherapy, we deem our approach justifiable. Because the number of patients receiving individual SGAs and ADs for augmentation/combination were small, they were pooled producing two larger groups. It is, hence, noteworthy in this context that the identified contrasts evidenced groupwise may not reflect differences in individual substances. With respect to the applied ADs as well as SGAs, it might be of further note that we did not distinguish between the extended and immediate release formulations of the respective individual agents given the different formulation availabilities across the participating European countries.

With respect to the applied psychopharmacotherapy in general, we are aware of further treatment options that are recommended by international treatment guidelines alongside with SGA augmentation and AD combination that were, however, not considered due to the given study design. For example, switching from one AD agent to another one, representing a psychopharmacotherapeutic strategy that is endorsed in case of definite non-response and/or intolerable side-effects (Bauer, Severus et al., 2017; Dold and Kasper, 2017), was not investigated in the present study. It is worthwhile to note in this context that in our previous investigations (Souery et al., 2011) as well as a recent meta-analysis (Bschor et al., 2018), switching among AD substances failed to demonstrate a superiority in terms of treatment outcome. It should be further taken into account that our MDD patients received exclusively conventional treatments, while promising off-label compounds (Sanches et al., 2021; Tundo et al., 2021) or innovative add-on medications including esketamine, that has recently been approved as very effective psychopharmacotherapeutic agent in case of insufficient response to AD treatment in MDD (Kraus et al., 2019; Kasper et al., 2020; Sanders Benjamin, 2021), have not yet been considered. It is of additional note in the context of the administered medication that we adhered to the traditional indication-based nomenclature instead of the increasingly recommended Neuroscience based Nomenclature (Zohar et al., 2015; Frazer and Blier, 2016) in order to guarantee comparability with our previous reports and available international literature.

The probably most important limitation is inherent to the predominant cross-sectional study design with the retrospective assessment of treatment outcome that does not allow us to draw any causal conclusions. Clearly acknowledging that this procedure yields less accurate results than prospective evaluations derived from longitudinal RCTs, it should be highlighted in this context that recent evidence unequivocally confirmed the ability of MDD patients to precisely remember and report retrospective symptoms of their past MDEs even months thereafter (Dunlop et al., 2019). It is noteworthy in this context that our treatment outcome measures were calculated based on the total score reduction between the rMADRS, representing a time-point when the depressive symptoms reached their maximum (at least four weeks before study enrollment), and the cMADRS, referring to a time-point of study entry (at least after four weeks of an adequate psychopharmacotherapy). Hence, the respective variables reflecting reduction of depressive symptoms during the current MDE might be regarded as longitudinal measures, and may further provide hints towards causality. In order to warrant continuous accuracy minimizing the risk of inappropriate rating and bias, all study ratings were exclusively performed by experienced psychiatrists who were specifically trained for the respective evaluations.

5. Conclusion

A more severe presentation of MDD including the presence of psychotic features and a longer duration of psychiatric hospitalizations during the lifetime might guide clinicians towards choosing SGAs augmentation rather than AD combination. Accordingly, more severely ill patients might rather be deemed eligible for augmentation with SGAs than AD combination that was, however, dispensed in the majority of our MDD patients. Such supposedly increased illness severity in patients prescribed SGAs might also be the reason for the observed co-augmentation with BZDs and MSs as well as the higher daily dosages of the first-line ADs. Despite clear, evidence-based recommendations in the most guidelines for SGA augmentation in MDD patients who experience psychotic features this strategy was used in only two out of three patients with psychotic depression. Eventually, patients with a rather unfavorable disease profile who often receive complex polypsychopharmacotherapies with uncertain benefits may profit more from fast-acting agents with potent AD, anti-suicidal and tranquilizing effects. New glutamatergic substances lacking addiction potential, which have even shown superior efficacy as compared to SGAs, seem to be very promising in this regard (Dold et al., 2020a; McIntyre et al., 2021).

Disclosure statement

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. Dold has received travel grants and consultant/speaker honoraria from Medizin Medien Austria and Janssen. Dr. Fabbri has served as speaker for Janssen. 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. Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. 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. 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 received grants/research support, consulting fees, and/or honoraria from Angelini, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd., sun Pharma and Takeda. All other authors declare that they have no conflicts of interest.

Ethical statement

We testify on behalf of all co-authors that our article submitted to Progress in Neuro-Psychopharmacology & Biological Psychiatry entitled "Evidence on Sociodemographic and Clinical Correlates of Antidepressant Combination or Augmentation with Second-Generation Antipsychotics in Major Depressive Disorder" has not been previously published elsewhere, and is not currently being considered for publication in another journal. All authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves

jointly and individually responsible for its content.

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Statement of ethics

The present research complies with internationally-accepted standards for research practice and reporting, and has been performed with approvals of appropriate ethics committees and with appropriate participants' informed consent in compliance with the Helsinki Declaration.

Author contributions

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.

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