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Clinical correlates of augmentation/combination treatment strategies in major depressive disorder

Dold M, Bartova L, Mendlewicz J, Souery D, Serretti A, Porcelli S, Zohar J, Montgomery S, Kasper S. Clinical correlates of augmentation/combination treatment strategies in major depressive disorder.

Objective: This multicenter, multinational, cross-sectional study aimed to investigate clinical characteristics and treatment outcomes associated with augmentation/combination treatment strategies in major depressive disorder (MDD).
Method: Sociodemographic, clinical, and treatment features of 1410 adult MDD patients were compared between MDD patients treated with monotherapy and augmentation/combination medication using descriptive statistics, analyses of covariance (ANCOVA), and Spearman's correlation analyses.
Results: 60.64% of all participants received augmentation and/or combination strategies with a mean number of 2.18 ± 1.22 simultaneously prescribed psychiatric drugs. We found male gender, older age, Caucasian descent, higher weight, low educational status, absence of occupation, psychotic symptoms, melancholic and atypical features, suicide risk, in-patient treatment, longer duration of hospitalization, some psychiatric comorbidities (panic disorder, agoraphobia, obsessive-compulsive disorder, and bulimia nervosa), comorbid somatic comorbidity in general and concurrent hypertension, thyroid dysfunction, diabetes, and heart disease in particular, higher current and retrospective Montgomery and Åsberg Depression Rating Scale total scores, treatment resistance, and higher antidepressant dosing to be significantly associated with augmentation/combination treatment. These findings were corroborated when examining the number of concurrently administered psychiatric drugs in the statistical analyses.
Conclusion: Our findings suggest a clear association between augmentation/combination strategies and treatment-resistant/difficult-to-treat MDD conditions characterized by severe symptomatology and high amount of psychiatric and somatic comorbidities.

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Key words: major depressive disorder; augmentation; combination; treatment response; comorbidities

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Significant outcomes

- 60.64% of the analyzed 1410 unipolar depressive patients received augmentation/combination treatment with a mean number of simultaneously administered psychiatric drugs of 2.18 ± 1.22.
- In comparison with the prescription rates of augmentation/combination strategies in previous surveys, we found an increased administration of add-on medications in major depressive disorder (MDD). Thus, the trend of using polypharmaceutical treatment strategies in MDD is still increasing.
- Establishing augmentation/combination treatment strategies was significantly associated with treatment-resistant/difficult-to-treat MDD conditions characterized by severe depressive symptomatology, high suicide risk, and high amount of psychiatric and somatic comorbidities.

Limitations

- The participants were enrolled from tertiary care settings (university/academic psychiatric treatment centers) and might be therefore not representative for MDD populations in primary care settings.
- Due to the observational cross-sectional design of this multicenter study, treatment response could not be measured as accurately as in a prospective trial.

Introduction

A considerable number of patients with major depressive disorder (MDD) do not respond adequately to antidepressant monotherapy (1). Therefore, treatment resistance represents one of the most important clinical challenges in the pharmacological management of MDD. As dose escalation of the current antidepressant (2, 3) and a switch to another, new antidepressant compound (4) after insufficient response to a previous antidepressant cannot be generally recommended as evidence-based treatment option, augmentation and/or combination strategies are commonly applied in the clinical routine care to improve treatment response (5, 6). Usually, combination treatment is defined by the simultaneous administration of two drugs of the same substance group such as two antidepressants and augmentation by the concomitant use of two drugs of different substance classes, for example, the coadministration of an antidepressant together with an antipsychotic drug. Some augmentation treatments can be regarded as well-established treatment option in treatment-resistant MDD. For instance, the efficacy of the second-generation antipsychotics (SGA) (7) and lithium (8–10) as augmenting agents to antidepressants could be demonstrated in a large number of randomized clinical trials and meta-analyses. Therefore, current treatment guidelines consistently recommend these augmentation strategies as evidence-based therapeutic approach in treatment-resistant MDD (11, 12). Moreover, some SGAs received the official approval for this indication by regulatory authorities as augmenting agents of antidepressants (e.g., quetiapine XR in the USA and Europe, aripiprazole in the USA, and olanzapine in combination with fluoxetine in the USA). Accordingly, pharmacoepidemiological surveys consistently revealed a substantial increase in augmentation/combination treatment strategies in general and SGA prescriptions in particular in MDD over the last decades (5, 13, 14).

However, despite the frequent use of augmentation/combination in MDD, there is an enormous lack of studies adequately investigating this phenomenon, especially in terms of the sociodemographic and clinical factors associated with augmentation/combination treatment.

Aims of the study

The main aims of the present international, multicenter, cross-sectional trial were (i) to explore the prevalence of augmentation/combination treatment strategies in our naturalistic MDD patient sample, (ii) to investigate differences in sociodemographic, clinical, and treatment features between patients receiving augmentation/combination and antidepressant monotherapy, and (iii) to determine between-group differences of these features with regard to the mean number of concurrently administered psychiatric drugs. Moreover, (iv) explanatory variables associated with augmentation/combination treatment were identified using a binary logistic regression method and (v) the association between the number of prescribed psychiatric drugs and depressive symptom severity was examined applying correlation analyses.

Material and methods

Study design

This international, multicenter, cross-sectional study with retrospective assessment of treatment response was conducted by the European 'Group for the Study of Resistant Depression (GSRD)' between November 2011 and September 2016. A total of 10 academic sites across eight European countries (Austria, Belgium, France, Germany, Greece, Israel, Italy, and Switzerland) took part in this project. All participants provided written informed consent before inclusion, and the study was approved by the ethics committees of the recruiting sites.

Participants

Male and female in- and out-patients (aged ≥18 years) with a Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR diagnosis

of MDD (single episode 296.2X or recurrent episodes 296.3X; confirmed by the Mini-International Neuropsychiatric Interview [MINI] (15)) were enrolled. Patients were required to receive ≥1 antidepressant trial during their present MDD episode (≥4 weeks in adequate dose [Table S1]) prior to study entry. Patients were excluded if they had (i) any current primary psychiatric disorder other than MDD, (ii) any substance disorder (except nicotine and caffeine) in the previous 6 months, or (iii) any concurrent severe personality disorder. All patients receiving treatment in one of the 10 participating centers during the recruitment period were screened for meeting the inclusion criteria. If eligible, study participation was offered.

Data collection

Sociodemographic, clinical, treatment, and pharmacological information of all participants were obtained during a clinical interview which was specifically accomplished for this study (cross-sectional data collection process). The interviews were performed by specifically trained psychiatrists of the referral recruitment centers using standardized online case report forms and comprised also specific questionnaires (e.g., the MINI). The interview was supplemented by a review of medical records. All collected data were subsequently entered in an online database. In the specific interview, severity of depression was evaluated by the Montgomery and Åsberg Depression Rating Scale (MADRS) (16) and the 17- and 21-item Hamilton Rating Scale for Depression (HAM-D) (17). For every included patient, two MADRS scores were estimated: (i) a MADRS at the timepoint of the cross-sectional data collection process ('current MADRS') and (ii) a so-called retrospective MADRS measuring the symptom severity at the onset of the current MDD episode. This retrospective MADRS rating was based on the patients' information during the clinical interview. Moreover, the rater could additionally consider medical records to estimate the retrospective MADRS total score. Estimating the current and retrospective MADRS total score, we sought to calculate the MADRS total score change during the current MDD episode as a measurement for treatment response (retrospective MADRS score – present MADRS score). Non-response to the current treatment was defined by a MADRS total score of ≥22 and <50% MADRS total score reduction (from the onset of the present MDD episode) after one antidepressant trial (≥4 weeks duration in adequate dose, see Table S1). After treatment failures (MADRS total score of ≥22 and <50% MADRS total score improvement) to ≥2 consecutive adequate antidepressant trials, a patient was classified to be treatment resistant.

The outcome of this study was augmentation/combination treatment and the augmentation/combination patient group comprised participants receiving any kind of psychopharmacological add-on treatment in addition to their ongoing first-line antidepressant medication (i.e., either augmentation treatment, combination of at least two different antidepressant drugs, or both strategies simultaneously).

Statistical analyses

In this study, two variables were used to evaluate augmentation/combination treatment. First, patients were divided according to the administration of augmentation/combination strategies in a dichotomous manner (augmentation/combination-treated patients vs. monotherapy-treated patients). Second, the number of simultaneously administered psychiatric drugs served as variable. Descriptive statistics (means, standard deviations (SD), and/or percentages) were used to illustrate the sample characteristics. To investigate between-group comparisons, chi-squared tests were applied for categorical variables and analyses of covariance (ANCOVA) models including recruitment center as random factor for continuous variables. Whenever indicated, *post hoc* analyses were carried out to discriminate individual effects. Binary logistic regression analyses (with center as covariate) were performed to analyze the association between the independent variables and the use of augmentation/combination strategies as dichotomous dependent variable. To avoid a potential bias due to multiplicity, all variables were separately analyzed. Spearman's correlation analyses were employed to examine the association between the number of administered psychiatric drugs and the continuous variables yielded in this study. All *P*-values were two-tailed, and the significance level for all analyses was defined as $P \leq 0.05$. The data analyses were performed using the software SPSS, version 24.0.

Results

Study sample

Altogether, 2609 patients were screened regarding study participation and finally, 1410 participants with MDD could be included. Their main demographic and clinical characteristics are summarized in Table 1. Briefly, 96.17% of the enrolled subjects

Table 1. Patients' sociodemographic and clinical features stratified according to MDD patients treated with augmentation/combination strategies and antidepressant monotherapy

Characteristics	MDD sample total (n = 1410)	Augmentation/ combination (n = 855)	Monotherapy (n = 555)	x^2/F	d.f.	P-value (ANCOVA/x^2)
Gender, n (%)						
Male	467 (33.12)	304 (35.56)	163 (29.37)	5.81	1	0.02
Female	943 (66.88)	551 (64.44)	392 (70.63)			
Age, mean (SD), years	50.28 (14.11)	53.07 (14.28)	45.96 (12.71)	15.48	23.047	0.001
Marital status, n (%)						
Married/Live with	703 (49.86)	422 (49.36)	281 (50.63)	0.22	1	0.64
Single/Divorced/Separated/Widowed	707 (50.14)	433 (50.64)	274 (49.37)			
Ethnic origin, n (%)						
Caucasian	1356 (96.17)	834 (97.54)	522 (94.05)	11.13	1	0.001
Weight, mean (SD), kg	73.23 (16.80)	75.65 (17.23)	69.50 (15.41)	6.50	17.829	0.02
Educational status, n (%) (n = 1395)						
University education/Non-university high education/High Level general education	755 (54.12)	425 (50.24)	330 (60.11)	13.07	1	<0.001
General Secondary/Technical Education/Elementary School/ None	640 (45.88)	421 (49.76)	219 (39.89)			
Occupational status, n (%) (n = 1408)						
Employed	659 (46.80)	303 (35.52)	356 (64.14)	110.64	1	<0.001
Without occupation	749 (53.20)	550 (64.48)	199 (35.86)			
Depressive episode, n (%)						
Single	127 (9.01)	72 (8.42)	55 (9.91)	0.91	1	0.34
Recurrent	1283 (90.99)	783 (91.58)	500 (90.10)			
With psychotic features	154 (10.92)	125 (14.62)	29 (5.23)	30.53	1	<0.001
With melancholic features	856 (60.71)	625 (73.10)	231 (41.62)	139.86	1	<0.001
With atypical features	33 (2.34)	30 (3.51)	3 (0.54)	12.97	1	<0.001
Current suicide risk (dichotomous)*	649 (46.03)	451 (52.75)	198 (35.68)	39.49	1	<0.001
Degree of suicide risk in patients with current suicide risk, n (%) (n = 649)						
High/moderate	377 (58.09)	267 (59.20)	110 (55.56)	0.75	1	0.39
Low	272 (41.91)	184 (40.80)	88 (44.44)			
Treatment setting, n (%)						
In-patient	488 (34.61)	451 (52.75)	37 (6.67)	315.78	1	<0.001
Out-patient	922 (65.39)	404 (47.25)	518 (93.33)			
Duration of the current MDD episode, mean (SD), days	204.74 (164.64)	191.28 (170.06)	225.36 (153.91)	0.06	13.434	0.81
Number of MDD episodes during lifetime, mean (SD)	3.33 (2.45)	3.39 (2.58)	3.21 (2.17)	0.55	11.010	0.48
Age at onset of MDD, mean (SD), years	37.20 (15.44)	37.68 (15.92)	36.48 (14.66)	0.65	15.781	0.43
Duration of psychiatric hospitalizations during lifetime, mean (SD), weeks (n = 1328)	5.59 (20.45)	8.55 (25.57)	1.06 (4.74)	4.37	20.789	<0.05
Psychiatric comorbidities, n (%)						
Any anxiety disorder	294 (20.85)	183 (21.40)	111 (20.00)	0.40	1	0.53
Generalized anxiety disorder	151 (10.71)	89 (10.41)	62 (11.17)	0.20	1	0.65
Panic disorder	114 (8.09)	86 (10.06)	28 (5.05)	11.38	1	0.001
Agoraphobia	113 (8.01)	82 (9.59)	31 (5.59)	7.32	1	0.01
Social phobia	45 (3.19)	31 (3.63)	14 (2.52)	1.33	1	0.25
Obsessive-compulsive disorder	22 (1.56)	21 (2.46)	1 (0.18)	11.52	1	0.001
Posttraumatic stress disorder	20 (1.42)	16 (1.87)	4 (0.72)	3.19	1	0.07
Anorexia nervosa	1 (0.07)	1 (0.12)	0 (0.00)	0.65	1	0.42
Bulimia nervosa	8 (0.57)	6 (0.70)	2 (0.36)	4.28	1	0.04
Somatic comorbidities, n (%)						
Any somatic comorbidity	653 (46.31)	455 (53.22)	198 (35.68)	41.65	1	<0.001
Hypertension	267 (18.94)	223 (26.09)	44 (7.93)	72.25	1	<0.001
Thyroid dysfunction	204 (14.47)	152 (17.78)	52 (9.37)	19.23	1	<0.001
Migraine	156 (11.06)	78 (9.12)	78 (14.05)	8.32	1	0.004
Diabetes	84 (5.96)	65 (7.60)	12 (2.70)	10.49	1	0.001
Heart disease	72 (5.11)	60 (7.02)	12 (2.70)	16.37	1	<0.001
Arthritis	65 (4.61)	38 (4.44)	27 (4.86)	0.14	1	0.72
Asthma	48 (3.40)	30 (3.51)	18 (3.24)	0.07	1	0.79
HAM-D total 21-item, mean (SD)	19.78 (9.05)	19.88 (9.35)	19.62 (8.57)	0.29	12.651	0.59
HAM-D total 17-item, mean (SD)	18.76 (8.74)	18.63 (8.89)	18.96 (8.50)	0.48	12.841	0.49
HAM-D total 6-item, mean (SD)	9.53 (4.93)	9.45 (5.10)	9.63 (4.65)	1.10	14.055	0.31
MADRS total, mean (SD)	24.61 (11.29)	25.56 (11.53)	23.13 (10.73)	14.66	13.666	0.002
MADRS total at onset of current MDD episode, mean (SD)	34.06 (7.70)	35.44 (8.35)	31.95 (6.00)	13.10	12.760	0.003
MADRS total change (present MADRS–retrospective MADRS), mean (SD)	−9.36 (10.80)	−9.74 (11.04)	−8.77 (10.41)	1.18	11.041	0.30
Treatment response, n (%)						

Table 1. (Continued)

Characteristics	MDD sample total (n = 1410)	Augmentation/ combination (n = 855)	Monotherapy (n = 555)	x^2/F	d.f.	P-value (ANCOVA/x^2)
Response	346 (24.54)	198 (23.16)	148 (26.67)	7.84	2	0.02
Non-Response	492 (34.89)	285 (33.33)	207 (37.30)			
Resistance	572 (40.57)	372 (43.51)	200 (36.04)			
Psychopharmacotherapy						
Number of psychiatric drugs, mean (SD)	2.18 (1.22)	2.95 (0.97)	1.00 (0.00)	116.63	9.837	<0.001
Administered first-line antidepressant (in the current MDD episode), n (%)						
Selective serotonin reuptake inhibitors	734 (52.06)	402 (47.02)	332 (59.82)	95.14	10	<0.001
Serotonin-norepinephrine reuptake inhibitors	336 (23.83)	230 (26.90)	106 (19.10)			
Noradrenergic and specific serotonergic antidepressants	121 (8.58)	86 (10.06)	35 (6.31)			
Tricyclic antidepressants	74 (5.25)	55 (6.43)	19 (3.42)			
Agomelatine	69 (4.89)	17 (1.99)	52 (9.37)			
Noradrenaline-dopamine reuptake inhibitors	32 (2.27)	25 (2.92)	7 (1.26)			
Serotonin antagonist and reuptake inhibitors	28 (1.99)	28 (3.27)	0 (0.00)			
Vortioxetine	6 (0.43)	3 (0.35)	3 (0.54)			
Monoamine oxidase inhibitors	5 (0.35)	5 (0.58)	0 (0.00)			
Noradrenaline reuptake inhibitors	3 (0.21)	2 (0.23)	1 (0.18)			
Tianeptine	2 (0.14)	2 (0.23)	0 (0.00)			
Fluoxetine equivalents†, mean (SD), mg/day	39.86 (20.78)	42.50 (23.29)	36.06 (15.76)	10.55	13.032	0.01

d.f., degrees of freedom; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; n, number of participants; SD, standard deviation.

*Current suicide risk was assessed by clinical judgment.

†Fluoxetine dose equivalents were calculated according to Hayasaka et al. (2015).

were of Caucasian descent and the mean patient age was 50.28 ± 14.11 years. 66.88% were female, 65.39% received out-patient treatment, and 90.99% suffered from recurrent depressive episodes. The mean duration of the current depressive episode was 204.74 ± 164.64 days and the mean number of MDD episodes during lifetime amounted to 3.33 ± 2.45. Melancholic characteristics emerged in 60.71%, psychotic symptoms in 10.92%, and atypical features in 2.34% of the patients. 46.31% exhibited somatic comorbidities, 20.85% comorbid anxiety disorders, 1.56% concurrent obsessive-compulsive disorder (OCD), and 1.42% comorbid posttraumatic stress disorder (PTSD). Most of the participants were enrolled in Austria (29.60%), France (29.45%), Italy (14.62%), Germany (7.52%), and Greece (7.38%). At recruitment, severity of depression measured by the mean total scores of the MADRS and the 21-item HAM-D were 24.61 ± 11.29 and 19.78 ± 9.05 points, respectively. The mean retrospective MADRS total score amounted to 34.06 ± 7.70.

Augmentation/combination strategies in the MDD patient sample

60.64% of all included MDD patients (855 of 1409) were treated with augmentation/combination strategies, that is, they received at least two different psychiatric drugs at the same time. A total of 348 (24.68%) were treated with two, 269 (19.08%) with three, 177 (12.55%) with four, 54 (3.83%) with five, and seven (0.50%) with at least six different psychiatric drugs concurrently. The mean number of simultaneously administered drugs amounted to 2.18 ± 1.22. In the augmentation/combination group, the mean number was 2.95 ± 0.97. Antidepressant combination treatment was established in 29.50% of the patients. 33.06% received benzodiazepines (BZD)/BZD-like drugs, 25.67% antipsychotics, 11.28% mood stabilizers, 7.23% pregabalin, and 6.45% low-potency antipsychotics (comprising the so-called low-potency first-generation antipsychotics and the SGA quetiapine <100 mg/day) as augmenting agents to their ongoing pharmacotherapy with antidepressants (Fig. 1).

Clinical features associated with augmentation/combination medication

In comparison with monotherapy-treated MDD patients, a significantly higher proportion of patients receiving augmentation/combination exhibited male gender (35.56% vs. 29.37%, $P = 0.02$), Caucasian origin (97.54% vs. 94.05%, $P = 0.001$), a low level of education (49.76% vs. 39.89%, $P < 0.001$), no employment (64.48% vs. 35.86%, $P < 0.001$), psychotic features (14.62% vs. 5.23%, $P < 0.001$), melancholic features (73.10% vs. 41.62%, $P < 0.001$), atypical features (3.51% vs. 0.54%, $P < 0.001$), suicide risk (52.75% vs. 35.68%, $P < 0.001$), and in-patient treatment (52.75% vs. 6.67%, $P < 0.001$)

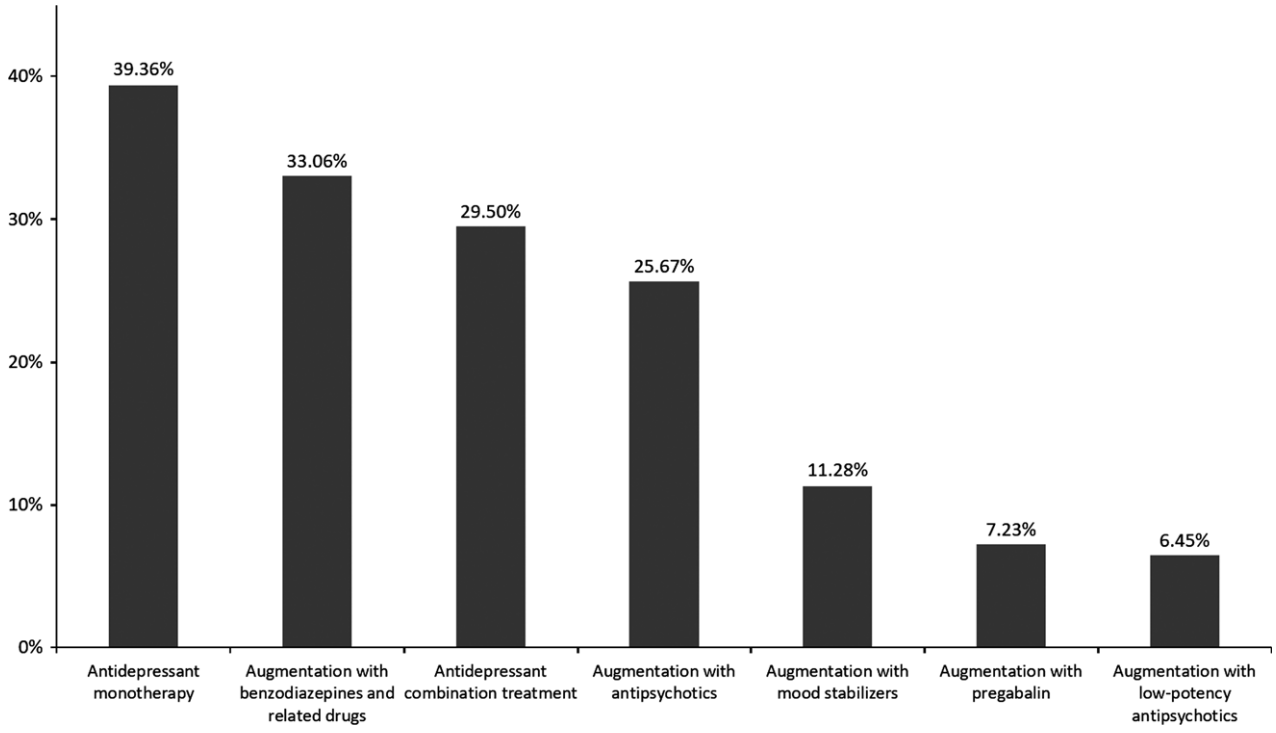

Fig. 1. Percentage of the 1410 MDD patients receiving antidepressant monotherapy or various augmentation and combination strategies itemized according to the different substance classes administered in addition to the ongoing medication with the antidepressant drug (≥1 drug of the relevant substance class had to be prescribed). The augmentation group low-dose antipsychotics comprised the so-called low-potency first-generation antipsychotic drugs and the SGA quetiapine <100 mg/day.

(Table 1). Furthermore, the augmentation/combination group displayed higher mean age (53.07 ± 14.28 years vs. 45.96 ± 12.71 years, $P = 0.001$), higher mean weight (75.65 ± 17.23 kg vs. 69.50 ± 15.41 kg, $P = 0.02$), and longer mean overall duration of hospitalizations due to MDD during lifetime (8.55 ± 25.57 weeks vs. 1.06 ± 4.74 weeks, $P < 0.05$). With regard to psychiatric comorbidities, a higher rate of comorbid panic disorder (10.06% vs. 5.05%, $P = 0.001$), comorbid agoraphobia (9.59% vs. 5.59%, $P = 0.01$), comorbid OCD (2.46% vs. 0.18%, $P = 0.001$), and comorbid bulimia nervosa (0.70% vs. 0.36%, $P = 0.04$) was found for augmentation/combination-medicated patients. Significantly more subjects treated with augmentation/combination medication suffered from a somatic comorbidity in general (53.22% vs. 35.68%, $P < 0.001$) and hypertension (26.09% vs. 7.93%, $P < 0.001$), thyroid dysfunction (17.78% vs. 9.37%, $P < 0.001$), diabetes (7.60% vs. 2.70%, $P = 0.001$), and heart disease (7.02% vs. 2.70%, $P < 0.001$) in particular, whereas the prevalence of migraine was lower in the augmentation/combination group (9.12% vs. 14.05%, $P = 0.004$). In terms of symptom severity, the current (25.56 ± 11.53 vs. 23.13 ± 10.73, $P = 0.002$) and retrospective (35.44 ± 8.35 vs. 31.95 ± 6.00, $P = 0.003$) MADRS total scores were higher in patients receiving augmentation/combination strategies than monotherapy. When evaluating response pattern, augmentation/combination-treated participants were more likely to be classified as being treatment resistant (43.51% vs. 36.04%, $P = 0.02$) and inversely, they showed a lower rate of treatment response (23.16% vs. 26.67%, $P = 0.02$). Concerning the applied first-line antidepressant treatment, the administered doses were higher in the augmentation/combination group (in fluoxetine equivalents calculated according to Hayasaka et al. (18): 42.50 ± 23.29 mg/day vs. 36.06 ± 15.76 mg/day, $P = 0.01$). Serotonin–norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), and serotonin antagonist and reuptake inhibitors (SARIs) were more often used in the context of augmentation/combination strategies, whereas selective serotonin reuptake inhibitors (SSRIs) and agomelatine were more frequently prescribed as monotherapy agents ($P < 0.001$, all percentages are indicated in Table 1).

We found no significant between-group difference for the variable 'duration of the current MDD episode'. However, without applying recruitment center as random factor in the ANCOVA

calculations, the MDD episode duration was significantly longer in the monotherapy than in the augmentation/combination group (225.36 ± 153.91 days vs. 191.28 ± 170.06 days, $P = 0.001$). For all other investigated variables, the use of recruitment center as random factor did not alter the findings with regard to statistically significant differences.

The same variables that yielded significant between-group differences in the chi-square tests and ANCOVAS were also statistically significantly associated with augmentation/combination medication in the logistic regression analyses. The odds ratios for all comparisons are displayed in Table 2.

Association between clinical features and the number of psychiatric drugs

When evaluating the impact of clinical and demographic features on the number of concurrently dispensed psychiatric drugs (Table 3), we found a significantly higher mean drug number in MDD patients characterized by Caucasian descent, low educational status, no employment, recurrent MDD, psychotic symptoms, melancholic characteristics, atypical features, in-patient treatment setting, comorbid agoraphobia, comorbid OCD, comorbid PTSD, comorbid somatic comorbidity, comorbid hypertension, comorbid thyroid disease, comorbid diabetes, comorbid heart disease, and treatment resistance. All mean numbers of the simultaneously prescribed psychiatric drugs are indicated in Table 3.

In the correlation analyses (Table 4), there was a positive correlation between the number of psychiatric drugs and age ($r = 0.248$, $P < 0.001$), weight ($r = 0.201$, $P < 0.001$), number of MDD episodes during lifetime ($r = 0.077$, $P = 0.01$), duration of hospitalizations due to MDD during lifetime ($r = 0.545$, $P < 0.001$), the 21-item HAM-D total score ($r = 0.068$, $P = 0.01$), the MADRS total score ($r = 0.181$, $P < 0.001$), the retrospective MADRS total score ($r = 0.279$, $P < 0.001$), and the antidepressant dosing expressed by fluoxetine equivalents ($r = 0.181$, $P < 0.001$). A negative correlation was found for the duration of the current MDD episode ($r = -0.219$, $P < 0.001$).

Discussion

In this European multicenter, cross-sectional study, 60.64% of all 1410 MDD patients received

Table 2. Binary logistic regression analyses investigating the association between explanatory variables and the administration of augmentation/combination treatment

	B	SE	Adjusted OR	95% CI	*P*-value
Male gender	0.29	0.12	1.33	1.06–1.67	0.02
Age	0.04	0.01	0.75	0.60–0.95	<0.001
Caucasian descent	0.92	0.29	2.51	1.44–4.38	0.001
Weight	0.02	0.01	1.02	1.02–1.03	<0.001
High educational level	−0.40	0.11	0.67	0.54–0.84	<0.001
Employment	−1.18	0.11	0.31	0.25–0.38	<0.001
Psychotic features	1.14	0.21	3.11	2.04–4.74	<0.001
Melancholic features	1.34	0.12	3.80	3.03–4.76	<0.001
Atypical features	1.90	0.61	6.71	2.04–2.22	0.002
Current suicide risk (dichotomous)*	0.70	0.11	2.01	1.61–2.50	<0.001
In-patient treatment	2.75	0.18	15.63	10.99–22.22	<0.001
Duration of psychiatric hospitalizations during lifetime	0.21	0.02	1.24	1.19–1.29	<0.001
Comorbid panic disorder	0.75	0.23	2.11	1.36–3.28	0.001
Comorbid agoraphobia	0.59	0.22	1.80	1.17–2.75	0.01
Comorbid obsessive-compulsive disorder	2.65	1.03	1.41	1.89–111.11	0.01
Comorbid bulimia nervosa	1.54	0.82	4.66	1.04–23.15	<0.05
Any comorbid somatic comorbidity	0.72	0.11	2.06	1.65–2.56	<0.001
Comorbid hypertension	1.41	0.18	4.10	2.91–5.78	<0.001
Comorbid thyroid dysfunction	0.74	0.17	2.10	1.50–2.92	<0.001
Comorbid migraine	−0.49	0.17	0.61	0.44–0.86	0.004
Comorbid diabetes	0.84	0.27	2.33	1.38–3.92	0.002
Comorbid heart disease	1.23	0.32	3.42	1.82–6.41	<0.001
MADRS total, current	0.02	0.01	1.02	1.01–1.03	<0.001
MADRS total, at onset of the present MDD episode	0.06	0.01	1.07	1.05–1.08	<0.001
Achievement of treatment response	−0.17	0.07	0.84	0.73–0.96	0.01
Number of psychiatric drugs	12.17	1.42	192240	11985–3083384	<0.001
Administered first-line antidepressant (in the current MDD episode)	−0.06	0.03	0.94	0.88–0.99	0.04
Fluoxetine equivalents	0.02	0.01	1.02	1.01–1.03	<0.001

B, regression coefficient; CI, confidence interval; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; OR, odds ratio; SE, standard error.
*Current suicide risk was assessed by clinical judgment.
The present table displays all variables that are associated with augmentation/combination treatment. Due to limited space and to ensure enhanced readability, exclusively the statistically significant results are presented. The odds ratios (ORs) are adjusted for the covariate recruitment center.

Table 3. Mean numbers of simultaneously administered psychiatric drugs for dichotomous sociodemographic and clinical characteristics

Characteristics	*n*	Number of psychiatric drugs, mean (SD)	x^2/F	*P*-value (ANCOVA)
Gender, *n* (%)				
Male/Female	467/943	2.27 (1.21)/2.14 (1.22)	3.16	0.08
Marital status, *n* (%)				
Married, Live with/Single, Divorced, Separated, Widowed	703/707	2.17 (1.21)/2.20 (1.23)	0.28	0.60
Ethnic origin, *n* (%)				
Caucasian/Non-Caucasian	1356/54	2.21 (1.22)/1.63 (0.92)	11.70	0.001
Educational status, *n* (%) (*n* = 1395)				
University education, Non-university high education, High Level general education/General Secondary, Technical Education, Elementary School, None	755/640	2.11 (1.23)/2.27 (1.20)	5.70	0.02
Occupational status, *n* (%) (*n* = 1408)				
Employed/Without occupation	659/749	1.86 (1.13)/2.47 (1.22)	94.10	<0.001
Depressive episode, *n* (%)				
Single/Recurrent	127/1283	1.94 (1.04)/2.21 (1.23)	5.38	0.02
With psychotic features	154/1256	2.74 (1.19)/2.12 (1.20)	37.00	<0.001
With melancholic features	856/554	2.51 (1.24)/1.68 (0.99)	173.46	<0.001
With atypical features	33/1377	2.79 (1.02)/2.17 (1.22)	8.35	0.004
Current suicide risk (dichotomous)*	649/761	2.41 (1.24)/1.99 (1.17)	42.070	<0.001
Degree of suicide risk in patients with current suicide risk, *n* (%) (*n* = 649)				
High, moderate/Low	377/272	2.46 (1.26)/2.34 (1.22)	1.49	0.22
Treatment setting, *n* (%)				
In-patient/Out-patient	488/922	3.06 (1.11)/1.72 (0.99)	537.37	<0.001
Psychiatric comorbidities, *n* (%)				
Any anxiety disorder	294/1116	2.18 (1.20)/2.18 (1.23)	<0.001	1.00
Generalized anxiety disorder	151/1259	2.14 (1.20)/2.19 (1.22)	0.23	0.64
Panic disorder	114/1296	2.36 (1.09)/2.17 (1.23)	2.59	0.11
Agoraphobia	113/1297	2.43 (1.23)/2.16 (1.22)	5.19	0.02
Social phobia	45/1365	2.18 (1.05)/2.18 (1.22)	0.001	0.97
Obsessive-compulsive disorder	22/1388	3.05 (1.05)/2.16 (1.22)	11.41	0.001
Post-traumatic stress disorder	20/1390	2.90 (1.41)/2.17 (1.21)	7.04	0.008
Anorexia nervosa	1/1409	2.00 (—)/2.18 (1.22)	0.02	0.88
Bulimia nervosa	8/1402	1.38 (0.74)/2.19 (1.22)	3.55	0.06
Somatic comorbidities, *n* (%)				
Any somatic comorbidity	653/757	2.37 (1.21)/2.03 (1.21)	28.23	<0.001
Hypertension	267/1143	2.67 (1.15)/2.07 (1.21)	53.70	<0.001
Thyroid dysfunction	204/1207	2.56 (1.22)/2.12 (1.21)	22.97	<0.001
Migraine	156/1254	1.99 (1.23)/2.21 (1.22)	4.58	0.03
Diabetes	84/1326	2.62 (1.21)/2.16 (1.21)	11.49	0.001
Heart disease	72/1338	2.58 (1.10)/2.16 (1.22)	8.31	0.004
Arthritis	65/1345	2.03 (1.05)/2.19 (1.23)	1.07	0.30
Asthma	48/1362	2.08 (1.05)/2.19 (1.22)	0.34	0.56
Treatment response, *n* (%)				
Response/Non-Response/Resistance	346/492/572	1.95 (1.06)/2.10 (1.18)/2.40 (1.31)	17.35	<0.001

N, number of participants; SD, standard deviation.

*Current suicide risk was assessed by clinical judgment.

This table displays the mean number of concurrently prescribed psychiatric drugs if the investigated variable was present and in the absence of the relevant variable (behind the horizontal line; unless otherwise indicated).

augmentation/combination treatment with a mean number of concurrently administered psychiatric drugs of 2.18. Among the investigated sociodemographic and clinical features, the following variables were found to be associated with augmentation/combination medication: male gender, older age, Caucasian descent, higher weight, low educational status, the absence of occupation, psychotic symptoms, melancholic features, atypical features, suicide risk, in-patient treatment, longer overall duration of hospitalizations due to MDD during lifetime, comorbid panic disorder, comorbid agoraphobia, comorbid OCD, comorbid bulimia nervosa, comorbid somatic comorbidity in general and concurrent hypertension, thyroid dysfunction, diabetes, and heart disease in particular, higher current and retrospective MADRS total scores, treatment resistance, and higher antidepressant dosing. These findings were corroborated when analyzing the influence of the various variables on the number of simultaneously prescribed psychiatric drugs.

Table 4. Spearman's correlation analyses investigating the association between the numbers of concurrently administered psychiatric drugs and continuous demographic and clinical variables

Characteristics	*r*	*P*-value
Age, mean (SD), years	0.248	<0.001
Weight, mean (SD), kg	0.201	<0.001
Duration of the current MDD episode, mean (SD), days	−0.219	<0.001
Number of MDD episodes during lifetime, mean (SD)	0.077	0.01
Age at onset of MDD, mean (SD), years	0.003	0.91
Duration of hospitalizations during lifetime, mean (SD), weeks (n = 1328)	0.545	<0.001
HAM-D total 21-item, mean (SD)	0.068	0.01
HAM-D total 17-item, mean (SD)	0.031	0.25
MADRS total, mean (SD)	0.181	<0.001
MADRS total at onset of current MDD episode, mean (SD)	0.279	<0.001
MADRS total change (present MADRS–retrospective MADRS), mean (SD)	−0.031	0.25
Fluoxetine equivalents, mean (SD), mg/day	0.181	<0.001

HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; *r*, correlation coefficient; SD, standard deviation.

One major finding of our study represents the association between the administration of augmentation/combination medication and treatment resistance to previous medication. This observed prescription practice reflects clinical trial results and recommendation of treatment guidelines, whereupon augmentation and combination strategies should be preferentially applied in treatment-resistant and difficult-to-treat MDD conditions. Accordingly, also severe symptomatology (expressed by the significantly higher present and retrospective MADRS total scores in the augmentation/combination group compared to the monotherapy group) served as factor significantly associated with the use of augmentation/combination in our survey. In the same way, the higher suicide risk, the higher rate of patients treated within an in-patient setting, the longer duration of previous psychiatric hospitalizations, and the higher percentage of patients without occupation in the augmentation/combination group can be regarded as possible parameters for severe and treatment-resistant MDD conditions for which polypsychopharmaceutical strategies are used. In summary, augmentation/combination is more preferably established in more complicated/severe MDD patients characterized for instance by treatment resistance, high symptom severity, suicide risk, and comorbidities.

At present, the best evidence for augmentation strategies in treatment-resistant MDD is available for SGAs and lithium. The efficacy of SGA augmentation could be demonstrated in a large number of randomized clinical trials and meta-analyses. Nelson and Papakostas (7) for instance found in their meta-analysis of 16 placebo-controlled SGA augmentation trials (n = 3480) significant superiority of adjunctive aripiprazole, olanzapine, quetiapine, and risperidone over placebo in response and remission rates. Moreover, some SGAs received the official approval as add-on medication after non-response to antidepressant monotherapy by regulatory authorities. For example, quetiapine XR is licensed in the USA and the EU, aripiprazole in the USA, and olanzapine has the regulatory approval in the USA in combination with fluoxetine. Paralleled by the enhancement of available evidence for the efficacy of SGA augmentation, pharmacoepidemiological studies found consistently a substantial increase of SGA prescription in MDD over the last years (5, 13). For instance, a significant rise of the proportion of MDD patients receiving SGAs from 12.8% in 2000 to 28.3% in 2007 was found in a pharmacovigilance program analyzing 1826 in-patients in German-speaking countries (5). In our study, 32.13% of all MDD patients were medicated with antipsychotic drugs (including the low-potency first-generation antipsychotics and the SGA quetiapine <100 mg/day) in combination with antidepressant treatment. Thus, our data suggest the continuous proceeding of the trend of increased administration of antipsychotics in MDD.

Beside the SGAs, there is evidence for the efficacy of an augmentation with lithium in refractory MDD patients (8, 9) and accordingly treatment guidelines consistently recommended this strategy (11, 12). Nevertheless, adjunctive lithium was less frequently prescribed in our survey (4.11% of all participants) than for instance augmentation with antipsychotics (25.67% of all participants). Probably, the use of lithium in the clinical practice is limited by the need of continuous plasma level measurements to ensure the achievement of the therapeutic window and due to the anticipation of adverse effects (19, 20). On the other hand, the increased risk for metabolic adverse effects and sedation should be critically taken into account when considering SGA augmentation strategies. From a clinical viewpoint, augmentation of antidepressants with antipsychotic drugs is especially advised in MDD patients with psychotic features (12, 21), whereas lithium should be preferably considered in MDD patients characterized by high risk for suicidal behavior (22, 23).

Even if we could not itemize our study sample according to the different prescribed augmenting drugs, we determined a higher proportion of MDD patients exhibiting suicide risk and psychotic, melancholic, and atypical features in the

augmentation/combination-treated patient group compared to the antidepressant monotherapy group. These findings suggest that augmentation/combination was preferably established to treat specific target symptoms. In the same way, it can be assumed that the observed association between augmentation/combination strategies and some psychiatric comorbidities such as agoraphobia or OCD is attributable to the use of adjunctive agents for the treatment of these specific comorbidities.

In our survey, 29.50% of all participants received antidepressant combination treatment. In spite of the frequent use, the evidence for this measure is rather sparse and study findings on this topic were inconclusive (24–26). However, the efficacy of this strategy depends first of all on the concurrently prescribed agents. Therefore, treatment guidelines consistently recommend establishing antidepressant combination preferably with reuptake inhibitors such as SSRIs or SNRIs on the one hand and inhibitors of presynaptic autoreceptors such as NaSSAs or SARIs (e.g., mirtazapine or trazodone) on the other hand (12). Following this approach, synergistic effects can be expected due to the complementary mechanisms of action of these compounds (27). Furthermore, these combinations appear auspicious from a clinical viewpoint as presynaptic autoreceptor inhibitors are for instance, in contrast to SSRIs/SNRIs, characterized by meaningful sedating properties. That these recommendations are considered in the clinical routine care can be seen from our findings, according to which especially NaSSAs, TCAs, and SARIs were more often used in the context of augmentation/combination treatment than as monotherapy agents.

Whereas our patient sample was not itemized according to the different applied augmentation/combination strategies, clinical characteristics of treatment-resistant MDD patients receiving antidepressant combination medication were compared to those treated with SGA augmentation in a naturalistic study of Gobbi et al. (28). The authors found psychotic features, various comorbidities, high depressive symptom severity, and a high degree of treatment resistance to be associated with the add-on prescription of SGAs.

The observed widespread prescription of BZD/BZD-like drugs and the calcium channel modulator pregabalin as adjunctive compounds to antidepressants in MDD is consistent with findings of pharmacoepidemiological studies and investigations based on pharmacovigilance databases (5, 13). However, it should be considered that we could not ascertain if the medications with BZD/BZD-like drugs were established first of all due to the need of tranquillization, for the management of adverse effects (e.g., sleep disturbances), or to treat comorbidities such as anxiety disorders. For instance, BZD are often used for the acute treatment of panic attacks (29, 30). Nevertheless, there is also evidence that for example eszoplicone augmentation of antidepressants does not only have sustained efficacy on anxiety and sleep disturbances but also improves other HAM-D depressive symptoms such as mood or guilt (31).

For all augmentation/combination strategies, possible drug interactions and additional adverse effects provoked by the adjunctive compounds must be critically taken into account and weighed against the potential advantages in terms of antidepressive efficacy (27). Consequently, it cannot be ruled out, that the higher mean weight in the augmentation/combination group of our study is attributable to the polypharmaceutical approach as some psychiatric drugs can cause weight gain as adverse effect. The same applies to the higher comorbidity rates found for some cardiovascular and endocrine diseases in augmentation/combination-treated MDD patients.

Study limitations

As all participants were exclusively enrolled from academic psychiatric treatment centers, the study sample might therefore not be representative for MDD patients in primary care settings. Moreover, the precondition of ≥4-week antidepressant pharmacotherapy before study entry should be taken into account as potential study limitation. Furthermore, possible cross-site differences should be considered because the application of recruitment center as random factor in the ANCOVA altered the results for the variable duration of the current MDD episode in terms of significant between-group differences. The cross-sectional study design represents the primary limitation when analyzing treatment response. This is why we aimed to capture the changes in depressive symptoms by assessing the MADRS total score at the onset of the present MDD episode in a retrospective way. However, this information cannot be as accurate as in a prospective trial by nature. Moreover, we are not aware of specific investigations evaluating the accuracy of the estimation of retrospective MADRS scores. A further limitation of this study represents the lack of stratification according to the different drugs used for augmentation or combination medication. Concerning the rating scales assessments (e.g., HAM-D and MADRS), we cannot definitively rule out a possible bias due to a potential lack of inter-rater reliability as this

phenomenon was not statistically examined. However, all specialists who participated in the data collection process of this study received special training in accomplishing the HAM-D and MADRS ratings. The issue of multiple testing (multiplicity) can be regarded as potential limitation with respect to the statistical analyses. Owing to the large number of examined variables and the subsequently high number of performed statistical tests, applying Bonferroni's correction for multiple comparisons was regarded to be overly conservative. However, the multiplicity issue should be critically considered when interpreting our results.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Required minimum doses for the antidepressant drug treatment before study entry (administered for ≥4 weeks).