Psychotic Features in Patients With Major Depressive Disorder:
A Report From the European Group for the Study of Resistant Depression

Markus Dold, MD[a]; Lucie Bartova, MD[a]; Alexander Kautzky, MD[a]; Stefano Porcelli, MD[b]; Stuart Montgomery, MD, PhD[c]; Joseph Zohar, MD, PhD[d]; Julien Mendlewicz, MD[e]; Daniel Souery, MD, PhD[e,f]; Alessandro Serretti, MD, PhD[b]; and Siegfried Kasper, MD[a,*]

ABSTRACT

Objective: To elucidate the impact of the presence of psychotic features in patients diagnosed with major depressive disorder (MDD) on sociodemographic, psychosocial, clinical, and response characteristics.

Methods: A total of 1,410 *DSM-IV-TR* MDD patients were included in the present European multicenter study, which was conducted between 2011 and 2016. Analyses of covariance, χ^2 tests, and binary logistic regression analyses were performed to explore differences in sociodemographic and clinical variables between MDD patients with and without psychotic symptoms.

Results: A prevalence rate of 10.92% for psychotic features was found in MDD. Compared to nonpsychotic MDD patients, those with psychotic features were characterized by a higher likelihood for melancholic characteristics (73.38% vs 59.16%, $P = .0006$), a higher rate of current suicide risk (60.39% vs 44.27%, $P = .0002$), greater likelihood of receiving inpatient treatment (55.84% vs 32.01%, $P < .0001$), greater depressive symptom severity (measured by various rating scales), and more often receiving augmentation/combination treatment strategies in general (81.17% vs 58.12%, $P < .0001$) and add-on therapy with antipsychotics (50.00% vs 22.69%, $P < .0001$) and benzodiazepines (47.40% vs 31.29%, $P = .0001$) in particular. Moreover, psychotic symptoms in MDD were highly predictive of treatment resistance, expressed by a more than 2.2-fold higher likelihood for resistance compared to nonpsychotic MDD patients (79.87% vs 35.75%, $P < .0001$). Only 3.25% of the patients with psychotic MDD achieved treatment response (vs 27.15% of those with nonpsychotic MDD, $P < .0001$).

Conclusions: These findings suggest that adequate diagnosis of psychotic features in MDD should be ensured in routine clinical care. As a combination of antipsychotics and antidepressants represents the first-line treatment option in psychotic MDD, the finding of a 2-fold higher prescription rate for antipsychotic drugs in psychotic versus nonpsychotic MDD patients reflects the current evidence.

J Clin Psychiatry 2019;80(1):17m12090

To cite: Dold M, Bartova L, Kautzky A, et al. Psychotic features in patients with major depressive disorder: a report from the European Group for the Study of Resistant Depression. *J Clin Psychiatry.* 2019;80(1):17m12090.

To share: https://doi.org/10.4088/JCP.17m12090

[a]Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

[b]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

[c]Imperial College, University of London, London, United Kingdom

[d]Psychiatric Division, Chaim Sheba Medical Center, Tel Hashomer, Israel

[e]School of Medicine, Free University of Brussels, Brussels, Belgium

[f]Psy Pluriel—European Centre of Psychological Medicine, Brussels, Belgium

**Corresponding author:* Siegfried Kasper, MD, Professor and Chairman, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria (sci-biolpsy@meduniwien.ac.at).

In major depressive disorder (MDD) with psychotic features ("psychotic depression"), depressive symptoms emerge together with delusions and/or hallucinations. In contrast to schizoaffective disorders, the psychotic symptoms in psychotic depression are present only within a depressive episode. In the current editions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*)[1] and the *International Classification of Diseases* (*ICD-10*),[2] MDD with psychotic features is classified as a depressive subtype. It is estimated that approximately 13%–25% of MDD patients exhibit psychotic features.[3–6] This patient group has been reported to differ meaningfully from nonpsychotic MDD patients in terms of neurobiological findings, clinical characteristics, family medical history, and treatment response patterns.[7–13] For instance, psychotic MDD is associated with severe depressive symptomatology,[14] increased suicide risk,[15,16] and poor treatment outcome.[13,14] As a consequence of such findings, the suggestion emerged that psychotic MDD may represent either a separate diagnostic entity different from nonpsychotic MDD or a distinct diagnostic subtype of MDD.[17–19]

However, there has been no large clinical study in which treatment response patterns were systematically assessed. Moreover, only little is known about which pharmacologic treatment strategies are used in psychotic MDD compared with in nonpsychotic MDD. Therefore, in this observational, post hoc analysis of data from a large European multicenter trial using an exploratory approach, we (1) determined the presence of psychotic features in a large MDD patient sample (n = 1,410); (2) compared sociodemographic, clinical, and pharmacologic characteristics between MDD patients with and without psychotic symptoms; and (3) explored the association between these variables and the occurrence of psychotic features by applying binary logistic regressions.

METHODS

Study Design

This European multisite, observational, cross-sectional study with retrospective assessment of treatment response was carried out between 2011 and 2016 by the European Group for the Study of Resistant

Clinical Points

- Of 1,410 patients with major depressive disorder (MDD), 10.92% exhibited psychotic features.
- The presence of psychotic symptoms in MDD was highly associated with treatment resistance. Psychotic MDD was characterized by a higher proportion of patients displaying melancholic features, suicide risk, severe depressive symptoms, and undergoing inpatient treatment than nonpsychotic MDD.
- In comparison to those with nonpsychotic MDD, more MDD patients with psychotic features were treated with augmentation/combination medications. When medications were itemized according to the different substance classes, patients with psychotic MDD received more antipsychotic and benzodiazepine augmentation strategies.

Depression (GSRD). The primary aim of this research project was to examine clinical and biological correlates of treatment-resistant depression. Altogether, 10 tertiary (mainly university/academic) centers in Austria, Belgium, France, Germany, Greece, Israel, Italy, and Switzerland took part in this study. At each recruitment center, ethics committee approval was obtained and all participants gave written informed consent before study inclusion.

Patients

Eligible patients were aged 18 years and older, received inpatient or outpatient treatment, and met the *DSM-IV-TR* criteria for MDD (classification code: 296.2x or 296.3x). The MDD diagnosis had to be confirmed by the Mini-International Neuropsychiatric Interview (MINI).[20] The patients were at different stages of treatment but had to undergo pharmacotherapy with at least 1 antidepressant during their present MDD episode before study enrollment (≥ 4 weeks of adequate dosing [Supplementary Table 1]). Key exclusion criteria comprised (1) any current primary psychiatric disorder other than MDD, (2) any substance disorder in the previous 6 months with the exception of nicotine and caffeine, and (3) any severe personality disorder.

Evaluations

Data on sociodemographic, clinical, treatment, and response variables of all participants were collected in a detailed clinical interview using standardized online case report forms. These interviews were carried out by specialists from the referral centers supported by use of specific questionnaires (ie, a cross-sectional data collection process). Specifically, the presence of psychotic features was structurally examined by the MINI. Moreover, the degree of suicide risk, the presence of melancholic and atypical features, and the presence of psychiatric comorbidities were evaluated by the MINI. The Montgomery-Asberg Depression Rating Scale (MADRS)[21] and the 21-item Hamilton Depression Rating Scale ($HDRS_{21}$)[22] were used to measure depressive symptom severity. Additionally, the severity at the onset of the current MDD episode was evidenced by retrospective MADRS scores based on the patients' assertions and information obtained from medical records. Hence, the MADRS total score change during the current depressive episode could be calculated (retrospective MADRS score minus current MADRS score) to examine treatment response patterns. Nonresponse to pharmacotherapy was defined as (1) a MADRS total score of ≥ 22 and (2) a < 50% MADRS total score reduction after 1 antidepressant trial (≥ 4 weeks' duration in adequate dose; see Supplementary Table 1), whereas a patient was classified as treatment-resistant after nonresponse to ≥ 2 consecutive adequate antidepressant trials. Information with regard to the current and previous medication and the presence of somatic comorbidities of the participants was collected based on the patients' report and medical record information.

Statistical Analyses

Statistical calculations were performed using IBM SPSS software, version 24. Sociodemographic, clinical, treatment, and response variables were compared between MDD patients with and without psychotic features. We employed descriptive statistics (means, standard deviations, and percentages) to present the patient sample characteristics. To examine between-group differences, χ^2 tests were used for categorical variables and analyses of covariance for continuous variables (with presence of psychotic features as fixed effect and recruitment center as random factor). In case of a significant between-group difference in these statistics, a binary logistic regression analysis with the relevant independent variable and recruitment site as covariate was accomplished to estimate the association of the variable with the presence of psychotic symptoms as a dichotomous dependent variable. All data analyses were 2-sided (significance level of $P = .05$), and Bonferroni-Holm adjustment was applied except with sociodemographic variables.

RESULTS

The analyzed patient sample consisted of 1,410 MDD subjects. Their sociodemographic and clinical characteristics are indicated in Table 1 and Supplementary Table 2. The depressive symptom severity at study enrollment was indicated by a mean ± SD MADRS total score of 24.61 ± 11.29 and a mean ± SD $HDRS_{21}$ score of 19.78 ± 9.05.

One hundred fifty-four (10.92%) of the 1,410 included MDD patients met the MINI criteria for the presence of psychotic features. In comparison to the MDD subjects without psychotic symptoms, patients with psychotic MDD had higher rates of melancholic features (73.38% vs 59.16%, $\chi^2 = 11.63$, $P = .0006$; odds ratio [OR] = 1.90), current suicide risk (60.39% vs 44.27%, $\chi^2 = 14.35$, $P = .0002$; OR = 1.92), and undergoing inpatient treatment (55.84% vs 32.01%, $\chi^2 = 34.44$, $P < .0001$; OR = 2.69).

In measuring depressive symptom severity, we found that MDD patients with psychotic features exhibited a higher

Table 1. Sociodemographic and Clinical Variables Across the Analyzed Patient Groups[a]

Characteristic	MDD Total Sample (n = 1,410)	MDD With Psychotic Features (n = 154)	MDD Without Psychotic Features (n = 1,256)	χ^2/F	*P* Value (ANCOVA/χ^2)	Adjusted OR (95% CI)/B ± SE	*P* Value (Logistic Regression)
Sex, n (%)							
Male	467 (33.12)	57 (37.01)	410 (32.64)	1.18	.2768		
Female	943 (66.88)	97 (62.99)	846 (67.36)				
Age, mean (SD), y	50.28 (14.11)	52.40 (13.92)	50.02 (14.12)	3.93	.0476		
Marital status, n (%)							
Married/live with partner	703 (49.86)	76 (49.35)	627 (49.92)	0.02	.8938		
Single/divorced/separated/widowed	707 (50.14)	78 (50.65)	629 (50.08)				
White, n (%)	1,356 (96.17)	147 (95.45)	1,209 (96.26)	0.24	.6239		
Weight, mean (SD), kg	73.23 (16.80)	73.79 (14.69)	73.16 (17.05)	0.19	.6650		
Educational status, n (%) (n = 1,395)[b]							
University education/non-university higher education/high-level general education	755 (54.12)	75 (49.02)	680 (54.75)	1.80	.1795		
General secondary/technical education/ elementary school/none	640 (45.88)	78 (50.98)	562 (45.25)				
Occupational status, n (%) (n = 1,408)[b]							
Employed	659 (46.80)	59 (38.31)	600 (47.85)	5.01	.0252		
Without occupation	749 (53.20)	95 (61.69)	654 (52.15)				
Depressive episode, n (%)							
Single	127 (9.01)	7 (4.55)	120 (9.55)	4.20	.0404		
Recurrent	1,283 (90.99)	147 (95.45)	1,136 (90.45)				
With melancholic features	856 (60.71)	113 (73.38)	743 (59.16)	11.63	**.0006**	1.90 (1.31–2.77)	**.0007**
With atypical features	33 (2.34)	2 (1.30)	31 (2.47)	0.82	.3649		
With catatonic features	7 (0.50)	0 (0.00)	7 (0.56)	0.86	.3530		
Current suicide risk, n (%)	649 (46.03)	93 (60.39)	556 (44.27)	14.35	**.0002**	1.92 (1.36–2.70)	**<.0001**
Degree of suicide risk in patients with current suicide risk, n (%) (n = 649)[b]							
High/moderate	377 (58.09)	60 (64.52)	317 (57.01)	1.84	.1748		
Low	272 (41.91)	33 (35.48)	239 (42.99)				
Treatment setting, n (%)							
Inpatient	488 (34.61)	86 (55.84)	402 (32.01)	34.44	**<.0001**	2.69 (1.91–3.77)	**<.0001**
Outpatient	922 (65.39)	68 (44.16)	854 (67.99)				
Psychiatric comorbidities, n (%)							
Any anxiety disorder	294 (20.85)	21 (13.64)	273 (21.74)	5.45	.0195		
Generalized anxiety disorder	151 (10.71)	13 (8.44)	138 (10.99)	0.93	.3349		
Panic disorder	114 (8.09)	4 (2.60)	110 (8.76)	7.01	.0081		
Agoraphobia	113 (8.01)	6 (3.90)	107 (8.52)	3.98	.0461		
Social phobia	45 (3.19)	5 (3.25)	40 (3.18)	0.002	.9670		
Obsessive-compulsive disorder	22 (1.56)	3 (1.95)	19 (1.51)	0.17	.6845		
Posttraumatic stress disorder	20 (1.42)	2 (1.30)	18 (1.43)	0.02	.8941		
Somatic comorbidities, n (%)							
Any somatic comorbidity	653 (46.31)	61 (39.61)	592 (47.13)	3.12	.0772		
Hypertension	267 (18.94)	26 (16.88)	241 (19.19)	0.48	.4908		
Thyroid dysfunction	204 (14.47)	33 (21.43)	171 (13.61)	6.77	.0093		
Migraine	156 (11.06)	11 (7.14)	145 (11.54)	2.70	.1003		
Diabetes	84 (5.96)	11 (7.14)	73 (5.81)	0.43	.5102		
Heart disease	72 (5.11)	9 (5.84)	63 (5.02)	0.19	.6594		
Arthritis	65 (4.61)	4 (2.60)	61 (4.86)	1.59	.2070		
$HDRS_{21}$ total score, mean (SD)	19.78 (9.05)	24.50 (8.18)	19.20 (8.99)	48.62	**<.0001**	0.07 ± 0.01	**<.0001**
MADRS total score, mean (SD)	24.61 (11.29)	31.49 (8.37)	23.76 (11.31)	67.29	**<.0001**	0.08 ± 0.01	**<.0001**
MADRS total score at onset of current MDD episode, mean (SD)	34.06 (7.70)	36.47 (7.57)	33.76 (7.66)	17.11	**<.0001**	0.05 ± 0.01	**<.0001**
MADRS total score change (present MADRS minus retrospective MADRS), mean (SD)	−9.36 (10.80)	−4.98 (8.38)	−9.90 (10.95)	28.99	**<.0001**	−0.05 ± 0.01	**<.0001**
Treatment response, n (%)[c]							
Response	346 (24.54)	5 (3.25)	341 (27.15)	113.84	**<.0001**	4.63 (3.30–6.49)	**<.0001**
Nonresponse	492 (34.89)	26 (16.88)	466 (37.10)				
Resistance	572 (40.57)	123 (79.87)	449 (35.75)				
Psychopharmacotherapy							
No. of psychiatric drugs, mean (SD)	2.18 (1.22)	2.74 (1.19)	2.12 (1.20)	37.00	**<.0001**	0.38 ± 0.07	**<.0001**
Polypsychopharmacy, n (%)	855 (60.64)	125 (81.17)	730 (58.12)	30.53	**<.0001**	3.11 (2.04–4.72)	**<.0001**
Monotherapy, n (%)	555 (39.36)	29 (18.83)	526 (41.88)				

(continued)

Table 1. Sociodemographic and Clinical Variables Across the Analyzed Patient Groups (continued)[a]

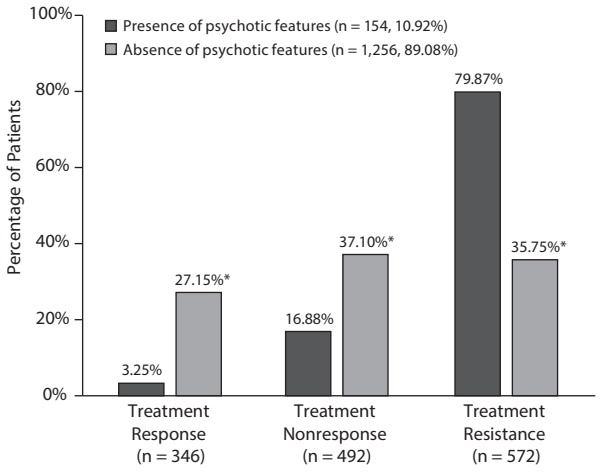
Characteristic	MDD Total Sample (n = 1,410)	MDD With Psychotic Features (n = 154)	MDD Without Psychotic Features (n = 1,256)	χ^2/F	*P* Value (ANCOVA/χ^2)	Adjusted OR (95% CI)/B ± SE	*P* Value (Logistic Regression)
Administered first-line antidepressant (in the current MDD episode), n (%)							
Selective serotonin reuptake inhibitors	734 (52.06)	72 (46.75)	662 (52.71)	18.57	.0432		
Serotonin-norepinephrine reuptake inhibitors	336 (23.83)	42 (27.27)	294 (23.41)				
Noradrenergic and specific serotonergic antidepressants	121 (8.58)	15 (9.74)	106 (8.44)				
Tricyclic antidepressants	74 (5.25)	6 (3.90)	68 (5.41)				
Agomelatine	69 (4.89)	1 (0.65)	68 (5.41)				
Norepinephrine-dopamine reuptake inhibitors	32 (2.27)	5 (3.25)	27 (2.15)				
Serotonin antagonist and reuptake inhibitors	28 (1.99)	8 (5.19)	20 (1.59)				
Vortioxetine	6 (0.43)	3 (1.95)	3 (0.24)				
Monoamine oxidase inhibitors	5 (0.35)	1 (0.65)	4 (0.32)				
Norepinephrine reuptake inhibitors	3 (0.21)	1 (0.65)	2 (0.16)				
Tianeptine	2 (0.14)	0 (0.00)	2 (0.16)				
Fluoxetine equivalents,[d] mean (SD), mg/d	39.86 (20.78)	44.60 (19.30)	39.27 (20.89)	8.11	.0045		
Applied psychopharmacologic combination and augmentation strategies (in addition to the ongoing antidepressant treatment), n (%)							
Combination with at least 1 additional antidepressant	416 (29.50)	60 (38.96)	356 (28.34)	7.56	.0059		
Augmentation with at least 1 antipsychotic drug	362 (25.67)	77 (50.00)	285 (22.69)	51.19	**<.0001**	3.32 (2.36–4.68)	**<.0001**
Augmentation with at least 1 mood stabilizer	159 (11.28)	25 (16.23)	134 (10.67)	4.39	.0361		
Augmentation with at least 1 BZD or BZD-like drug	466 (33.05)	73 (47.40)	393 (31.29)	14.84	**.0001**	1.93 (1.38–2.70)	**.0001**
Augmentation with at least 1 low-potency antipsychotic[e]	91 (6.45)	14 (9.09)	77 (6.13)	1.99	.1582		
Augmentation with pregabalin	102 (7.23)	12 (7.79)	90 (7.17)	0.08	.7769		

[a]The *P* values indicated in bold were significant after Bonferroni-Holm correction. With regard to the binary logistic regression analyses, adjusted odds ratios (ORs) with 95% CIs are presented for dichotomous independent variables, and regression coefficients (Bs) with standard errors (SEs) are presented for continuous independent variables. The ORs and regression coefficients are adjusted for the covariate recruitment center. The data for all investigated variables within this study are presented in Supplementary Table 2.
[b]The percentages take into account the lower total n values for the patient groups as well as for the total sample.
[c]Nonresponse was defined by a previous single failed trial and treatment resistance by 2 or more failed trials.
[d]Fluoxetine dose equivalents were calculated according to Hayasaka et al.[23]
[e]Comprising the so-called low-potency first-generation antipsychotics and the second-generation antipsychotic quetiapine (< 100 mg/d).
Abbreviations: ANCOVA = analysis of covariance, BZD = benzodiazepine, $HDRS_{21}$ = 21-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

mean ± SD $HDRS_{21}$ total score (24.50 ± 8.18 vs 19.20 ± 8.99, $F = 48.62$, $P < .0001$; regression coefficient [B] = 0.07), current MADRS total score (31.49 ± 8.37 vs 23.76 ± 11.31, $F = 67.29$, $P < .0001$; B = 0.08), and retrospective MADRS total score (36.47 ± 7.57 vs 33.76 ± 7.66, $F = 17.11$, $P < .0001$; B = 0.05). When analyzing treatment response, we found a lower MADRS total score change (−4.98 ± 8.38 vs −9.90 ± 10.95, $F = 28.99$, $P < .0001$; B = −0.05) and a lower proportion of treatment responders (3.25% vs 27.15%, $\chi^2 = 113.84$, $P < .0001$) in the psychotic features group, whereas this patient group included significantly more treatment-resistant patients (79.87% vs 35.75%, $P < .0001$) (Figure 1).

In terms of the applied psychopharmacotherapy, MDD patients with psychotic features were more likely to receive augmentation/combination treatment strategies in general (81.17% vs 58.12%, $\chi^2 = 30.53$, $P < .0001$; OR = 3.11) and add-on medication with antipsychotics (50.00% vs 22.69%, $\chi^2 = 51.19$, $P < .0001$; OR = 3.32) and benzodiazepines or benzodiazepine-like drugs (47.40% vs 31.29%, $F = 14.84$, $P = .0001$; OR = 1.93) in particular. Furthermore, we found

Figure 1. Presence and Absence of Psychotic Features in Patients With Major Depressive Disorder Exhibiting Treatment Response, Nonresponse, and Resistance



*$P < .0001$.

a higher mean ± SD number of simultaneously administered psychiatric drugs (2.74 ± 1.19 vs 2.12 ± 1.20, $F = 37.00$, $P < .0001$; B = 0.38) in patients suffering from psychotic MDD.

DISCUSSION

In this European multicenter, cross-sectional investigation, 10.92% of the 1,410 MDD patients displayed psychotic features. In comparison to nonpsychotic MDD patients, they were characterized by a higher likelihood of having melancholic features and suicide risk, undergoing inpatient treatment, having severe depressive symptom severity and poor treatment response, and receiving augmentation/combination medication strategies in general and add-on treatment with antipsychotics and benzodiazepines or benzodiazepine-like drugs in particular.

The prevalence rate for psychotic symptoms in our MDD patient sample was slightly above 10% and therefore lower compared to the prevalence rates in some previous studies, which were mainly between 13% and 25%.[3–6] In a recent retrospective medical report chart review (n = 1,314), for instance, Gaudiano et al[5] found a prevalence rate of psychotic features in MDD of 13.2%. However, that survey comprised data exclusively from hospitalized patients, as was also the case in most of the previous investigations on this topic. This difference regarding the treatment setting probably accounts for our lower prevalence rate, since in our study, the majority of participants (almost two-thirds) were treated as outpatients. This assumption is corroborated by our finding of a significant association between receiving inpatient treatment and exhibiting psychotic features. Moreover, when analyzing exclusively inpatients in our patient sample, we found that the prevalence rate of psychotic MDD amounted to 17.62%. Concordantly, a survey evaluating an MDD outpatient population exclusively revealed an even lower prevalence rate of 5.3% for psychotic symptoms.[24]

Analyzing sociodemographic variables, we found no significant differences between patients with psychotic and nonpsychotic MDD. Thus, we could not replicate previous findings demonstrating that patients with psychotic depression were more likely to be non-white.[5,25] As 96.17% of our patient sample was white, the dissimilar group allocation concerning the different ethnic groups should be critically considered in this regard.

One main finding of this study is the association between the presence of psychotic features and high depressive symptom severity and treatment resistance. Whereas the association with high symptom severity was already observed in previous surveys,[14] we investigated the impact of psychotic symptoms on treatment response patterns for the first time by systematically estimating treatment response with rating scales (MADRS total score change assessment). The findings for other variables can also be interpreted as markers for high depressive symptom severity and treatment resistance. For instance, we explored an association between psychotic symptoms and (1) suicide risk, (2) inpatient treatment, (3) melancholic features, and (4) a larger use of augmentation/combination treatment strategies. These clinical features can be regarded as possible parameters for severe and treatment-resistant MDD conditions. In summary, our data suggest that the presence of psychotic symptoms served as a meaningful risk factor for treatment failures in MDD expressed by a more than 2.2-fold higher likelihood for treatment resistance in comparison to nonpsychotic MDD patients. Only 3.25% of the patients suffering from psychotic MDD met our predefined response criterion, whereas 27.15% of the nonpsychotic MDD patients could be classified as treatment responders. Our findings emphasize the need for adequately diagnosing psychotic features in MDD in the clinical routine care, as these symptoms can be regarded as highly predictive of treatment resistance.

Given that our study required a ≥ 4-week treatment period before study entry and subsequently the accomplishment of the data collection process, it should be critically considered that this time frame might be too short for patients suffering from psychotic depression to achieve sufficient treatment response. As many patients with psychotic MDD need a longer time period to adequately respond to the pharmacotherapy (often because antipsychotic drugs were not added to the antidepressant medication from the onset of the treatment), our analyses could therefore potentially omit some patients in the treatment response group who would have possibly responded after a longer treatment period. Thus, the use of 1 time point exclusively to measure clinical response characteristics should be critically taken into account in terms of the interpretation of our statistical findings.

Psychotic features in MDD were highly associated with increased overall administration of augmentation/combination treatment strategies. Itemizing according to the individual add-on medications, we found a significantly higher use of antipsychotics and benzodiazepines and benzodiazepine-like drugs in psychotic MDD. The prescription rates for antipsychotics were 2-fold higher in psychotic compared to nonpsychotic MDD. Hence, the applied psychopharmacologic strategies reflect the recommendations of the treatment guidelines for the management of unipolar depression consistently advising a combination of antipsychotic and antidepressant drugs in psychotic MDD,[26–28] as sufficient symptom improvement cannot ordinarily be achieved by monotherapy with antidepressants or antipsychotics.[29] Moreover, some guidelines also consider electroconvulsive therapy to be first-line treatment in psychotic MDD.[30] As meta-analyses[31–33] found antidepressant-antipsychotic combination treatment to be significantly superior to antidepressant and antipsychotic monotherapy, adjunctive pharmacotherapy with antipsychotic drugs can be therefore regarded as a well-established evidence-based treatment option in the pharmacological management of psychotic MDD. Our findings suggest that the prescription pattern

in the clinical routine care follows the current evidence. Even if the patient group receiving add-on treatment with antipsychotic drugs did not receive the so-called low-potency first-generation antipsychotics and the second-generation antipsychotic quetiapine < 100 mg/d, it should be critically considered in this regard that we did not explicitly ascertain the administered antipsychotic doses. As a consequence, we cannot ensure that all patients received their antipsychotic medication at an adequate dose. For instance, Andreescu et al[34] found in their survey (n = 100) that only 5% of all psychotic MDD patients were treated with an antidepressant-antipsychotic combination in a sufficient dose. This potential lack of adequate dosing should be taken into account with respect to the low response rate identified for the psychotic MDD patient group in our study (3.25%). Taken together with the increased treatment resistance, the observed prescription pattern suggests that psychotic MDD is a type of treatment-resistant depression characterized by poor response to antidepressant and antipsychotic monotherapy. However, our study was not primarily designed to elucidate the research question if psychotic MDD represents rather a separate diagnostic entity or a subtype of MDD.

Regarding the observed widespread prescription of benzodiazepines and benzodiazepine-like drugs in addition to antidepressants in psychotic MDD, it should be critically considered that we could not ascertain if the benzodiazepines and benzodiazepine-like compounds were dispensed primarily (1) to treat specific target symptoms, (2) due to the need of tranquillization, (3) for the management of adverse effects (eg, sleep disturbances), or (4) to treat comorbidities such as anxiety disorders. Moreover, the increased administration of benzodiazepines and benzodiazepine-like agents in psychotic MDD might reflect the high symptom severity in this patient group, as benzodiazepines are especially often used to treat acute severe psychiatric conditions due to their ability for rapid tranquillization.

Study Limitations

The primary limitation of this European multicenter study is its observational cross-sectional design. Using such a naturalistic approach, we aimed to recruit a best-possible real-world MDD patient sample. As depressed patients with psychotic features are commonly excluded from randomized controlled clinical trials due to strict inclusion criteria, the naturalistic approach applied in this study appears to be more appropriate to investigate psychotic MDD. Nevertheless, it should be taken into account that our patient sample might not be fully representative of MDD populations in primary care settings since (1) ≥ 4-week antidepressant treatment represented a precondition for study enrollment, (2) recent substance disorders served as exclusion criteria, and (3) the majority of participants were recruited from university/academic psychiatric treatment centers. These issues could potentially hamper the generalizability of our findings. Furthermore, a lack of diversity in the patient sample should be considered as 96.17% of the participants were white. Concerning the MADRS and $HDRS_{21}$ evaluation, a potential bias due to the lack of the statistical calculation of interrater reliability should be regarded. However, all raters received special training in conducting the MADRS and $HDRS_{21}$ ratings. Moreover, retrospective MADRS scores were applied to estimate treatment response. These ratings cannot be as accurate as in a prospective evaluation and could be subjected to potential memory biases, which might be different in psychotic MDD patients compared to those without psychotic symptoms.

The present study aimed to elucidate clinical features of psychotic MDD in comparison to nonpsychotic MDD. Further research projects identifying biomarkers and/or using neuroimaging techniques are required to examine opportunities to differentiate psychotic MDD patients from those without psychotic symptoms earlier in the course of the disease. Subsequently, patients could receive an appropriate treatment in the early phase of their depressive episode.

Submitted: December 17, 2017; accepted July 16, 2018.

Published online: January 15, 2019.

Potential conflicts of interest: **Dr Dold** has received a travel grant from Janssen-Cilag. **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 Zohar** has received grant/research support from Lundbeck, Servier, and Pfizer; has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and 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 has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. **Dr Serretti** has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boheringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. Within the last 3 years, **Dr Kasper** received grants/research support, consulting fees, and/or honoraria from Angelini, AOP Orphan Pharmaceuticals, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, and Servier. **Drs Bartova**, **Kautzky**, and **Porcelli** declare that they have no conflicts of interest.

Funding/support: The Group for the Study of Resistant Depression (GSRD) received an unrestricted grant sponsored by Lundbeck A/S.

Role of the sponsor: The sponsor had no role in designing the study, data collection, data analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Additional information: All members of the GSRD are included as authors of this article.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
2. WHO. *The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic Criteria for Research*. Geneva, Switzerland: World Health Organization; 1993.
3. Ohayon MM, Schatzberg AF. Prevalence of depressive episodes with psychotic features in the general population. *Am J Psychiatry*. 2002;159(11):1855–1861.
4. Johnson J, Horwath E, Weissman MM. The validity of major depression with psychotic features based on a community study. *Arch Gen Psychiatry*. 1991;48(12):1075–1081.
5. Gaudiano BA, Weinstock LM, Epstein-Lubow G, et al. Clinical characteristics and medication use patterns among hospitalized patients admitted with psychotic vs nonpsychotic major depressive disorder. *Ann Clin Psychiatry*. 2016;28(1):56–63.
6. Coryell W, Pfohl B, Zimmerman M. The clinical

and neuroendocrine features of psychotic depression. *J Nerv Ment Dis*. 1984;172(9):521–528.
7. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in *DSM-IV*? *Am J Psychiatry*. 1992;149(6):733–745.
8. Simpson S, Baldwin RC, Jackson A, et al. The differentiation of *DSM-III-R* psychotic depression in later life from nonpsychotic depression: comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features. *Biol Psychiatry*. 1999;45(2):193–204.
9. Cubells JF, Price LH, Meyers BS, et al. Genotype-controlled analysis of plasma dopamine beta-hydroxylase activity in psychotic unipolar major depression. *Biol Psychiatry*. 2002;51(5):358–364.
10. Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis. *Am J Psychiatry*. 1997;154(11):1497–1503.
11. Coryell W, Leon A, Winokur G, et al. Importance of psychotic features to long-term course in major depressive disorder. *Am J Psychiatry*. 1996;153(4):483–489.
12. Østergaard SD, Bille J, Søltoft-Jensen H, et al. The validity of the severity-psychosis hypothesis in depression. *J Affect Disord*. 2012;140(1):48–56.
13. Glassman AH, Roose SP. Delusional depression: a distinct clinical entity? *Arch Gen Psychiatry*. 1981;38(4):424–427.
14. Buoli M, Caldiroli A, Altamura AC. Psychotic versus non-psychotic major depressive disorder: a comparative naturalistic study. *Asian J Psychiatr*. 2013;6(4):333–337.
15. Gournellis R, Tournikioti K, Touloumi G, et al. Psychotic (delusional) depression and suicidal attempts: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2018;137(1):18–29.
16. Zalpuri I, Rothschild AJ. Does psychosis increase the risk of suicide in patients with major depression? a systematic review. *J Affect Disord*. 2016;198:23–31.
17. Charney DS, Nelson JC. Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. *Am J Psychiatry*. 1981;138(3):328–333.
18. Maj M, Pirozzi R, Di Caprio EL. Major depression with mood-congruent psychotic features: a distinct diagnostic entity or a more severe subtype of depression? *Acta Psychiatr Scand*. 1990;82(6):439–444.
19. Ostergaard SD, Rothschild AJ, Uggerby P, et al. Considerations on the *ICD-11* classification of psychotic depression. *Psychother Psychosom*. 2012;81(3):135–144.
20. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
22. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
23. Hayasaka Y, Purgato M, Magni LR, et al. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. *J Affect Disord*. 2015;180:179–184.
24. Gaudiano BA, Dalrymple KL, Zimmerman M. Prevalence and clinical characteristics of psychotic versus nonpsychotic major depression in a general psychiatric outpatient clinic. *Depress Anxiety*. 2009;26(1):54–64.
25. Cassano P, Chang T, Trinh NH, et al. Differential impact of isolated psychotic symptoms on treatment outcome of major depressive disorder in the STAR*D cohort of Whites, Blacks and Latinos. *J Affect Disord*. 2013;150(2):578–584.
26. Bauer M, Pfennig A, Severus E, et al; World Federation of Societies of Biological Psychiatry. Task Force on Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J Biol Psychiatry*. 2013;14(5):334–385.
27. Cleare A, Pariante CM, Young AH, et al; Members of the Consensus Meeting. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015;29(5):459–525.
28. Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. *Int J Psychiatry Clin Pract*. 2017;21(1):13–23.
29. Rothschild AJ. *Clinical Manual for Diagnosis and Treatment of Psychotic Depression*. Washington, DC: Psychiatric Association Publishing; 2009.
30. Leadholm AK, Rothschild AJ, Nolen WA, et al. The treatment of psychotic depression: is there consensus among guidelines and psychiatrists? *J Affect Disord*. 2013;145(2):214–220.
31. Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? a systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. *J Clin Psychiatry*. 2012;73(4):486–496.
32. Wijkstra J, Lijmer J, Burger H, et al. Pharmacological treatment for psychotic depression. *Cochrane Database Syst Rev*. 2015;(7):CD004044.
33. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry*. 2015;76(4):e487–e498.
34. Andreescu C, Mulsant BH, Peasley-Miklus C, et al; STOP-PD Study Group. Persisting low use of antipsychotics in the treatment of major depressive disorder with psychotic features. *J Clin Psychiatry*. 2007;68(2):194–200.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Erika F. H. Saunders, MD, at esaunders@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Psychotic Features in Patients With Major Depressive Disorder: A Report From the European Group for the Study of Resistant Depression

Author(s): Markus Dold, MD; Lucie Bartova, MD; Alexander Kautzky, MD; Stefano Porcelli, MD; Stuart Montgomery, MD, PhD; Joseph Zohar, MD, PhD; Julien Mendlewicz, MD; Daniel Souery, MD, PhD; Alessandro Serretti, MD, PhD; and Siegfried Kasper, MD

DOI Number: https://doi.org/10.4088/JCP.17m12090

List of Supplementary Material for the article

1. Table 1 — Required minimum doses for the antidepressant drug treatment before study enrollment (dispensed for ≥4 weeks)
2. Table 2 — Socio-demographic and clinical variables across the analyzed patient groups.

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Required minimum doses for the antidepressant drug treatment before study enrollment (dispensed for ≥4 weeks).

Antidepressants	Required daily minimum dose
Selective serotonin reuptake inhibitors (SSRIs)	
Citalopram	20 mg
Escitalopram	10 mg
Fluoxetine	20 mg
Fluvoxamine	50 mg
Paroxetine	20 mg
Sertraline	50 mg
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	
Duloxetine	60 mg
Milnacipran	100 mg
Venlafaxine	75 mg
Tricyclic antidepressants (TCAs)	
Amitryptiline	150 mg
Clomipramine	150 mg
Desimipramine	150 mg
Dosulepine	200 mg
Dothiepin	200 mg
Imipramine	150 mg
Maprotiline	150 mg
Nortriptiline	100 mg
Protriptyline	75 mg
Monoamine oxidase inhibitors (MAO-I)	
Moclobemide	450 mg
Phenelzine	60 mg
Other antidepressants	
Agomelatine	25 mg
Amoxapine	300 mg
Bupropion	300 mg
Mianserine	30 mg
Mirtazapine	15 mg
Reboxetine	8 mg
Tianeptine	37.5 mg
Trazodone	150 mg

Supplementary Table 2. Socio-demographic and clinical variables across the analyzed patient groups.

Characteristics	MDD sample total (n=1410)	MDD with psychotic features (n=154)	MDD without psychotic features (n=1256)	x^2/F	p-value (ANCOVA/x^2)	adjusted OR (95% CI) / B ± SE	p-value (logistic regression)
Gender, n (%)							
Male	467 (33.12)	57 (37.01)	410 (32.64)	1.18	.2768		
Female	943 (66.88)	97 (62.99)	846 (67.36)				
Age, mean (SD), years	50.28 (14.11)	52.40 (13.92)	50.02 (14.12)	3.93	.0476		
Marital status, n (%)							
Married/Live with	703 (49.86)	76 (49.35)	627 (49.92)	0.02	.8938		
Single/Divorced/Separated/Widowed	707 (50.14)	78 (50.65)	629 (50.08)				
Ethnic origin, n (%)							
Caucasian	1356 (96.17)	147 (95.45)	1209 (96.26)	0.24	.6239		
Weight, mean (SD), kg	73.23 (16.80)	73.79 (14.69)	73.16 (17.05)	0.19	.6650		
Educational status, n (%) (n=1395)							
University education / Non-university high education / High Level general education	755 (54.12)	75 (49.02)	680 (54.75)	1.80	.1795		
General Secondary / Technical Education/ Elementary School/ None	640 (45.88)	78 (50.98)	562 (45.25)				
Occupational status, n (%) (n=1408)							
Employed	659 (46.80)	59 (38.31)	600 (47.85)	5.01	.0252		
Without occupation	749 (53.20)	95 (61.69)	654 (52.15)				
Depressive episode, n (%)							
Single	127 (9.01)	7 (4.55)	120 (9.55)	4.20	.0404		
Recurrent	1283 (90.99)	147 (95.45)	1136 (90.45)				
With melancholic features	856 (60.71)	113 (73.38)	743 (59.16)	11.63	**.0006**	1.90 (1.31-2.77)	**.0007**
With atypical features	33 (2.34)	2 (1.30)	31 (2.47)	0.82	.3649		
With catatonic features	7 (0.50)	0 (0.00)	7 (0.56)	0.86	.3530		
Current suicide risk (dichotomous)	649 (46.03)	93 (60.39)	556 (44.27)	14.35	**.0002**	1.92 (1.36-2.70)	**<.0001**
Degree of suicide risk in patients with current suicide risk, n (%) (n=649)							
High / moderate	377 (58.09)	60 (64.52)	317 (57.01)	1.84	.1748		
Low	272 (41.91)	33 (35.48)	239 (42.99)				
Treatment setting, n (%)							
Inpatient	488 (34.61)	86 (55.84)	402 (32.01)	34.44	**<.0001**	2.69 (1.91-3.77)	**<.0001**
Outpatient	922 (65.39)	68 (44.16)	854 (67.99)				
Duration of the current MDD episode, mean (SD), days	204.74 (164.64)	229.29 (173.24)	201.44 (163.26)	3.34	.0680		
Number of MDD episodes during lifetime, mean (SD)	3.33 (2.45)	3.29 (2.65)	3.33 (2.43)	0.03	.8535		
Age at onset of MDD, mean (SD), years	37.20 (15.44)	38.50 (15.49)	37.04 (15.44)	1.16	.2828		
Duration of psychiatric hospitalizations during lifetime, mean (SD), weeks (n=1328)	5.59 (20.45)	9.32 (38.02)	5.12 (16.95)	5.59	.0182		
Psychiatric comorbidities, n (%)							
Any anxiety disorder	294 (20.85)	21 (13.64)	273 (21.74)	5.45	.0195		
Generalized anxiety disorder	151 (10.71)	13 (8.44)	138 (10.99)	0.93	.3349		
Panic disorder	114 (8.09)	4 (2.60)	110 (8.76)	7.01	.0081		
Agoraphobia	113 (8.01)	6 (3.90)	107 (8.52)	3.98	.0461		
Social phobia	45 (3.19)	5 (3.25)	40 (3.18)	0.002	.9670		
Obsessive-compulsive disorder	22 (1.56)	3 (1.95)	19 (1.51)	0.17	.6845		
Posttraumatic stress disorder	20 (1.42)	2 (1.30)	18 (1.43)	0.02	.8941		
Anorexia nervosa	1 (0.07)	0 (0.00)	1 (0.08)	0.12	.7261		
Bulimia nervosa	8 (0.57)	1 (0.65)	7 (0.56)	0.02	.8859		
Somatic comorbidities, n (%)							
Any somatic comorbidity	653 (46.31)	61 (39.61)	592 (47.13)	3.12	.0772		
Hypertension	267 (18.94)	26 (16.88)	241 (19.19)	0.48	.4908		
Thyroid dysfunction	204 (14.47)	33 (21.43)	171 (13.61)	6.77	.0093		
Migraine	156 (11.06)	11 (7.14)	145 (11.54)	2.70	.1003		
Diabetes	84 (5.96)	11 (7.14)	73 (5.81)	0.43	.5102		
Heart disease	72 (5.11)	9 (5.84)	63 (5.02)	0.19	.6594		
Arthritis	65 (4.61)	4 (2.60)	61 (4.86)	1.59	.2070		
Asthma	48 (3.40)	2 (1.30)	46 (3.66)	2.33	.1268		
HAM-D total 21-item, mean (SD)	19.78 (9.05)	24.50 (8.18)	19.20 (8.99)	48.62	**<.0001**	0.07 ± .01	**<.0001**
MADRS total, mean (SD)	24.61 (11.29)	31.49 (8.37)	23.76 (11.31)	67.29	**<.0001**	0.08 ± .01	**<.0001**
MADRS total at onset of current MDD episode, mean (SD)	34.06 (7.70)	36.47 (7.57)	33.76 (7.66)	17.11	**<.0001**	0.05 ± .01	**<.0001**
MADRS total change (present MADRS - retrospective MADRS), mean (SD)	-9.36 (10.80)	-4.98 (8.38)	-9.90 (10.95)	28.99	**<.0001**	-0.05 ± .01	**<.0001**
Treatment response, n (%)[a]							
Response	346 (24.54)	5 (3.25)	341 (27.15)	113.84	**<.0001**	4.63 (3.30-6.49)	**<.0001**

Characteristics	MDD sample total (n=1410)	MDD with psychotic features (n=154)	MDD without psychotic features (n=1256)	x^2/F	p-value (ANCOVA/x^2)	adjusted OR (95% CI) / B ± SE	p-value (logistic regression)
Non-Response	492 (34.89)	26 (16.88)	466 (37.10)				
Resistance	572 (40.57)	123 (79.87)	449 (35.75)				
Psychopharmacotherapy							
Number of psychiatric drugs, mean (SD)	2.18 (1.22)	2.74 (1.19)	2.12 (1.20)	37.00	**<.0001**	0.38 ± .07	**<.0001**
Polypsychopharmacy, n (%)	855 (60.64)	125 (81.17)	730 (58.12)	30.53	**<.0001**	3.11 (2.04-4.72)	**<.0001**
Monotherapy, n (%)	555 (39.36)	29 (18.83)	526 (41.88)				
Administered first-line antidepressant (in the current MDD episode), n (%)							
Selective serotonin reuptake inhibitors	734 (52.06)	72 (46.75)	662 (52.71)	18.57	.0432		
Serotonin-norepinephrine reuptake inhibitors	336 (23.83)	42 (27.27)	294 (23.41)				
Noradrenergic and specific serotonergic antidepressants	121 (8.58)	15 (9.74)	106 (8.44)				
Tricyclic antidepressants	74 (5.25)	6 (3.90)	68 (5.41)				
Agomelatine	69 (4.89)	1 (0.65)	68 (5.41)				
Noradrenaline-dopamine reuptake inhibitors	32 (2.27)	5 (3.25)	27 (2.15)				
Serotonin antagonist and reuptake inhibitors	28 (1.99)	8 (5.19)	20 (1.59)				
Vortioxetine	6 (0.43)	3 (1.95)	3 (0.24)				
Monoamine oxidase inhibitors	5 (0.35)	1 (0.65)	4 (0.32)				
Noradrenaline reuptake inhibitors	3 (0.21)	1 (0.65)	2 (0.16)				
Tianeptine	2 (0.14)	0 (0.00)	2 (0.16)				
Fluoxetine equivalents[b], mean (SD), mg/day	39.86 (20.78)	44.60 (19.30)	39.27 (20.89)	8.11	.0045		
Applied psychopharmacological combination and augmentation strategies (in addition to the ongoing antidepressant treatment), n (%)							
Combination with at least 1 additional antidepressant	416 (29.50)	60 (38.96)	356 (28.34)	7.56	.0059		
Augmentation with at least 1 antipsychotic drug	362 (25.67)	77 (50.00)	285 (22.69)	51.19	**<.0001**	3.32 (2.36-4.68)	**<.0001**
Augmentation with at least 1 mood stabilizer	159 (11.28)	25 (16.23)	134 (10.67)	4.39	.0361		
Augmentation with at least 1 benzodiazepine (BZD)/BZD-like drug	466 (33.05)	73 (47.40)	393 (31.29)	14.84	**.0001**	1.93 (1.38-2.70)	**.0001**
Augmentation with at least 1 low-potency antipsychotic[c]	91 (6.45)	14 (9.09)	77 (6.13)	1.99	.1582		
Augmentation with pregabalin	102 (7.23)	12 (7.79)	90 (7.17)	0.08	.7769		

The p-values indicated in bold were significant after Bonferroni-Holm correction. With regard to the binary logistic regression analyses, adjusted odds ratios (OR) with the 95% confidence intervals are presented for dichotomous independent variables and regression coefficients (B) with standard errors (SE) for continuous independent variables. The ORs and the regression coefficients are adjusted for the covariate recruitment center.

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

[b]Fluoxetine dose equivalents were calculated according to Hayasaka et al. [23].

[c]comprising the so-called low-potency first-generation antipsychotics and the second-generation antipsychotic quetiapine <100 mg/day.

Abbreviations (alphabetical order): ANCOVA = analysis of covariance; B = regression coefficient; BZD = benzodiazepines; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; n = number of participants; OR = odds ratio; SD = standard deviation; SE = standard error.