The relation between major depressive disorder and comorbid generalized anxiety disorder - results from a European multicenter, cross-sectional survey

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Introduction

This international, multicenter, cross-sectional study comprising 1346 adult in- and outpatients with the primary diagnosis of major depressive disorder (MDD) from altogether ten psychiatric tertiary centers in eight European countries (Austria, Belgium, France, Germany, Greece, Israel, Italy, and Switzerland) sought to examine the association between predominant MDD and comorbid generalized anxiety disorder (GAD).

Patients and Methods

All 1346 participants with MDD were recruited within the European research program "Clinical and biological correlates of resistant depression and related phenotypes" carried out by the "Group for the Study of Resistant Depression (GSRD)". This multicenter, multinational, cross-sectional survey enrolled MDD patients fulfilling the DSM-IV-TR criteria (Dold et al. 2016; 2017). The presence of comorbid GAD in predominant MDD was evaluated by the Mini International Neuropsychiatric Interview (MINI). The patients' socio-demographic, clinical, and treatment information was structurally collected within a detailed interview and the current depressive symptom severity was measured by the Montgomery and Åsberg Depression Rating Scale (MADRS) total score and the 17-item and 21-item Hamilton Rating Scale for Depression (HAM-D) total score. Moreover, symptom severity at the onset of the present MDD episode was assessed by retrospective MADRS evaluations. Different socio-economic, clinical, and treatment features between MDD patients with and without concurrent GAD were compared using descriptive statistics, chi-square tests, analyses of covariance (ANCOVA), as well as binary logistic regression analyses.

Results

The mean patient age was 50.3 ± 14.2 years and 67.3% were female. 90.6% of the participants suffered from recurrent depressive episodes. 65.1% were treated within an outpatient setting. Melancholic features were present in 61.1% and psychotic symptoms in 9.9% of the participants. Altogether, 47.0% suffered from somatic comorbidities with hypertension as the leading secondary diagnosis (19.4%) followed by thyroid diseases (14.7%). The depressive symptom severity at study enrollment was 24.3 ± 11.3 points measured by the MADRS total score and 19.4 ± 9.0 by the 21-item HAM-D.

21.2% of all analyzed MDD patients exhibited at least one comorbid anxiety disorder. In terms of the individual anxiety disorders, 10.8% (n=286) suffered from GAD, 8.3% from panic disorder, 8.1% from agoraphobia, 3.3% and social phobia.

Compared to the control group comprising MDD patients without concurrent GAD, the MDD + comorbid GAD patient group displayed higher depressive symptom severity (mean MADRS total score: 26.3 ± 10.1 vs 24.0 ± 11.4, p=.02) poorer treatment response (≥50% MADRS total reduction: 16.6% vs 26.0%, p=.02; mean MADRS total change: -7.3 ± 9.4 vs -9.9 ± 11.0 , p=.003), and a higher percentage of patients receiving augmentation treatment with benzodiazepines (44.1% vs 32.6%, p=.01) and pregabalin (11.7% vs 7.1%, p=.03) (Table 1). Furthermore, the MDD+GAD group was characterized by a lower proportion of patients with melancholic features (47.6% vs 62.8%, p=<.001), a higher percentage with concurrent asthma (6.2% vs 3.0%, p=.04), and a higher mean MADRS total score (26.3 ± 10.1 vs 24.0 ± 11.4, p=.02).

In the logistic regression analyses, severe depressive symptoms (mean MADRS total score: OR=1.03, p=.01), poorer treatment response (mean MADRS total decrease: OR=0.97, p=.01), and increased administration of pregabalin (OR=2.39, p=.01) were statistically significantly associated with the presence of concurrent GAD (Table 2).

Characteristics	MDD total (n=1346)	MDD with comorbid GAD (n=145)	MDD without comorbid GAD (n=1201)	p-value (ANCOVA/ x^2)
Gender, n (%)				
Male	440 (32.69)	47 (32.41)	393 (32.72)	.94
Female	906 (67.31)	98 (67.59)	808 (67.28)	
Age, mean (SD), years	50.38 (14.21)	48.02 (13.46)	50.67 (14.28)	.17
Marital status, n (%)				
Married / Live with	667 (49.55)	69 (47.59)	598 (49.79)	.63
Single	337 (25.04)	41 (28.28)	296 (24.65)	
Divorced/Separated/Widowed	342 (25.41)	35 (24.14)	307 (25.56)	
Ethnic origin, n (%)				
Caucasian	1296 (96.29)	137 (94.48)	1159 (96.50)	.06
Weight, mean (SD), kg	72.84 (17.54)	71.24 (18.40)	73.04 (17.43)	.83
Highest level of education and/or degree, n (%)				
University education	248 (18.42)	22 (15.17)	226 (18.82)	.16
Non-university high education	148 (11.00)	13 (8.97)	135 (11.24)	
High Level general education secondary / Technical Education	347 (25.78)	50 (34.48)	297 (24.73)	
General Secondary / Technical Education	488 (36.26)	50 (34.48)	438 (36.47)	
Elementary School	111 (8.25)	10 (6.90)	101 (8.41)	
None	4 (0.30)	0 (0.00)	4 (0.33)	
Depressive episode, n (%)				
Single	127 (9.44)	18 (12.41)	109 (9.08)	.19
Recurrent	1219 (90.56)	127 (87.59)	1092 (90.92)	
With psychotic features	133 (9.88)	12 (8.28)	121 (10.07)	.50
With melancholic features	823 (61.14)	69 (47.59)	754 (62.78)	<.001
With atypical features	33 (2.45)	2 (1.38)	31 (2.58)	.38
Setting, n (%) (n=1336)				
Inpatient	466 (34.88)	43 (30.07)	423 (35.46)	.20
Outpatient	870 (65.12)	100 (69.93)	770 (64.54)	
Somatic comorbidities, n (%)				
Any somatic comorbidity	633 (47.03)	69 (47.59)	564 (46.96)	.88
Hypertension	261 (19.39)	27 (18.62)	234 (19.48)	.81
Thyroid disease	198 (14.71)	17 (11.72)	181 (15.07)	.28
Diabetes	82 (6.09)	9 (6.21)	73 (6.08)	.95
Heart disease	72 (5.35)	8 (5.52)	64 (5.33)	.92
Arthritis	62 (4.61)	4 (2.76)	58 (4.83)	.26
Asthma	45 (3.34)	9 (6.21)	36 (3.00)	.04
Current suicide risk (dichotomous)	626 (46.51)	72 (49.66)	554 (46.13)	.35
Suicide risk, n (%) (n=626)				
High / moderate	357 (57.03)	43 (59.72)	314 (56.68)	.62
Low	269 (42.97)	29 (40.28)	240 (43.32)	
HAM-D total 21-item, mean (SD)	19.44 (9.03)	21.74 (8.30)	19.16 (9.08)	.11
HAM-D total 17-item, mean (SD)	18.43 (8.70)	20.86 (8.35)	18.13 (8.70)	.22
MADRS total, mean (SD)	24.26 (11.30)	26.25 (10.14)	24.02 (11.41)	.02
MADRS total at onset of current MDD episode, mean (SD)	34.00 (7.80)	33.73 (6.99)	34.03 (7.89)	.20
MADRS total change, mean (SD)	-9.65 (10.84)	-7.26 (9.43)	-9.94 (10.97)	.003
Treatment response (dichotomous), n (%)				
Response (≥50% MADRS total reduction) (n=1331)	332 (24.94)	24 (16.55)	308 (25.97)	.02
Resistance (n=1331)	455 (33.80)	45 (31.03)	410 (34.14)	.48
Psychopharmacotherapy				
Number of drugs, mean (SD)	2.19 (1.21)	2.19 (1.18)	2.19 (1.21)	.42
Polypharmacy, n (%)	822 (61.07)	87 (60.00)	735 (61.20)	.78
Monotherapy, n (%)	524 (38.93)	58 (40.00)	466 (38.80)	
Applied psychopharmacological combination and augmentation strategies (in addition to the ongoing antidepressant treatment), n (%)				
Combination with ≥1 add-on antidepressant	397 (29.49)	35 (24.14)	362 (30.14)	.07
Augmentation with ≥1 antipsychotic drug	351 (26.08)	37 (25.52)	314 (26.14)	.88
Augmentation with ≥1 mood stabilizer	152 (11.29)	12 (8.28)	140 (11.66)	.23
Augmentation with ≥1 BZD/BZD-like drug	456 (33.88)	64 (44.14)	392 (32.64)	.01
Augmentation with ≥1 low-potency antipsychotic	88 (6.54)	4 (2.76)	84 (6.99)	.05
Augmentation with pregabalin	102 (7.58)	17 (11.72)	85 (7.08)	.03

Table 1. Patients' demographic, clinical, and treatment variables for the comparison MDD with vs without comorbid anxiety.
Abbreviations: BZD = benzodiazepines; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; n = number of participants; SD = standard deviation.

	B	SE	adjusted OR	95% CI	p-value
Comorbid asthma	0.98	0.47	2.45	1.02 - 5.95	.04
HAM-D total 21-item	0.07	0.02	1.08	1.04 - 1.11	<.001
HAM-D total 17-item	0.07	0.02	1.08	1.04 - 1.11	<.001
MADRS total	0.03	0.01	1.03	1.01 - 1.05	.01
MADRS total change	-0.03	0.01	0.97	0.96 - 0.99	.01
Augmentation with pregabalin	0.88	0.33	2.39	1.27 - 4.55	.01

Table 2. Binary logistic regression analyses investigating the association between explanatory variables and the presence of comorbid GAD.
The present table displays all variables that are associated with comorbid GAD. Due to limited space and to ensure enhanced readability, exclusively the statistically significant results are presented. The odds ratios (OR) are adjusted for the covariate recruitment center.
Abbreviations (alphabetical order): B = regression coefficient; CI = confidence interval; MADRS = Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; OR = odds ratio; SE = standard error.

Conclusions

In summary, our findings indicate that GAD is the most often manifested comorbid anxiety disorder in patients with primary MDD diagnosis (point prevalence: 10.8%). We could determine that concurrent GAD is associated with high depressive symptom severity, poor treatment response, and frequent use of augmentation strategies (with benzodiazepines and pregabalin), whereas psychotherapy on the other hand was less often established in case of the presence of comorbid GAD. These findings could be also observed when comparing concurrent GAD to other comorbid anxiety disorders in unipolar depression such as panic disorder, agoraphobia, and social phobia. Taken together, our study findings indicate that the different anxiety disorders show different clinical characteristics if they represent a comorbidity of MDD.

References

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