Factors Associated with Augmentation Agent Use in Patients with Treatment-Resistant Depression

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Background

- Treatment-resistant depression (TRD) is defined as the failure to respond to two or more treatments of adequate dose and duration in the same episode of major depressive disorder (MDD).[1]
- In 2013, the EMA reported that approximately one-third of patients with MDD do not adequately respond to treatment.[1]
- Given inconsistent definitions of TRD and heterogeneity in the selection of optimal treatments, more information is needed to better understand subgroups within this patient population.
- For patients with MDD with inadequate response to antidepressants, physicians may consider the use of augmentation pharmacotherapy, which refers to the addition of drugs that are not antidepressants to improve clinical response.
- To date, limited data are available which describe factors associated with use of augmentation agents for TRD.

Objectives

- Characterize and compare patients with TRD treated with an augmentation agent and treated without an augmentation agent

Methods

- This study used patient data from a cross-sectional survey of 225 healthcare providers (HCPs), distributed evenly across Germany, France and the United Kingdom (UK). For each HCP, information was collected on the treatment provided to five patients with TRD seen in the past 12 months. Further details on the survey design were described in Orsini et al. (2022).[2]
- Patients were stratified by augmentation agent use (typical and atypical antipsychotics, lithium, thyroid hormone, mood stabilizers, buspirone; AU) and no augmentation agent use (NAU) in their first failed, second failed, and current/most recent treatment regimen in their TRD episode.
- Patients' demographics as well as provider, comorbid conditions, and depression characteristics were compared between AU and NAU using chi-squared (for categorical variables) and Student's t tests or Wilcoxen rank sum tests (for continuous variables).
- A logistic regression model, adjusted for all variables in Table 2, was developed to identify factors associated with AU.
  - Multiple imputations by chained equations (MICE) with predictive mean matching was performed using the MICE package version 3.15.0 in R to impute missing values.[3]
- Multicollinearity was assessed and variables with variance inflation factors exceeding 10 were removed.

Table 1. Patient Attrition

	N	%
Step 1: All responses collected in the survey	1125	100.0%
Step 2: Patients with comorbidities collected	1077	95.7%
Step 3: Patients currently/most recently treated with a pharmacologic therapy	1047	93.1%
Step 4: Survey responses from psychiatrist providers	878	78.0%
Step 5: Patients without lifetime history of bipolar disorders	790	70.2%

Results

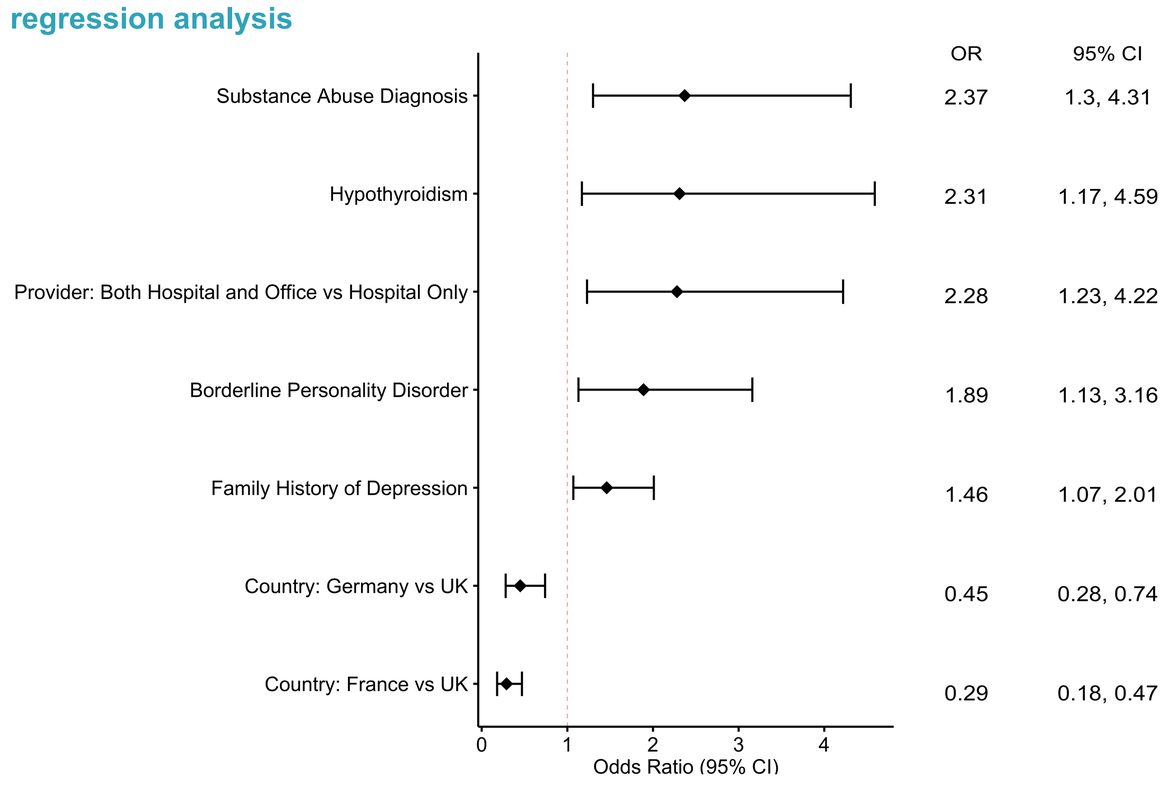
- After applying the patient selection criteria, the final study population consisted of 790 patients (70.2% of all patients collected in the survey; Table 1).
- A large majority of patients from the UK (78.3%) were in the AU cohort while 49.2% of patients from France and 56.2% of patients from Germany were in the AU cohort (Table 2).
- Compared to the NAU cohort, the AU cohort had:
  - A lower proportion of patients whose provider practiced only in the office setting while having a higher proportion of patients whose provider practiced in both the hospital and office settings (23.6% vs 31.5% and 12.7% vs 5.7%, respectively; p=0.002).
  - A higher proportion of patients with a family history of depression (49.9% vs 38.7%; p=0.002), suicide attempts (30.0% vs 20.1%, p=0.002), borderline personality disorder (16.4% vs 9.0%, p=0.002), substance abuse (14.0% vs 5.7%, p<0.001), childhood trauma/adverse childhood event (24.5% vs 18.0%, p=0.029), and hypothyroidism (9.6% vs 3.9%, p=0.002).
  - A higher mean number of years since first MDD diagnosis (5.8 vs 4.3 years; p=0.001).
  - A higher number of prior MDD episodes (53.8% vs 41.1% with 3 or more episodes; p=0.009).
- A forest plot of the significant characteristics revealed from the logistic regression model is displayed in Figure 1.
  - Patients in France or Germany were less likely to be treated with an augmentation agent compared to patients in the UK (France Odds Ratio (OR): 0.28 [95% confidence interval (CI): 0.18, 0.46]; Germany OR: 0.45 [0.27, 0.73]).
  - AU was higher in patients with providers who practiced in both the hospital and office settings compared to the hospital setting only (OR: 2.28 [1.23, 4.23]).
  - Several comorbidities were associated with AU: family history of depression (OR: 1.46 [1.07, 2.01]), borderline personality disorder (OR: 1.88 [1.13, 3.14]), substance abuse diagnosis (OR: 2.37 [1.30, 4.32]), and hypothyroidism (OR: 2.30 [1.16, 4.57]).
  - Effect estimates were consistent in a sensitivity analysis of modified MICE parameters. Multicollinearity was not observed.

Table 2: Patient Characteristics

Characteristic	Total, N = 790[1]	No Augmentation Therapy, N=333[1]	Augmentation Therapy, N=457[1]	p-value[2]
Country				<0.001***
United Kingdom	161 (20.4%)	35 (21.7%)	126 (78.3%)	
France	321 (40.6%)	163 (50.8%)	158 (49.2%)	
Germany	308 (39.0%)	135 (43.8%)	173 (56.2%)	
Gender				0.2
Male	378 (47.8%)	171 (51.4%)	207 (45.3%)	
Female	408 (51.6%)	161 (48.3%)	247 (54.0%)	
Non-binary	4 (0.5%)	1 (0.3%)	3 (0.7%)	
Age (years)				0.5
18-29	121 (15.3%)	52 (15.6%)	69 (15.1%)	
30-39	169 (21.4%)	74 (22.2%)	95 (20.8%)	
40-49	162 (20.5%)	74 (22.2%)	88 (19.3%)	
50-59	184 (23.3%)	67 (20.1%)	117 (25.6%)	
60-69	120 (15.2%)	49 (14.7%)	71 (15.5%)	
70+	34 (4.3%)	17 (5.1%)	17 (3.7%)	
Hospital or Office Practice Setting				0.002**
Hospital	449 (56.8%)	184 (55.3%)	265 (58.0%)	
Office	213 (27.0%)	105 (31.5%)	108 (23.6%)	
Both hospital and office	77 (9.7%)	19 (5.7%)	58 (12.7%)	
Neither (Only in academic setting)	51 (6.5%)	25 (7.5%)	26 (5.7%)	
Academic Practice Setting	97 (12.3%)	46 (13.8%)	51 (11.2%)	0.3
Family History of Depression	357 (45.2%)	129 (38.7%)	228 (49.9%)	0.002**
General Anxiety Diagnosis	236 (29.9%)	101 (30.3%)	135 (29.5%)	0.8
Panic Attacks/Panic Diagnosis	154 (19.5%)	58 (17.4%)	96 (21.0%)	0.2
Social Anxiety Diagnosis	147 (18.6%)	58 (17.4%)	89 (19.5%)	0.5
Suicidal Ideation	383 (48.5%)	153 (45.9%)	230 (50.3%)	0.2
Suicide Attempts	204 (25.8%)	67 (20.1%)	137 (30.0%)	0.002**
Post-Traumatic Stress Disorder	72 (9.1%)	23 (6.9%)	49 (10.7%)	0.066
Obsessive-Compulsive Disorder	62 (7.8%)	31 (9.3%)	31 (6.8%)	0.2
Borderline Personality Disorder	105 (13.3%)	30 (9.0%)	75 (16.4%)	0.002**
Insomnia	244 (30.9%)	99 (29.7%)	145 (31.7%)	0.5
Substance Abuse Diagnosis	83 (10.5%)	19 (5.7%)	64 (14.0%)	<0.001***
Childhood Trauma/Adverse Childhood Event	172 (21.8%)	60 (18.0%)	112 (24.5%)	0.029*
Cancer	32 (4.1%)	13 (3.9%)	19 (4.2%)	0.9
Cardiovascular Diseases	101 (12.8%)	37 (11.1%)	64 (14.0%)	0.2
Musculoskeletal Diseases	135 (17.1%)	57 (17.1%)	78 (17.1%)	>0.9
Respiratory Diseases	129 (16.3%)	46 (13.8%)	83 (18.2%)	0.1
Metabolic Diseases	319 (40.4%)	126 (37.8%)	193 (42.2%)	0.2
Fatigue	126 (15.9%)	53 (15.9%)	73 (16.0%)	>0.9
Hypothyroidism	57 (7.2%)	13 (3.9%)	44 (9.6%)	0.002**
Years Since First MDD diagnosis				
Mean (SD)	5.1 (7.0)	4.3 (6.5)	5.8 (7.2)	0.001**
Unknown	223 (28%)	88 (26%)	135 (30%)	
Number of prior depressive episodes				0.009**
0	68 (8.6%)	36 (10.8%)	32 (7.0%)	
1	132 (16.7%)	65 (19.5%)	67 (14.7%)	
2	207 (26.2%)	95 (28.5%)	112 (24.5%)	
3	148 (18.7%)	58 (17.4%)	90 (19.7%)	
4	77 (9.7%)	29 (8.7%)	48 (10.5%)	
5+	158 (20.0%)	50 (15.0%)	108 (23.6%)	

[1]n (%)
[2]*p<0.05; **p<0.01; ***p<0.001

Figure 1: Forest plot of significant characteristics identified from logistic regression analysis



Conclusions

- This study identified family history of depression, borderline personality disorder, substance abuse diagnosis, and hypothyroidism to be associated with use of augmentation agents for treatment of patients with TRD.
- In this sample, providers in France and Germany were less likely to prescribe augmentation agents compared to those in the UK, which may reflect differences in treatment guidelines and attitudes towards augmentation agents as treatment for TRD across countries.

References

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