Elevated Anxiety in Patients with Unresolved Major Depressive Disorder

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Introduction

- In the United States (US), the approximate prevalence of adults aged 18 years or older who experienced at least one major depressive episode in the past 12 months increased from 7.8% in 2019 to 8.3% in 2021.[1,2]
- Despite stable treatment rates for patients with major depressive disorder (MDD) over the past decade,[3] the incremental economic burden of MDD in US adults increased by 38% from 2010 to 2018, indicating a high unmet treatment need.[3]
- Antidepressant treatments (ADTs) are generally the first-line of pharmacological agents for MDD, but they can fail to effectively alleviate depressive symptoms in some patients even when multiple ADTs are prescribed successively or in combination with other agents.[4]
- Several severity indicators may contribute to the lack of response to pharmacotherapy, including comorbid hyperarousal/ anxiety-related symptoms.[4]
- Patients with comorbid anxiety and MDD often have more severe symptoms with worsened outcomes compared with patients with MDD without anxiety. However, there is a lack of studies exploring the presence of elevated anxiety (EA) in patients with unresolved symptoms of MDD.

Objective

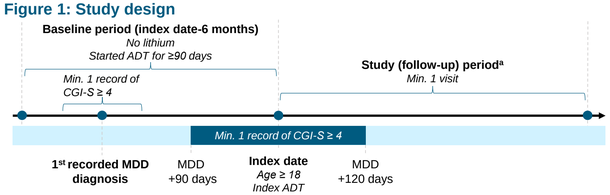
- To provide real-world evidence on the prevalence of EA in patients with unresolved symptoms of MDD despite being on any ADTs, and to descriptively compare illness severity and medical encounter utilization (MEU) between those with and without pre-existing EA.

Methods

Study Design and Patient Selection

- This retrospective disruptive longitudinal cohort study analyzed electronic health records from the NeuroBlu™ database (01/01/2000 – 12/31/2020) to evaluate a cohort of adult patients (≥18 years) with unresolved symptoms of MDD, as defined by the Clinical Global Impression-Severity (CGI-S) scale, a 7-point Likert scale used to assess illness severity and treatment efficacy.[5]
- Patients with unresolved MDD symptoms were identified based on CGI-S scores of ≥4, indicating they were "moderately ill", at both the first-recorded MDD diagnosis, and at 90-120 days after diagnosis (index date) and were required to have a prescription order for ≥90 consecutive days of any ADTs within 180 days prior to the index date (baseline period).
- In the 6 months prior to and including the index date, patients were required to have either ≥1 ICD-10 code for MDD in an inpatient/emergency room setting or ≥2 ICD-10 codes indicating depression in an outpatient setting, with ≥1 code for MDD.
- Patients were also required to have ≥1 visit within 16-365 days post-index (follow-up period) to account for variability in data availability in measurement data in real-world practice and were excluded if they had records of a diagnosis of bipolar disorder, any schizophrenia spectrum disorder, or prescription(s) of lithium.
- Patients with EA were identified as having a comorbid diagnosis of generalized anxiety disorder (GAD) and/or prescriptions of at least one anxiolytic drug for ≥14 days.
  - Sub-cohorts were then created based on the presence or absence of EA at baseline.
  - Patients with EA at baseline were referred to as the "pre-existing EA" cohort. Patients who did not have EA at baseline but were identified with EA during the follow-up period were referred to as the "new-onset EA" cohort.

Figure 1: Study design



ADT, antidepressant treatment; CGI-S, Clinical Global Impression-Severity; MDD, major depressive disorder; Min., minimum.
Notes: Cohort inclusion and exclusion criteria are reflected in italics, while time periods are reflected in bold. Index characteristics were examined ±15 days from the index date to account for variability in data measurement in real-world clinical practice.
[a]The study period was thus defined from day 16 to day 365 following the index date.

Study Outcomes and Analyses

- Clinical severity at index was evaluated for patients with and without pre-existing EA during the baseline period using CGI-S (1-7, with higher scores indicating greater illness severity).[6]
- Changes in clinical severity were assessed at index and 12 months post-index for patients with pre-existing and new-onset EA.
- Kaplan-Meier survival analyses were conducted to examine MEU defined as the number of inpatient, emergency room, and outpatient events during the follow-up period in patients with and without EA at baseline. Censoring was defined as the end of the study period (365 days post-index date) or loss to follow-up (for patients with last known visit date <365 days from index date). The number of patients at risk, the median time-to-event, and the event rate with a 95% confidence interval was reported every 30 days beginning from the index date until the end of the study period.
  - A decrease in anxiety-related MEU for patients with pre-existing EA was defined by the presence of GAD diagnosis and/or anxiolytics prescription during the baseline period and an absence of the same during the follow-up period.
  - Conversely, an increase in anxiety-related MEU for new-onset EA was defined by the absence of GAD diagnosis and/or anxiolytics prescription during the baseline period, and the presence of the same during the follow-up period.

Results

Baseline Characteristics

- A total of 3,342 patients were identified as having unresolved MDD symptoms, among which the majority of patients were females (70.56%), White (60.74%), and the mean age was 44.37 years (**Table 1**).
- A plurality of patients were moderately ill, with nearly half (45.57%) having a CGI-S of 4 at the first-recorded MDD diagnosis during the baseline period.
- During the baseline period, 1,782 (53.32%) patients were identified as having pre-existing EA, and 1,560 (46.67%) patients did not have pre-existing EA.

Table 1: Demographic and baseline clinical characteristics

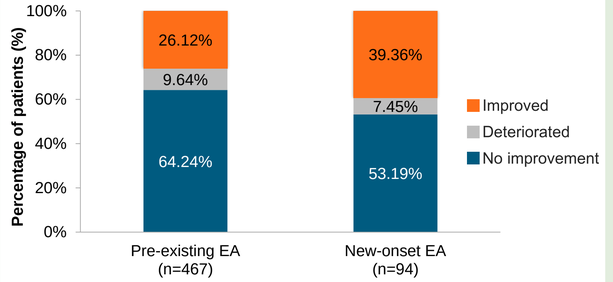
Demographic factors	N=3,342
Age at index (years), mean (SD)	44.37 (14.57)
Age group at index, %	
18-39	37.88
40-64	53.92
65+	8.20
Sex, %	
Female	70.56
Male	29.44
Race, %	
White	60.74
Black or African American	12.24
Native Hawaiian or Other Pacific Islander	2.66
Other race (unspecified)	1.50
Asian	1.14
American Indian or Alaska Native	0.27
Unknown	21.45
Ethnicity, %	
Not Hispanic or Latino	45.54
Hispanic or Latino	16.22
Unknown	38.24
Baseline clinical characteristics	**N=3,342**
Psychiatric diagnoses, %	
Diagnosis of MDD	
≥1 diagnosis of MDD from inpatient visits	15.86
≥2 diagnoses of MDD, OR MDD with other depression within 6 months from outpatient visits	84.14
Psychiatric comorbidities during the baseline period	24.78
Substance use disorders	18.79
Post-traumatic stress disorder	18.16
Other anxiety disorders (excluding GAD)	12.63
Personality disorders	6.46
Attention deficit hyperactivity disorder	3.08
Obsessive-compulsive disorder	0.27
Autism	
Illness severity, %	
CGI-S score at first-recorded MDD diagnosis	
4: Moderately ill	45.57
5: Markedly ill	38.72
6: Severely ill	14.57
7: Among the most extremely ill	1.14
CGI-S score at index date	
4: Moderately ill	60.47
5: Markedly ill	31.99
6: Severely ill	7.15
7: Among the most extremely ill	0.39
Pharmacotherapy treatments present during the baseline period, %	
Antidepressants	100.00
Number of antidepressant classes[a] present in prescription records	
1	61.28
2	34.56
3	4.01
4	0.15
Augmentation agents[b]	23.97
Anxiolytics[c]	46.17
Pre-existing elevated anxiety recorded during the baseline period[d], %	
Identified by a diagnosis of GAD or prescription of anxiolytic	53.32
Identified by a diagnosis of GAD	18.76
Identified by a prescription of anxiolytics	46.17

CGI-S, Clinical Global Impressions-Severity; MDD, Major Depressive Disorder; GAD, Generalized anxiety disorder.
[a] The following mapping was used: SSRI: fluoxetine, paroxetine, sertraline citalopram, escitalopram, fluvoxamine; SNRI: venlafaxine, duloxetine, desvenlafaxine, levomilnacipran, milnacipran; Atypical AD: bupropion, mirtazapine, trazodone, vortioxetine, vilazodone, nefazodone; TCA: imipramine, amitriptyline, clomipramine, nortriptyline, desipramine, trimipramine, protriptyline, maprotiline, doxepin; MAOI: isocarboxazid, phenelzine, selegiline, tranylcypromine
[b] Includes aripiprazole, quetiapine, risperidone, brexipiprazole, lurasidone, levomefolate, pramipexole, cariprazine
[c] Includes meprobamate, diazepam, oxazepam, buspirone, hydroxyzine, alprazolam, clorazepate, lorazepam, clonazepam, chlordiazepoxide, propranolol, clonidine, prazepam , bromazepam, halazepam
[d] Some patients were identified by both diagnosis of GAD and prescription of anxiolytic, these criteria are not mutually exclusive

Changes in Clinical Severity

- The distribution of CGI-S scores at the index date was similar between the cohorts with and without pre-existing EA at baseline.
  - The majority of patients in both cohorts had a score of 4 (Pre-existing EA: 1,041 [58.42%] vs Without pre-existing EA: 980 [62.82%]).
- Of the 1,560 patients without pre-existing EA, 239 patients (15.32%) were found to have new-onset EA during the follow-up period.
- A greater proportion of patients with pre-existing EA compared with new-onset EA (73.88% vs 60.64%) either experienced no improvement or showed deterioration in their CGI-S scores over 12 months (**Figure 2**).
- Additionally, among patients who had recorded CGI-S scores at 12 months, psychiatric comorbidities were explored between those with pre-existing EA and new-onset EA.
  - The pre-existing EA sub-cohort exhibited a high prevalence of psychiatric comorbidities, with other anxiety disorders (excluding GAD) being the most common (28.9%), followed by substance use disorders (25.1%) and post-traumatic stress disorder (23.6%).
  - In the new-onset EA sub-cohort, post-traumatic stress disorder (22.3%) was the most prevalent comorbidity, followed by substance use disorders (17.0%) and other anxiety disorders (excluding GAD) (16.0%).

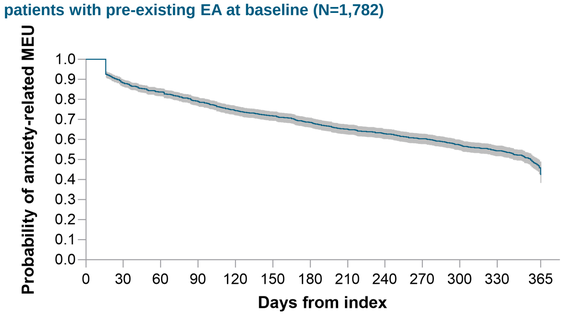
Figure 2: Changes in clinical severity (CGI-S scores) from index among patients with pre-existing and new-onset EA at 12 months post-index



Anxiety-Related MEU

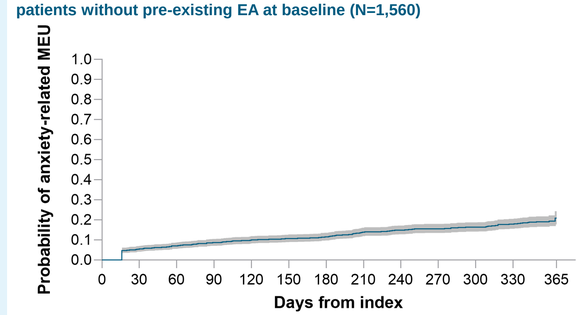
- Survival analysis demonstrated that patients identified as having pre-existing EA at baseline had a 2-fold higher probability of anxiety-related MEU by the end of the follow-up period than patients identified as not having EA at baseline (**Figures 3 and 4**).

Figure 3: Time to event analysis of anxiety-related MEU over time for patients with pre-existing EA at baseline (N=1,782)



Note: A decrease in anxiety-related MEU was defined by the presence of GAD diagnosis and/or anxiolytic prescription during the baseline period and an absence of the same during the follow-up period.

Figure 4: Time to event analysis of anxiety-related MEU over time for patients without pre-existing EA at baseline (N=1,560)



Note: An increase in anxiety-related MEU was defined by the absence of GAD diagnosis and/or anxiolytic prescription during the baseline period, and the presence of the same during the follow-up period.

Limitations

- Unresolved MDD was defined as patients diagnosed with MDD who remained "moderately ill" according to their clinicians even after 90 days of ADT. However, external factors affecting patients (e.g., acute environmental stressors) could have contributed to the score and severity and may not be correlated to ADT benefit or lack thereof.
- EA was identified based on the presence of a comorbid GAD diagnosis or anxiolytic drug prescriptions for ≥14 days. All identified EA patients using anxiolytics prescription orders may not have anxiety symptoms, and so this definition may overestimate the number of patients experiencing anxiety symptoms. However, as not all individuals with elevated anxiety receive a diagnosis of GAD or anxiolytic drug prescription, there are also likely patients with anxiety symptoms who are not captured by these data.
- The observations were limited by the data available in the NeuroBlu™ database as patients were either lost to follow-up or not captured because of out-of-network medical visits, thereby potentially underestimating MEU and treatment outcomes over a longer follow-up period.
- Furthermore, the lack of MEU records captured in the database may not necessarily reflect a decrease in anxiety symptoms or related outcomes and any related care outside the network. Nonetheless, the current insights from the analysis highlight a potential scientific gap that warrants additional research.
- Lastly, the analysis was descriptive and did not include statistical comparisons or adjustments of baseline characteristics between pre-existing and new-onset EA cohorts.

Conclusions

- The majority of the cohort were identified as having EA within the study period. EA is a likely co-occurring and burdensome symptom of patients with unresolved MDD, which may be clinically challenging over time with potential impact at the population level for a healthcare system.
- In this study, approximately two-thirds of patients with unresolved MDD and EA exhibited either no improvement or experienced deterioration in their CGI-S scores during the follow-up period. This finding is consistent with prior research indicating that patients with depression and EA, compared with those with depression and without EA, may be at risk of treatment failure and have unmet clinical needs,[7,8] highlighting the need for improved therapeutic options.
- Further, research with a different study design and/or clinical settings is needed to better recognize anxiety symptoms and understand the burden of anxiety in patients with unresolved MDD, including long-term implications on healthcare costs and patient outcomes.

Abbreviations

ADT, antidepressant treatment; CCI, Charlson Comorbidity Index; CGI-S, Clinical Global Index-Severity, EA, elevated anxiety; GAD, generalized anxiety disorder; ICD-10, International Classification of Diseases, Tenth Revision; MDD, major depressive disorder; MEU, medical encounter utilization; SD, standard deviation; US, United States

Acknowledgements

Support for study analyses was provided by Holmusk, a third-party analytic consulting company that was funded by Sage Therapeutics, Inc. (Cambridge, MA, USA) and Biogen Inc. (Cambridge, MA, USA). Medical writing and editorial support for the preparation of this poster was provided by Boston Strategic Partners, Inc. (Boston, MA, USA), which was funded by Sage Therapeutics, Inc. and Biogen Inc.

Disclosures: AJR has received consulting fees from Compass Inc., Curbstone Consultant LLC, Emmes Corp., Evecxia Therapeutics, Inc., Holmusk Technologies, Inc., ICON, PLC, Johnson and Johnson (Janssen), Liva-Nova, MindStreet, Inc., Neurocrine Biosciences Inc., Otsuka-US; speaking fees from Liva-Nova, Johnson and Johnson (Janssen); and royalties from Wolters Kluwer Health, Guilford Press and the University of Texas Southwestern Medical Center, Dallas, TX (for the Inventory of Depressive Symptoms and its derivatives). ES, MW, AC, SH, and TG are employees of Sage Therapeutics, Inc. and may own stock and/or stock options. MP and MN are employees of Biogen Inc. and may own stock; MP owns stock in Pfizer Inc.

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