Reductions in Depressive Symptoms After Brexpiprazole Augmentation Among Patients with Major Depressive Disorder Receiving Antidepressant Therapy in Real-World Settings

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INTRODUCTION

- Major depressive disorder (MDD) is a common psychiatric condition in the United States.[1]
- As many as 30% of patients treated with antidepressant therapy do not show adequate response.[2,3]
- Antidepressant therapies may be augmented by atypical antipsychotics when treatment response is not adequate.
- Brexpiprazole is a second-generation antipsychotic approved by the FDA for use as an adjunctive therapy to antidepressants for the treatment of MDD since July 2015.
- Efficacy of brexpiprazole over placebo among patients with MDD has been demonstrated in several clinical trials.[4]
- Assessments of the effectiveness of brexpiprazole in real-world settings are limited.
- The primary aim of this study was to assess changes in depressive symptoms among patients receiving brexpiprazole as adjunctive therapy to an antidepressant for MDD using real-world data.
- A secondary aim of this study was to assess changes in symptoms of anxiety and response to treatment among the same cohort of patients.

METHODS

Data Source

- Data are from a real-world dataset of over 600,000 patients with MDD in the US with linked claims and electronic medical record (EMR) data (OM1, Inc. Boston MA).
- The index date was defined as the date of the first brexpiprazole prescription (written or filled) between July 2015 and January 2023.
- Patients with ≥2 MDD diagnoses before the index date plus treatment with brexpiprazole for ≥30 days while on antidepressant therapy for ≥60 days before and ≥30 days after the index date were eligible. Cohort attrition is provided in Table 1.

Study Design

- This is a retrospective observational cohort study.
- Clinical outcomes were assessed over the 12 months following the index date. The most recent score prior to the index date or prior to the end of each follow-up time window was used.
- Follow-up was 12 months post-index with three time-windows for outcomes assessment: >0 to 3 months, >3 to 6 months, and >6 to 12 months.

Statistical analysis

- Descriptive statistics are presented for baseline demographics and clinical comorbidity history for patients with at least one baseline and follow-up PHQ-9 score.
- Descriptive statistics are presented for primary outcome variables; 95% confidence intervals are presented for mean differences between baseline and follow-up PHQ-9 scores.

Primary Outcome

- The **Patient Health Questionnaire-9 Item (PHQ-9)** was used to assess depressive symptoms.[5]
- PHQ-9 scores between 0-4 were categorized as in remission from depression.
- PHQ-9 scores documented in routine clinical care (observed) were supplemented with PHQ-9 scores estimated using a machine learning model applied to available relevant clinical notes.[6]
- Recorded and estimated scores are presented separately. Due to similarity in trends, scores were combined for interpretation.

Secondary Outcomes

- The **Generalized Anxiety Disorder-7 Item (GAD-7)** was used to assess symptoms of anxiety.[7]
- **The Clinical Global Impressions – Improvement (CGI-I)** was used to assess improvement after initiation of treatment.[8]
- Scores of very much improved (1) or much improved (2), were used to identify response to treatment.[9,10]
- CGI-I scores recorded in routine clinical care (observed) were supplemented with CGI-I scores estimated using a machine learning model.
- Recorded and estimated scores are presented separately. Due to similarity in trends, scores were combined for interpretation.

RESULTS

- There were a total of 1,073 patients with MDD who received brexpiprazole as an adjunctive therapy to an antidepressant with at least one PHQ-9 score during baseline and at least one score during follow-up (Table 1).
- The average age at brexpiprazole initiation was 48.8 (SD=15.6) years; 78.0% of patients were female (Table 2).
- Most patients (60.9%) had a comorbid diagnosis of an anxiety disorder in the year prior to initiating brexpiprazole (Table 3).
- The average PHQ-9 score at baseline was 12.0 (SD=6.1) which decreased to 9.7 (SD=5.8) at >0-3 months, 9.7 (SD=6.0) at >3-6 months, and 8.9 (SD=6.1) at >6-12 months after brexpiprazole initiation (Table 4).
- The percentage of patients with PHQ-9 scores indicating remission (0-4) increased from 11.0% at baseline to 19.3%, 21.2%, and 27.2% at >0-3 months, >3-6 months, and >6-12 months after brexpiprazole initiation, respectively (Table 4).
- The average change in PHQ-9 scores from baseline period was -2.1 (95% CI: -2.5, -1.7) at >0-3 months, -2.3 (95% CI: -2.7, -2.0 at >3-6 months, and -2.8 (95% CI: -3.2 -2.4) at >6-12 months (Figure 1).
- There were 213 patients with at least one GAD-7 score during baseline and follow-up.
- The average GAD-7 score at baseline period was 10.4 (SD=5.6) which decreased to 8.6 (SD=5.4) at >0-3 months, 8.5 (SD=5.9) at >3-6 months, and 8.0 (SD=5.9) at >6-12 months after brexpiprazole initiation (Table 5).
- There were 1,250 patients with at least one CGI-I score during baseline and during follow-up.
- The percentage of patients with treatment response measured by the CGI-I increased from 26.1% at baseline to 30.2%, 35.5%, and 37.6% at >0-3 months, >3-6 months, and >6-12 months after brexpiprazole initiation, respectively (Figure 2).

Table 1. Cohort attrition

	Number of patients	% from previous step
1. OM1 PremiOM MDD dataset	603,887	100.0%
2. Initiated brexpiprazole between July 10, 2015 and January 31, 2023 and were treated for ≥30 days	22,125	3.7%
3. Initiated brexpiprazole as augmentation treatment to an antidepressant (after ≥60 days on an antidepressant and ≥30-days overlap with the antidepressant)	12,163	55.0%
4. At least two MDD diagnoses ≥30 days apart during the 12 months prior to brexpiprazole initiation	8,355	68.7%
5. 18 years or older at index	8,278	99.1%
6a.Have linked medical claims and EMR data beyond the 12 months prior to index and beyond the 12 months post index	4,665	56.4%
6b. Have linked medical claims and EMR data within the 12 months prior to index (inclusive) and within the 12 months post index	3,598	77.1%
7. Do not have at ≥2 psychotic disorder, bipolar disorder, or substance use disorder diagnoses ≥30 days apart during the 12 months prior to brexpiprazole initiation	3,085	85.7%
8. Patients who have a PHQ-9 at baseline and during follow-up	**1,073**	**34.8%**

Table 2. Demographics at baseline among patients with MDD taking brexpiprazole as augmentation to an antidepressant

Characteristic		Patients with baseline and follow-up PHQ-9 Scores (N=1,073)
Age (years)	N	1,073
	Mean (s.d.)	48.8 (15.6)
	Median (Q1-Q3)	50 (38-61)
Sex	Female	837 (78.0)
	Male	236 (22.0)
Race	White	635 (89.1)
	Black or African American	49 (6.9)
	American Indian or Alaska Native	2 (0.3)
	Asian	10 (1.4)
	Multiracial	1 (0.1)
	Native Hawaiian or Other Pacific Islander	1 (0.1)
	Other Race	15 (2.1)
	Unknown	360
Ethnicity	Not Hispanic or Latino	657 (92.9)
	Hispanic or Latino	35 (5.0)
	Other ethnicity	15 (2.1)
	Unknown	366
Insurance category	Commercial	529 (49.3)
	Medicaid	73 (6.8)
	Medicare	218 (20.3)
	Other insurance	21 (2.0)

Data are N (%) unless otherwise noted.

Table 3. Clinical comorbidity history during baseline among patients with MDD taking brexpiprazole as augmentation to an antidepressant

Characteristic		Patients with baseline and follow-up PHQ-9 Scores (N=1,073)
Charlson comorbidity index	N	1,073
	Mean (s.d.)	0.9 (1.5)
	Median (Q1-Q3)	0 (0-1)
Psychiatric comorbidities (within 12 months before or index date)		
Anxiety disorder	N (%)	653 (60.9)
Attention deficit hyperactivity disorder	N (%)	198 (18.5)
Post-traumatic stress disorder	N (%)	144 (13.4)
Insomnia-related sleep disorders	N (%)	90 (8.4)
Other comorbidities (any time prior to or on index date)		
Hypertension	N (%)	325 (30.3)
Dyslipidemia	N (%)	294 (27.4)
Type 2 diabetes	N (%)	141 (13.1)
Obesity	N (%)	217 (20.2)
Thyroid disease	N (%)	197 (18.4)

Table 4. PHQ-9 Scores and PHQ-9 categories at baseline, 3-month, 6-month and 12-month follow-up

Characteristic		Baseline	>0-3 Months	>3-6 Months	>6-12 Months
PHQ-9 (observed)	N	340	264	244	268
	Mean (s.d.)	13.4 (6.6)	10.9 (6.2)	10.9 (6.3)	10.1 (6.7)
	Median (Q1-Q3)	13 (8-18)	10 (6-15)	10 (6-15)	10 (5-15)
PHQ-9 category (observed)	Minimal/remission (0-4)	29 (8.5)	44 (16.7)	41 (16.8)	66 (24.6)
	Mild (5-9)	79 (23.2)	69 (26.1)	70 (28.7)	66 (24.6)
	Moderate (10-14)	78 (22.9)	75 (28.4)	65 (26.6)	66 (24.6)
	Moderately severe (15-19)	84 (24.7)	47 (17.8)	43 (17.6)	45 (16.8)
	Severe (20 or higher)	70 (20.6)	29 (11.0)	25 (10.2)	25 (9.3)
	Unknown	733	809	829	805
PHQ-9 (estimated)	N	859	767	761	811
	Mean (s.d.)	11.4 (5.8)	9.5 (5.8)	9.5 (5.9)	8.8 (6.0)
	Median (Q1-Q3)	11 (7-15)	9 (5-13)	9 (5-13)	8 (4-13)
PHQ-9 category (estimated)	Minimal/remission (0-4)	102 (11.9)	151 (19.7)	163 (21.4)	222 (27.4)
	Mild (5-9)	233 (27.1)	281 (36.6)	256 (33.6)	264 (32.6)
	Moderate (10-14)	273 (31.8)	176 (22.9)	193 (25.4)	173 (21.3)
	Moderately severe (15-19)	165 (19.2)	107 (14.0)	93 (12.2)	108 (13.3)
	Severe (20 or higher)	86 (10.0)	52 (6.8)	56 (7.4)	44 (5.4)
	Unknown	214	306	312	262
PHQ-9 (combined)	N	1,073	932	913	951
	Mean (s.d.)	12.0 (6.1)	9.7 (5.8)	9.7 (6.0)	8.9 (6.1)
	Median (Q1-Q3)	12 (7-16)	9 (5-14)	9 (5-13)	8 (4-13)
PHQ-9 category (combined)	Minimal/remission (0-4)	118 (11.0)	180 (19.3)	194 (21.2)	259 (27.2)
	Mild (5-9)	280 (26.1)	317 (34.0)	293 (32.1)	304 (32.0)
	Moderate (10-14)	318 (29.6)	236 (25.3)	238 (26.1)	208 (21.9)
	Moderately severe (15-19)	215 (20.0)	132 (14.2)	121 (13.3)	126 (13.2)
	Severe (20 or higher)	142 (13.2)	67 (7.2)	67 (7.3)	54 (5.7)
	Unknown	0	141	160	122

Data are N (%) unless otherwise noted.

Figure 1. Reduction in PHQ-9 Scores from baseline to 3-month, 6-month and 12-month follow-up (with 95% CI)

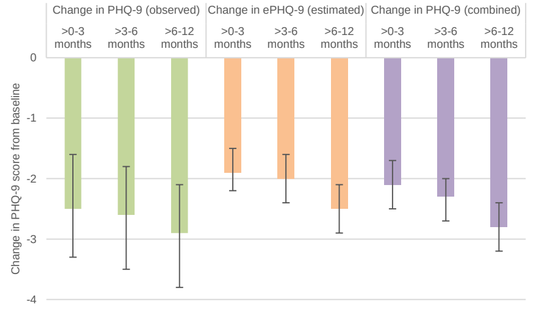
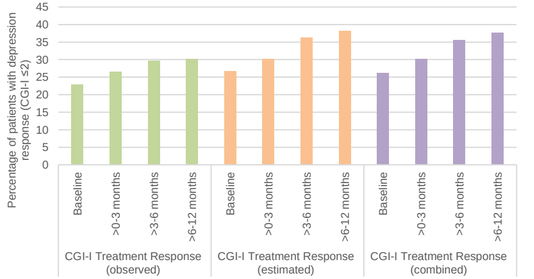


Table 5. GAD-7 scores and GAD-7 categories at baseline, 3-month, 6-month and 12-month follow-up

Characteristic		Baseline	>0-3 Months	>3-6 Months	>6-12 Months
GAD-7	N	213	175	165	171
	Mean (s.d.)	10.4 (5.6)	8.6 (5.4)	8.5 (5.9)	8.0 (5.9)
	Median (Q1-Q3)	11 (6-15)	8 (4-13)	7 (4-13)	7 (3-13)
GAD-7 Category	Minimal (0-4)	39 (18.3)	45 (25.7)	48 (29.1)	55 (32.2)
	Mild (5-9)	55 (25.8)	56 (32.0)	45 (27.3)	51 (29.8)
	Moderate (10-14)	63 (29.6)	50 (28.6)	42 (25.5)	37 (21.6)
	Severe (15-21)	56 (26.3)	24 (13.7)	30 (18.2)	28 (16.4)
	Unknown	0	38	48	42

Data are N (%) unless otherwise noted. Results are presented for patients with at least one GAD-7 assessment in baseline and in follow-up

Figure 2. Treatment response based on CGI-I scores at baseline, 3-month, 6-month and 12-month follow-up



Results are presented for patients with at least one CGI-I assessment in baseline and in follow-up.

CONCLUSIONS

In the year after brexpiprazole initiation as adjunctive therapy to an antidepressant among patients with MDD:

- Depressive symptoms significantly decreased on average and the percentage of patients in remission from depression more than doubled based on the PHQ-9.
- Symptoms of anxiety significantly decreased on average based on the GAD-7.
- The percentage of patients who demonstrated an improvement in response to treatment increased by 44% based on the CGI-I.

LIMITATIONS

- These analyses did not include a control group therefore the extent to which the observed changes are due to the treatment versus regression to the mean or temporal trends cannot be determined.
- The potential effect of confounders (time-varying or time-fixed) on the observed associations was not assessed in these analyses.

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