Validation Between Antidepressant Treatment Failure Proxy and PHQ-9 Score in Major Depressive Disorder Using A Linked Insurance Claims and Electronic Health Record Dataset

EPH277

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Introduction

1 Context:

Major depressive disorder (MDD) is one of the most prevalent mental disorders in the United States, significantly impacting individuals' overall health and well-being.[1]

Although various treatment options are available, many patients continue to struggle with persistent symptoms.[2,3]

2 Unmet need:

Evaluating antidepressant response in patients with MDD using real-world data is challenging due to limited availability of structured symptom measures and variability in symptom presentation.[3,4]

3 Study rationale:

Given the high prevalence and persistent burden of MDD, there is a critical need to better understand the factors contributing to treatment non-response. By evaluating potential proxies of treatment non-response that are widely recorded in real-world data, it may be possible to discover a practical approach to detect patients who may benefit from alternative therapeutic approaches.

Aim

This study aims to assess if antidepressant treatment failure can serve as a proxy for treatment non-response using the Patient Health Questionnaire (PHQ)-9 in patients with MDD.

Trial design

STUDY PERIOD January 1, 2012 to June 30, 2022

Adult patients with MDD (N=2,218) newly diagnosed with ≥1 prescription of antidepressants.

Optum Market Clarity database

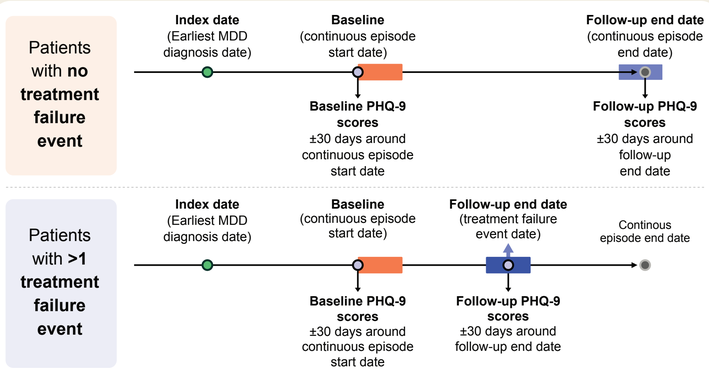
Treatment failure definition:

- **Treatment switch** occurring within 1 to 6 months during a continuous treatment episode.
- **Treatment augmentation** within 1 to 8 months during a continuous treatment episode.

A treatment episode was considered to be continuous if any gaps between treatment lines were less than 120 days apart.

For a detailed explanation of treatment pattern measures and failure definitions throughout the study visit posters **EPH138** and **EE734**.

PHQ-9 COLLECTION DIAGRAM



MODEL ANALYSIS

Regression models

Negative binomial regression estimated differences in **PHQ-9 follow-up scores** between treatment failure and non-failure groups, adjusting for baseline disease characteristics, with log of follow-up time as offset.

Linear regression assessed differences in **PHQ-9 follow-up score change from baseline** between treatment failure and non-failure groups using similar adjustments.

Validation analyses

A validation analysis was conducted to assess the relationship between failure events defined by **PHQ-9 score changes** (yes/no) and **proxy failure events** based on treatment patterns (yes/no).

PHQ-9 score change failure was defined as 'Yes' if the follow up PHQ-9 score increased or failed to decrease by 50% from baseline; otherwise, it was defined as 'No'.

To correct imbalance size between proxy failure vs. proxy non-failure group, **weighted outcomes** were calculated: **weight = number of patients having proxy failure / number of patients having non-proxy failure**.

Logistic regression analyses between PHQ-9 score failure and treatment pattern proxy failure were conducted on the overall population and across **defined MDD subsets**:

Defined MDD subset	Patients with **any baseline PHQ-9 score,** excluding those with no change	**Patients with a baseline PHQ-9 score of ≥5**, excluding those with no change	**Patients with a baseline PHQ-9 score of ≥10**, excluding those with no change	**Patients with a baseline PHQ-9 score of ≥15**, excluding those with no change
Terminology used	**No0**	**Mild MDD**	**Moderate MDD**	**Moderately severe MDD**

Since score failure and proxy failure occurred within similar timeframes, **reciprocal logistic regression** models were applied–alternating each as the dependent outcome. Both crude and adjusted model were used, incorporating **key covariates**: demographics, baseline commodities, medication, psychotherapy treatment and MDD severity status.

Key Conclusions

- Baseline PHQ-9 severity and treatment failure status were the strongest predictors of non-response.
- Patients with treatment failure, defined by a switch or augmentation within 1–8 months, showed less improvement in PHQ-9 scores compared to non-failure patients, supporting its validity as a proxy for treatment effectiveness.
- The findings suggest that in the absence of data on treatment response, treatment failure may be partly correlated with non-response but also explained by other factors.

Results

When analyzing **patient characteristics**, 78.5% of patients with MDD experienced treatment failure. Of those, a higher proportion were Black and Asian patients (**Table 1**).

Table 1. Demographic characteristics at baseline in patients with MDD with and without treatment failure

	No treatment failure (n=477)	Treatment failure (n=1,741)	*P*-value
Age			1.00
Mean (SD)	42.0 (13.90)	42.2 (13.61)	
Median (IQR)	42.00 (30.00, 55.00)	43.00 (30.00, 54.00)	
Sex (%)			1.00
Male	119 (24.9%)	431 (24.8%)	
Race (%)			0.015
Asian	9 (1.9%)	8 (0.5%)	
Black	73 (15.3%)	205 (11.8%)	
Caucasian	374 (78.4%)	1,430 (82.1%)	
Missing	21 (4.4%)	98 (5.6%)	
Region (%)			0.014
Midwest	247 (51.8%)	996 (57.2%)	
Northeast	65 (13.6%)	152 (8.7%)	
South	103 (21.6%)	340 (19.5%)	
West	27 (5.7%)	152 (8.7%)	
Unknown	35 (7.3%)	101 (5.8%)	
Type of Health Insurance (%)			0.613
Commercial	328 (68.8%)	1,138 (65.4%)	
Medicaid	78 (16.4%)	257 (14.8%)	
Medicare	26 (5.5%)	145 (8.3%)	
Other	11 (2.3%)	30 (1.7%)	
Unspecified	27 (5.7%)	151 (8.7%)	
Uninsured	7 (1.5%)	20 (1.1%)	

Some differences were observed in **baseline psychiatric comorbidities** and psychiatric **medication intake** between patients with treatment failure and those without (**Table 2**).

Table 2. Clinical characteristics and HCRU at baseline in patients with MDD with and without treatment failure

	No treatment failure (%) (n=477)	Treatment failure (%) (n=1,741)	*P*-value
Psychiatric diagnosis			
MDD	389 (81.6%)	1,484 (85.2%)	1.000
Anxiety	211 (44.2%)	866 (49.7%)	1.000
Adjustment disorder	72 (15.1%)	239 (13.7%)	1.000
Substance-related	42 (8.8%)	149 (8.6%)	1.000
ADHD	40 (8.4%)	85 (4.9%)	0.128
Psychiatric medications			
Antidepressants	469 (98.3%)	1,715 (98.5%)	1.000
Anxiolytics	178 (37.3%)	782 (44.9%)	0.117
Analgesics	168 (35.2%)	706 (40.6%)	1.000
Anti-convulsant	120 (25.2%)	523 (30.0%)	1.000
Mood stabilizer	61 (12.8%)	424 (24.4%)	<0.001
Annualized HCRU			
Outpatient	475 (99.6%)	1,734 (99.6%)	1.000
Emergency department	78 (16.4%)	258 (14.8%)	1.000
Inpatient	50 (10.5%)	125 (7.2%)	0.693

Patients with **treatment failure** had **significantly higher PHQ-9 scores** at baseline (continuous) and follow-up compared to scores of patients with no treatment failure (**Table 3**).

Table 3. PHQ-9 scores from index date to censured exposure end date in patients with MDD with and without treatment failure

	No treatment failure (%) (n=477)	Treatment failure (%) (n=1,741)	*P*-value
Baseline PHQ-9 Score (Continuous)			0.047
Mean (SD)	11.91 (6.18)	12.82 (6.27)	
Median (IQR)	10.00 (9.00, 16.00)	12.00 (9.00, 18.00)	
Baseline PHQ-9 Score (Categorical)			1.00
No MDD (Score 0–4)	53 (11.1%)	147 (8.4%)	
Mild (Score 5–9)	158 (33.1%)	529 (30.4%)	
Moderate (Score 10–14)	104 (21.8%)	385 (22.1%)	
Moderate to Severe (Score 15–19)	92 (19.3%)	383 (22.0%)	
Severe (Score 20–27)	70 (14.7%)	297 (17.1%)	
Follow-up PHQ-9 Score			<0.001
Mean (SD)	9.47 (6.15)	11.93 (6.36)	
Median (IQR)	9.00 (5.00, 12.00)	10.00 (8.00, 17.00)	
PHQ-9 Change Score			<0.001
Mean (SD)	−2.44 (6.12)	−0.89 (6.27)	
Median (IQR)	0.00 (−6.00, 0.00)	0.00 (−4.00, 1.00)	
Follow-up duration (months)			0.217
Mean (SD)	6.60 (8.81)	5.65 (7.77)	
Median (IQR)	3.37 (2.03, 7.30)	2.93 (1.63, 6.23)	

When stratified by baseline PHQ-9 score to define MDD severity, the results indicated a **trend of increased follow-up PHQ-9 scores in line with MDD severity (Fig. 1)**. Across disease severity groups, patients with treatment failure showed higher mean PHQ-9 scores compared to those with no failure. A greater score reduction was observed among patients with moderate to severe MDD and treatment failure vs. those without (**Fig. 2**).

Fig. 1. Mean follow-up PHQ-9 scores between patients with and without treatment failure events stratified by baseline MDD severity

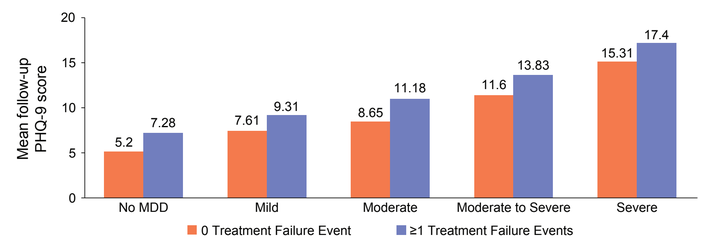
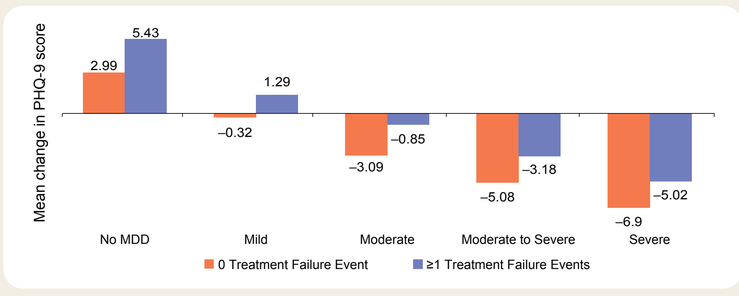


Fig. 2. Comparison of mean change of PHQ-9 from baseline to follow-up time between patients with and without treatment failure events stratified by baseline MDD severity



In **regression analyses**, failure status (follow-up score model *P*-value = 8.54×10^{-8}; score change model *P*-value = 5.13×10^{-13}) and **baseline PHQ-9 severity** (follow-up score model *P*-value ≤9.18×10^{-4}; score change model *P*-value <2.25×10^{-17}) were the only variables **significantly associated with PHQ-9 follow-up scores or score change in overall MDD dataset**, respectively (**Table 4**).

Table 4. Follow-up and change from baseline PHQ-9 models results across failure status and in overall MDD datasets

	Follow-up PHQ-9 score		PHQ-9 score change from baseline	
	Negative binomial ratio vs. reference group (95% CI)		Linear model results vs. reference group (mean [SE])	
	Crude	Adjusted	Crude	Adjusted
Failure status "Yes" ("No fail" as reference)	1.26 (1.14–1.4)	1.32 (1.19–1.47)	2.02 (0.29)	2.16 (0.3)
Baseline PHQ-9 according to MDD severity				
Mild	1.28 (1.08–1.51)	1.31 (1.11–1.56)	−4.03 (0.45)	−3.95 (0.46)
Moderate	1.82 (1.54–2.16)	1.86 (1.56–2.21)	−6.12 (0.47)	−6.2 (0.48)
Moderately severe	2.61 (2.2–3.09)	2.64 (2.21–3.14)	−8.2 (0.47)	−8.32 (0.48)
Severe	3.5 (2.93–4.18)	3.55 (2.96–4.25)	−10 (0.49)	−10.2 (0.5)
No MDD (reference)	1	1	0	0

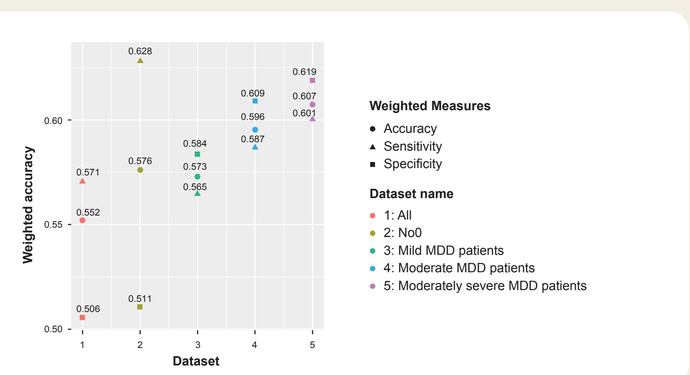
In **subset analyses**, effect sizes were calculated for overall and specific datasets. Negative binomial model performance was defined by Nagelkerke R^2 score (**Table 5**).

Table 5. Adjusted negative binomial model performance and results in the overall dataset and across defined MDD subsets

	Follow up PHQ-9 difference by failure proxy (yes or no) (95% CI)	Follow up PHQ-9 ratio by failure proxy (yes or no) (95% CI)	Formula	Nagelkerke R^2	Cohen's d
Overall dataset	6.12 (4.03–8.2)	1.32 (1.19–1.47)	Follow-up PHQ-9 score ~ baseline PHQ-9 severity status + fail proxy (yes or no) + baseline covariates (Dx, Rx, encounters + psychotherapy treatment)	0.26	−0.39
No0	11.18 (8.66–13.7)	1.71 (1.49–1.97)		0.19	−0.54
Mild MDD	11.77 (9.14–14.41)	1.76 (1.51–2.04)		0.19	−0.55
Moderate MDD	10.31 (7.27–13.36)	1.61 (1.36–1.89)		0.18	−0.52
Moderately severe MDD	10.45 (6.5–14.41)	1.59 (1.29–1.94)		0.16	−0.48

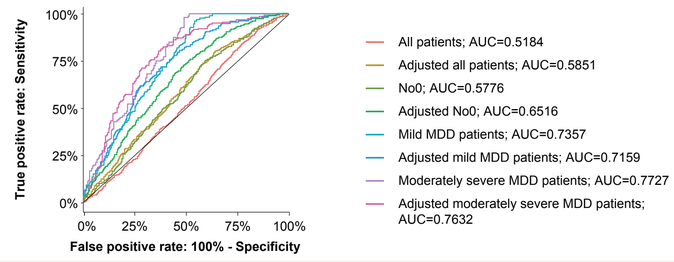
Weighted **validation analyses results** between proxy failure vs. no failure group showed the **highest accuracy** in moderately severe MDD patients (baseline PHQ-9 ≥15) (**Fig. 3**).

Fig. 3. Validation between score failure event (gold standard outcome) and treatment pattern proxy failure event



Logistic regression models of PHQ-9 score failure yielded a maximum **area under the curve (AUC) of 0.76** in moderately severe MDD patients (**Fig. 4**), suggesting that the score failure measure may be a key factor associated with increased odds of proxy failure events. In addition to disease severity, the use of anxiolytics (OR, 95% CI: 2.03 [1.4–2.96]) or mood stabilizers (OR, 95% CI: 2.68 [1.59–4.74]) were also identified as significant risk factors.

Fig. 4. Association between treatment failure and PHQ-9 score change from baseline using a logistic regression model



Additional Conclusion

Treatment complexity, defined by the number of treatment lines or generic drugs used, was associated with increased symptom burden and greater changes in PHQ-9 scores.

Abbreviations

ADHD, attention deficit hyperactivity disorder; AUC, area under the curve; CI, confidence interval; Dx, diagnosis; HCRU, healthcare resource utilization; IQR, interquartile range; MDD, major depressive disorder; OR, odds ratio; PHQ-9, Patient Health Questionnaire 9; Px, prescription; SD, standard deviation; SE, standard error.

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