Important Risk Factors to Proxies of Treatment Failures in Patients with Major Depressive Disorder: Insights from A Claims Database Study

EPH138

L. Zhang[1], C. White[1], S. St.Rose[2], F. De Crescenzo[2], A. Kilburg[2], S. D. Suessmuth[3] and R. Patel[4]

[1]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [2]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [4]Department of Psychiatry, University of Cambridge, Cambridge, UK

Introduction

Context:

Current pharmacologic interventions for major depressive disorder (MDD) fail to produce at least partial response in approximately one third of patients. This is referred to as treatment-resistant depression (TRD).[1]

1

TRD is characterized by a patient's inadequate response to ≥2 consecutive antidepressant treatments given for an adequate duration and dosage without achieving acceptable therapeutic effects.[2]

Difficult to treat depression (DTD) describes a clinical category of MDD, where patients do not achieve full symptom control despite various therapeutic approaches.[2]

Unmet need:

2 Many treatment failure definitions are centered on TRD, which may not be generalizable to broad failure or DTD population, particularly in real-world studies. This highlights the need for criteria that capture the full spectrum of treatment challenges relevant for medical decision makers.

Study rationale:

3 By establishing three narrow to broad proxy failure definitions, this study aims to provide relations across definitions and identify potential risk factors for MDD treatment failure.

Aim

To develop a spectrum of proxy definitions for treatment failure in MDD, ranging from specific to broad criteria, and to identify consistent risk factors across these definitions for practical medical decision making.

Methods

Data source
Optum Clinformatics claims database

Study period
January 1, 2012 to March 31, 2022

Index date
First MDD diagnosis

Inclusion criteria
Adults aged 18–65 years with newly diagnosed MDD and ≥2 MDD encounters

Required 12 months continuous enrollment in the healthcare plan prior to the index date

Exclusion criteria
Prior diagnosis of specific mental disorders: bipolar, delusional, schizoaffective, schizophreniform disorders, schizophrenia, brain tumor, seizure

MDD episodes were constructed by linking MDD diagnoses or antidepressant use, allowing for a 120-day gap.

This study analysis has been conducted at MDD episode level. The follow-up starting date is the episode starting date; baseline was the 4-month period before the index date or start of MDD episode.

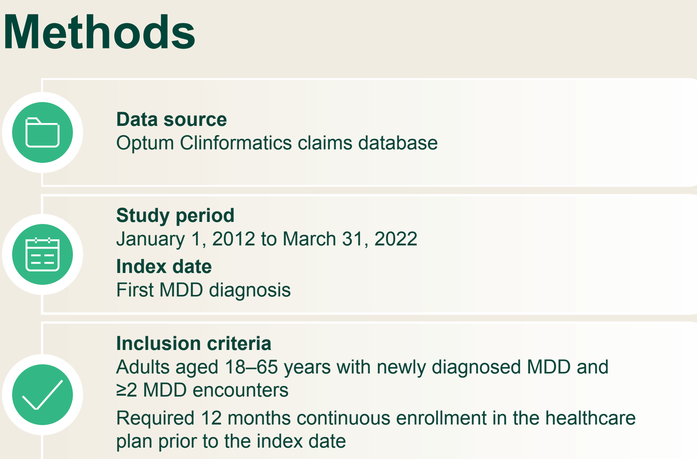
One patient may include multiple MDD episodes with the same index date.

Lines of treatment (LOTs) were formed by linking antidepressants with a 30-day gap allowance.

An MDD segment and treatment failure definitions are shown in **Fig. 1.**

Risk factors for treatment failure were assessed using LASSO regression.[3]

Fig. 1. MDD segment and treatment failure definitions



Treatment failure event

[a]Formed by linking MDD diagnoses to the treatment episodes. If a patient had >1 segment during follow-up time, they were considered "recurrent" patients.

A gap of <120 days was allowed between an MDD treatment episode and an MDD diagnosis.

LOT, lines of treatment; MDD, major depressive disorder

Key Conclusions

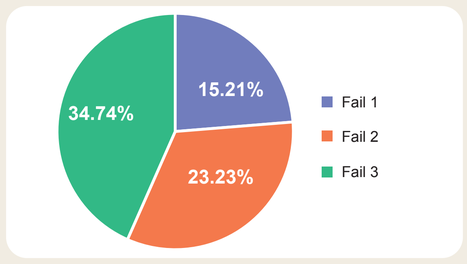
- Treatment failure in MDD is associated with greater clinical burden, including higher comorbidity rates and increased medication use.
- Baseline use of medication (antidepressants and mood stabilizers) strongly predicted future treatment failure, even in the absence of a formal MDD diagnosis at the time of medication prescription.
- Frequent treatment changes, whether guideline-based or not, reflect higher disease severity and may serve as practical real-world proxies for poor treatment response.

Results

There were **304,802** MDD episodes identified among **203,313** patients with MDD during the study period.

The proportion of MDD episodes according to the different treatment failure definitions is shown in **Fig. 2.**

Fig. 2. Proportion of MDD episodes by treatment failure definitions



Patients who had ≥2 treatment failure events (by Fail 1 definition) had a significantly higher prevalence of psychiatric (except ADHD) and non-psychiatric diagnosis at baseline versus those who had 0 or 1 treatment failure event **(Table 1)**.

Table 1. Prevalence of psychiatric and non-psychiatric diagnosis stratified by number of treatment failure events (by Fail 1 definition)

	Total Population (N=304,802)	0 Treatment Failure Event (n=258,449)	1 Treatment Failure Event (n=24,355)	≥2 Treatment Failure Events (n=21,998)	*P* value
Psychiatric diagnosis					
Anxiety	36,047 (11.8)	29,003 (11.2)	3,613 (14.8)	3,431 (15.6)	<0.001
General depression[a]	27,046 (8.9)	21,243 (8.2)	2,716 (11.2)	3,087 (14.0)	<0.001
Other mood disorders	7,239 (2.4)	5,468 (2.1)	796 (3.3)	975 (4.4)	<0.001
ADHD	8,031 (2.6)	6,754 (2.6)	677 (2.8)	600 (2.7)	1.000
PTSD	2,940 (1.0)	2,351 (0.9)	263 (1.1)	326 (1.5)	<0.001
Non-psychiatric diagnosis[a]					
Hypertension	49,373 (16.2)	40,073 (15.5)	4,606 (18.9)	4,694 (21.3)	<0.001
Obesity	23,326 (7.7)	19,270 (7.5)	2,018 (8.3)	2,038 (9.3)	<0.001
Diabetes (uncomplicated)[b]	21,852 (7.2)	17,544 (6.8)	2,106 (8.6)	2,202 (10.0)	<0.001
COPD	21,098 (6.9)	16,837 (6.5)	2,078 (8.5)	2,183 (9.9)	<0.001
Hypothyroidism	19,274 (6.3)	15,330 (5.9)	1,960 (8.0)	1,984 (9.0)	<0.001
Diabetes (complicated)[c]	15,517 (5.1)	12,612 (4.9)	1,448 (5.9)	1,457 (6.6)	<0.001

Data are presented as n (%)

[a]Indicates Elixhauser diseases

[b]Uncomplicated diabetes was defined as diabetes without any end organ damage such as peripheral neuropathy, nephropathy and/or PAD.

[c]Complicated diabetes was defined as diabetes associated with end organ damage such as peripheral neuropathy, nephropathy and/or PAD.

ADHD, attention deficit hyperactivity disorder; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; PTSD, post-traumatic stress disorder

Compared with patients who had 0 or 1 treatment failure event, those who had ≥2 treatment failure events (by Fail 1 definition) had a significantly higher use of drugs **(Table 2)**

Table 2. Prescription pattern of drugs[a] stratified by number of treatment failure events (by Fail 1 definition)

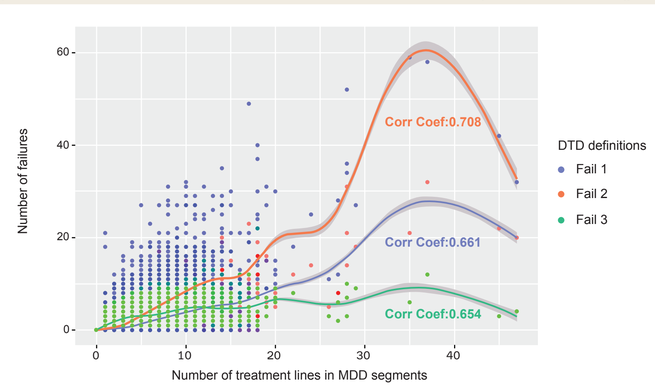
Variable	Total Population (N=304,802)	0 Treatment Failure Event (n=258,449)	1 Treatment Failure Event (n=24,355)	≥2 Treatment Failure Events (n=21,998)	*P* value
Antidepressants	82,212 (27.0)	58,087 (22.5)	11,310 (46.4)	12,815 (58.3)	<0.001
Analgesics	56,650 (18.6)	43,151 (16.7)	6,307 (25.9)	7,192 (32.7)	<0.001
Anxiolytics	51,086 (16.8)	38,324 (14.8)	5,931 (24.4)	6,831 (31.1)	<0.001
Anticonvulsants	27,833 (9.1)	20,757 (8.0)	3,190 (13.1)	3,886 (17.7)	<0.001
Hypnotics and sedatives	23,218 (7.6)	17,392 (6.7)	2,656 (10.9)	3,170 (14.4)	<0.001
Mood stabilizers	22,698 (7.4)	14,692 (5.7)	3,484 (14.3)	4,522 (20.6)	<0.001
Stimulants	16,655 (5.5)	13,337 (5.2)	1,601 (6.6)	1,717 (7.8)	<0.001
Other relevant drugs	9,986 (3.3)	8,032 (3.1)	981 (4.0)	973 (4.4)	<0.001
Other MDD medications	4,757 (1.6)	3,354 (1.3)	628 (2.6)	775 (3.5)	<0.001
Substance use disorder medications	3,190 (1.0)	2,300 (0.9)	389 (1.6)	501 (2.3)	<0.001
Antipsychotics (2nd generation)	3,345 (1.1)	1,889 (0.7)	526 (2.2)	930 (4.2)	<0.001
Antipsychotics (1st generation)	1,297 (0.4)	1,005 (0.4)	134 (0.6)	158 (0.7)	<0.001

Data are presented as n (%)

[a]4 months before each of the MDD segment start (including the index date, which was the first MDD diagnosis date)

The correlation co-efficient was the highest for Fail 2 and lowest for Fail 3 **(Fig. 3)**.

Fig. 3. Correlation between number of treatment lines and failure proxies in MDD segments

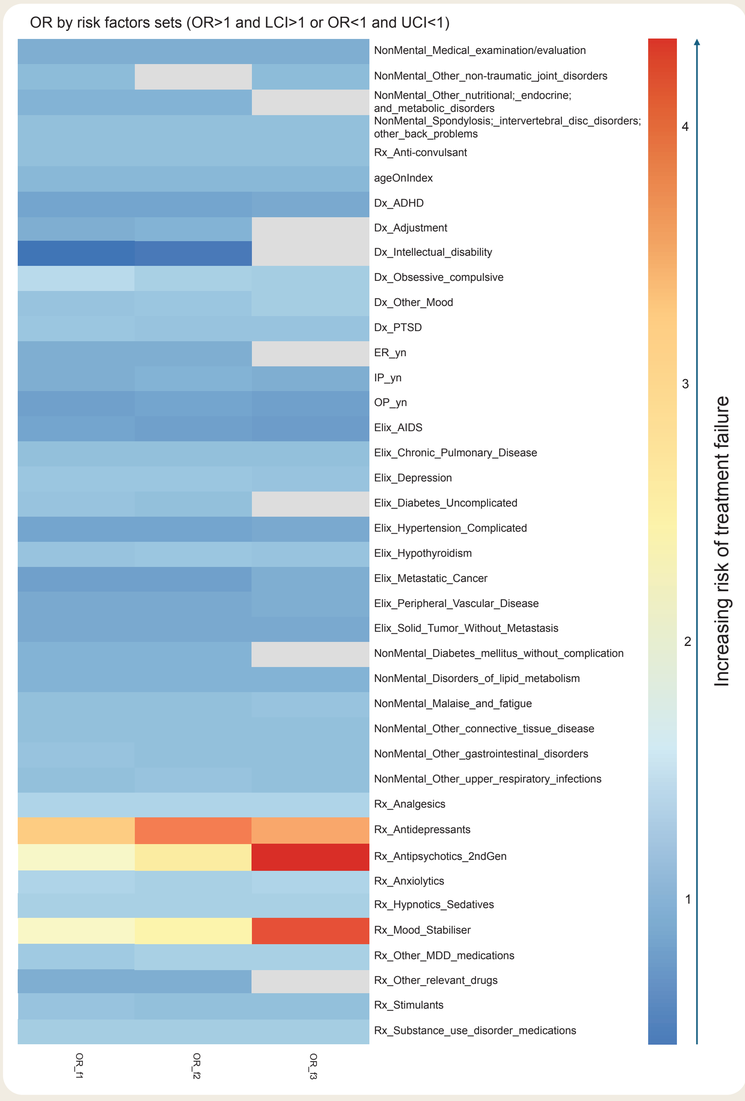


Points and curves plots are from a sample of 10% of 0.3 million of segments

The important risk factors increasing the odds ratio (OR) of treatment failure were the use of antipsychotics (2nd generation), mood stabilizers or antidepressants (broad list).

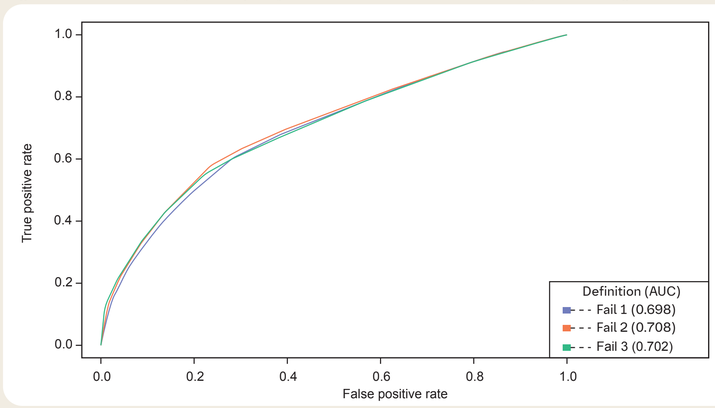
The risk factors reducing the OR were disease of intellectual disability or ADHD, which could be confounder with protective effect by medication usage during baseline and non-mental comorbidities diseases **(Fig. 4)**.

Fig. 4. Key predictors of MDD treatment failure by LASSO and logistics regression model on three failure outcomes



For the association analyses between treatment failure proxy outcomes with LASSO selected risk factors, the area under the curve values were as follows:
Fail 1: 0.698, Fail 2: 0.708, and Fail 3: 0.702 **(Fig. 5)**.

Fig. 5. Association analysis for proxy measures of treatment failure by LASSO regression



Additional Conclusions

- The number of treatment failure events was closely linked to treatment complexity, such as the number of lines or generic drugs used.
- These treatment patterns offer a valid and scalable approach for identifying DTD in the real-world scenario.

Abbreviations

ADHD, attention deficit hyperactivity disorder; AUC, area under the curve; COPD, chronic obstructive pulmonary disease; DTD, difficult-to-treat depression; LASSO, Least Absolute Shrinkage and Selection Operator; LCI, lower confidence interval; LOT, lines of treatment; MDD, major depressive disorder; OR, odds ratio; PAD, peripheral artery disease; PTSD, post-traumatic stress disorder; TRD, treatment-resistant depression; UCI, upper confidence interval.

References

1. Halaris A, *et al. J Pers Med.* 2021;11(2):155.
2. Paganin W. *Eur Psychiatry.* 2023;66(1):e73.
3. Ranstam J and Cook JA. *Br J Surg.* 2018;105(10):1348.

Disclosures

LZ, CW, SSR, FDC, AK, and SDS are full-time employees of Boehringer Ingelheim. RP has participated in Scientific Advisory Boards for Boehringer Ingelheim and Teva, has received grant funding from Janssen, and has received consulting fees from Holmusk, Akrivia Health, Columbia Data Analytics, Clinilabs, Social Finance, Boehringer Ingelheim, Bristol Myers Squibb, Supernus, Teva, and Otsuka.

Acknowledgements

The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. This study was funded by Boehringer Ingelheim (1447-0011). Writing, editorial support and formatting assistance were provided by Sarayu Pai, PhD, CMPP of Indegene Ltd., Bangalore, India and funded by Boehringer Ingelheim International GmbH.

Contact information: Ling Zhang
Email: ling_3.zhang@boehringer-ingelheim.com

Presented at the ISPOR Europe 2025, 9–12 November 2025, Glasgow, Scotland, UK