Epidemiology of Treatment-Resistant Depression in the United States

Xinyue Liu, PhD[a]; Yuki Mukai, MD[b]; Christine I. Furtek, BS[c]; Edward A. Bortnichak, PhD[a]; Kai-Li Liaw, PhD[a]; and Wenjun Zhong, PhD[a,*]

ABSTRACT

Background: The prevalence of treatment-resistant depression (TRD) among patients with pharmaceutically treated depression (PTD) varies greatly in publications. The aim of this study is to estimate the prevalence of TRD using 2 large claims databases in the US.

Methods: This cross-sectional study used data from the Humana and Optum databases. Patients aged ≥ 18 years who had at least 1 diagnosis of major depressive disorder (*ICD-10-CM* codes: F32.xx, F33.xx) and 1 antidepressant prescription filled in 2018 were identified as having PTD. Among patients with PTD, TRD was defined as experiencing failure of treatment with at least 2 antidepressants with ≥ 4 weeks of adequate treatment. We estimated the age- and gender-standardized prevalence of TRD and then used logistic regression to investigate if TRD risk varies by age, sex, race, and geographic region. Finally, we described the timeline of TRD development in incident PTD patients.

Results: We identified 296,055 and 277,941 patients with PTD in the Humana and Optum databases, among whom 17,640 (6.0%) and 16,131 (5.8%) had TRD. After age and sex standardization, TRD prevalence among PTD patients was 6.8% in Humana vs 5.8% in Optum. Females, middle-aged adults, and White patients had higher risk of TRD. The median time from index antidepressant use to TRD was about 6 months in incident PTD patients.

Conclusions: The prevalence of TRD among patients with PTD was similar in the 2 databases. TRD prevalence varies by sex, race, and age, with a higher prevalence in females, White patients, and those in the age group of 45–64 years. However, the absolute differences were small.

J Clin Psychiatry 2022;83(1):21m13964

To cite: Liu X, Mukai Y, Furtek CI, et al. Epidemiology of treatment-resistant depression in the United States. *J Clin Psychiatry.* 2022;83(1):21m13964.

To share: https://doi.org/10.4088/JCP.21m13964

[a]Pharmacoepidemiology, Center for Observational and Real-World Evidence (CORE), Merck & Co., Inc., West Point, Pennsylvania

[b]Global Clinical Development, Merck & Co., Inc., Kenilworth, New Jersey

[c]Clinical Sciences and Study Management, Merck & Co., Inc, Upper Gwynedd, Pennsylvania

**Corresponding author:* Wenjun Zhong, PhD, 770 Sumneytown Pike, West Point, PA 19486 (wenjun.zhong@merck.com).

Depression is a common health condition in the United States. According to the National Health and Nutrition Examination Survey 2013–2016,[1] which used scores from the Patient Health Questionnaire-9, 8.1% of American adults aged 20 and over had depression in a 2-week period.

Among patients with major depressive disorder (MDD), up to half are not successfully treated with currently available antidepressant drug therapies.[2,3] If a patient does not have response or remission after 2 or more treatment attempts of adequate dose and duration, the patient may be diagnosed with treatment-resistant depression (TRD), but no clear consensus exists about this definition. Also, the response to antidepressant treatments has significant interindividual and intraindividual variability, which is caused by the interaction of genetics, age, disease, and environment (internal).[4] Due to differences in definitions[5] and study populations, the reported TRD prevalence varied widely across studies, ranging from 6%[5] to 55%[3] among adults treated for depression.[6,7] Studies on demographic risk factors for TRD were also limited. Available studies suggested that older age and being divorced or widowed were associated with a greater risk of TRD; neither sex nor race was identified as risk factors for TRD.[8]

Patients with TRD represent a unique subgroup of patients with depression. To evaluate the public health significance and disease burden of TRD and develop effective pharmacologic treatments for TRD, it is essential to have an accurate and reliable estimate of TRD population size and risk factors. TRD epidemiology studies help researchers in designing clinical trials, so that patients enrolled in TRD trials will be more closely representative of the real-world TRD population. From the clinical practice perspective, the risk factors identified in TRD epidemiology studies can help psychiatrists assess the risk of TRD in patients with depression and better develop individualized disease management plans.

In this study, we estimated the TRD prevalence in patients with pharmaceutically treated depression (PTD) in the US in 2018, by adopting a commonly used TRD definition (failure of at least 2 antidepressant treatments). We examined 2 claim databases (Humana and Optum) and used age and sex standardization to compare the TRD prevalence in the 2 databases. We then used logistic regression to estimate if TRD risk varies by age, sex, race, and geographic region. We also described the timeline of TRD development in patients with incident PTD (defined in Methods).

Clinical Points

- Due to differences in definitions of treatment-resistant depression (TRD) and study populations, the reported TRD prevalence varied widely across studies, ranging from 6% to 55% among adults treated for depression.
- This study found the age- and sex-standardized prevalence of TRD in patients with pharmaceutically treated depression (PTD) was 6%–7% in 2 large claims databases (Humana and Optum) in the US based on the most recent available data. Females, middle-aged adults, and whites had higher risk of TRD.
- A limitation of the study is that patients' treatment acceptance and health care access were not considered in the analysis when treatment failures were used to define TRD and identify high-risk subpopulations.

METHODS

Data Sources

Both Humana (Humana Comprehensive Health Insights) and Optum (Optum Clinformatics Data Mart) are claim databases that consist of medical, pharmacy, and laboratory claims for commercial and Medicare covered lives linked by unique patient ID. As of 2018, the Humana database includes about 5 million patients with at least 1 month of enrollment with pharmacy and medical benefits, and the Optum database has about 20 million patients with at least 1 day of enrollment. Patients in the Humana database are older and are more likely to come from the South than patients in the Optum database (see Results).

Adult enrollees (≥ 18 years) in 2018 who had continuous medical and pharmacy benefits coverage from January 2017–December 2018 were included in this analysis. The year of 2017 was the baseline period, and the year of 2018 was the study period.

Patients With PTD

To identify patients with TRD, we first identified patients with PTD. Patients with PTD were defined as those with at least 1 MDD diagnosis (*ICD-10-CM* codes: F32.xx, F33.xx) and having at least 1 antidepressant dispensed in 2018. No temporality requirement for MDD diagnosis and antidepressant use was employed; ie, MDD diagnosis could have occurred before or after antidepressant use as long as both occurred in 2018. The index date of PTD was the earliest date when an antidepressant was dispensed in 2018. Patients who had psychiatric disorders including other depressive episodes (F32.8x, F33.8x), psychosis (F23.xx, F28.xx, F44.89), schizophrenia (F20.xx, F25.xx), dementia (F01.xx-F03.xx), and bipolar disorder (F30.xx, F31.xx) in 2017–2018 were excluded from the PTD population.

We further categorized patients with PTD into incident PTD patients and non-incident PTD patients based on when the PTD episode started. Incident PTD patients were those who had no antidepressants dispensed during a 12-month period before the PTD index date (first date of antidepressant dispensed in 2018). We assumed that a 12-month period free of antidepressants before the first antidepressant in 2018 would indicate the start of a new PTD episode. Non-incident PTD patients were those who had antidepressants dispensed during a 12-month period before PTD index date (first date of antidepressant dispensed in 2018).

TRD Identification

In this study, TRD patients were identified as those who experienced failure of at least 2 antidepressants after adequate treatment duration at adequate dose. We defined adequate treatment duration as receiving at least 4 weeks of antidepressant treatment (total gaps < 2 weeks). Antidepressant failure was defined as switching to another antidepressant or adding an augmentation medication after at least 4 weeks of treatment at adequate dose. We also conducted sensitivity analyses by changing the length of adequate treatment duration definition to 3 weeks and 6 weeks, respectively, to examine the impact of treatment duration on TRD prevalence. The antidepressants and augmentation medications and the adequate dose for each antidepressant are shown in Supplementary Table 1.[6,9]

Among incident PTD patients, we identified TRD patients by evaluating whether patients failed 2 or more antidepressants from the PTD index date to the end of 2018. Among non-incident PTD patients, antidepressants dispensed in 2017 were also included. We did not check antidepressant prescriptions dispensed in the years before 2017 because those antidepressant prescriptions may have been used to treat a prior depression episode. Patients with the following mood disorders were excluded from the TRD population: obsessive-compulsive disorder (F42.xx), adjustment disorder (F43.xx), substance induced mood disorder (F10.xx-F16.xx, F18.xx-F19.xx), and mood disorder due to general illness (F04.xx-F07.xx, F09.xx). We excluded patients with the above disorders from our TRD study population because the treatment of the above disorders may include drugs in the augmentation drug list for TRD, eg, antipsychotics, which may lead to misclassification as TRD patients. We did not exclude these patients from the initial PTD population because these disorders are common comorbidities of depression, and the diagnoses of these disorders and depression are not mutually exclusive.

Statistical Analyses

We reported the numbers of PTD and TRD patients in the Humana and Optum databases, and we calculated TRD prevalence in PTD on the basis of these numbers. We used direct standardization based on the US 2010 Census population to calculate age- and sex-standardized TRD prevalence in patients with PTD. We then used logistic regression to estimate if TRD risk varies by age, sex, race, and geographic region after controlling for other variables in the 2 databases, respectively. We combined all races other than Black and White because the data quality of race and ethnicity information is generally acceptable for Black and White but not for other races, and Hispanic information was likely to

Table 1. PTD and TRD Prevalence in Humana and Optum by Gender, Age, Race, and Geographic Region

	Humana					Optum				
	Study Population, n	PTD Patients, n	PTD Prevalence, %	TRD Patients, n	TRD Prevalence in PTD, %	Study Population, n	PTD Patients, n	PTD Prevalence, %	TRD Patients, n	TRD Prevalence in PTD, %
Sex										
Male	1,351,888	85,162	6.3	3,905	4.6	2,658,978	80,506	3	3,789	4.7
Female	1,635,376	210,893	12.9	13,735	6.5	2,873,591	197,421	6.9	12,341	6.3
Unknown	…	…	…	…	…	417	14	3.4	1	7.1
Age										
18–34 y	107,127	4,833	4.5	338	7	1,097,302	44,699	4.1	2,491	5.6
35–44 y	101,878	7,362	7.2	510	6.9	800,069	36,461	4.6	2,180	6
45–54 y	166,014	19,789	11.9	1,410	7.1	896,484	48,409	5.4	2,910	6
55–64 y	333,041	56,193	16.9	4,031	7.2	915,828	59,923	6.5	3,567	6
65–74 y	1,161,749	120329	10.4	7,028	5.8	878,781	53,255	6.1	3,173	6
75–84 y	857,106	71,329	8.3	3,727	5.2	635,466	27,352	4.3	1,520	5.6
85–94 y	170,038	11,356	6.7	444	3.9	309,056	7,842	2.5	290	3.7
95+ y	90,311	4,864	5.4	152	3.1	…	…	…	…	…
Race										
White	2,029,491	236,899	11.7	14,397	6.1	3,661,927	206,691	5.6	12,284	5.9
Black	352,587	25,504	7.2	1,296	5.1	483,585	20,984	4.3	1,206	5.7
Asian	26,967	1,126	4.2	36	3.2	253,513	4,510	1.8	250	5.5
Native American[a]	5,029	558	11.1	37	6.6	…	…	…	…	…
Hispanic	35,543	4,176	11.7	185	4.4	627,291	23,744	3.8	1,149	4.8
Other[a]	53,737	3,824	7.1	162	4.2	…	…	…	…	…
Unknown	483,910	23,968	5	1,527	6.4	506,670	22,012	4.3	1,242	5.6
Regions[b]										
Northeast	76,380	6,630	8.7	316	4.8	548,200	19,289	3.5	908	4.7
Midwest	672,785	59,958	8.9	3,587	6	1,393,643	84,825	6.1	4,829	5.7
West	304,162	28,463	9.4	1,482	5.2	1,348,482	56,454	4.2	3,037	5.4
South	1,933,937	201,004	10.4	12,255	6.1	2,243,337	117,421	5.2	7,360	6.3
Total	2,987,264	296,055	9.9	17,640	6	5,532,986	277,941	5	16,131	5.8

[a]Optum does not have these categories.
[b]The states included in each region (Optum) are included in Supplementary Table 2.
Abbreviations: PTD = pharmaceutically treated depression, TRD = treatment-resistant depression.

be underreported in claims data.[10,11] We acknowledge that Hispanic should be categorized as ethnicity, not race, but the Humana and Optum databases categorized persons of Hispanic ethnicity under race, thereby limiting our ability to construct an ethnicity variable. The logistic regression is as follows:

Logit(probability of TRD in PTD) = $\beta + \beta_1$ sex (race = male) + β_2 * age group (reference = 45–64) + β_3 * race (reference = White) + β_4 * region (reference = South)

We also examined the impact of TRD definition (adequate antidepressant treatment duration of 3 weeks and of 6 weeks) on the prevalence of TRD in sensitivity analyses. Finally, we described the timeline of TRD development in incident PTD patients by plotting Kaplan-Meier curves for 3 TRD definitions (adequate antidepressant treatment duration 3, 4, and 6 weeks) and reported the time between the index antidepressant to the identification of TRD.

All the data were deidentified and reported only at the aggregate level. Data analyses were conducted with SAS 9.4 (Cary, NC).

RESULTS

There were about 3 million and 6 million patients who had continuous enrollment in 2017 and 2018 in Humana and Optum, respectively. In both databases, female patients accounted for a little more than 50% of the population, White patients accounted for 65%–70%, and the South contributed the largest number of patients (65% in Humana and 41% in Optum). The Humana population was predominantly older adults and was older than Optum (patients 65+ years accounted for 76% in Humana and 33% in Optum).

PTD Prevalence

Overall, 10% of the Humana population and 5% of the Optum population had PTD in 2018, most of whom were non-incident PTD patients (70% in Humana and 72% in Optum, not shown in the table) (Table 1).

TRD Population and Prevalence

The raw prevalence of TRD in patients with PTD is also displayed in Table 1. Non-incident PTD patients had higher prevalence of TRD than incident PTD patients in both databases (Humana: 7.7% vs 2.0%, Optum: 8.1% vs 2.1%; not shown in the table) based on raw data. Although the prevalence of TRD in non-incident and incident PTD patients was quite different, we combined them with the aim to describe the overall treatment of depression as of 2018 in these populations, which were composed of both incident and non-incident PTD patients.

After age and sex standardization using the US 2010 Census population, the prevalence of TRD in PTD was 6.8% (95% CI, 6.7%–6.9%) in Humana and was 5.8% (95%

Table 2. Direct Standardization of TRD Patient Population Using US 2019 Population as Reference

		Humana Data Standardization					Optum Data Standardization				
Age	US 2019 Population[a,b]	PTD Prevalence, %	Expected PTD[a]	TRD Prevalence in PTD, %	Expected TRD[a]	TRD Population Composition, %	PTD Prevalence, %	Expected PTD[a]	TRD Prevalence in PTD, %	Expected TRD[a]	TRD Population Composition, %
Male											
18–34 y	37,332	2.90	1,082.6	5.47	59.2	3.8	2.60	970.6	4.65	45.1	6.1
35–44 y	20,257	4.84	980.4	4.83	47.4	3.0	2.78	563.1	4.70	26.5	3.6
45–54 y	19,923	8.33	1,659.6	5.57	92.4	5.9	3.11	619.6	4.70	29.1	3.9
55–64 y	19,865	11.73	2,330.2	5.29	123.3	7.9	3.78	750.9	4.92	36.9	5.0
65–74 y	14,889	6.08	905.3	4.34	39.3	2.5	3.59	534.5	4.70	25.1	3.4
75–84 y	6,752	5.07	342.3	4.15	14.2	0.9	2.63	177.6	4.81	8.5	1.2
85+ y	2,282	4.12	94.0	3.15	3.0	0.2	1.79	40.8	3.17	1.3	0.2
Male total	121,300	6.10	7,394.4	5.12	378.7	24.3	3.02	3,657.2	4.72	172.6	23.4
Female											
18–34 y	36,961	6.08	2,247.2	7.70	173.0	11.1	5.65	2,088.3	6.03	125.9	17.1
35–44 y	20,770	9.46	1,964.8	7.93	155.8	10.0	6.40	1,329.3	6.56	87.2	11.8
45–54 y	20,776	15.34	3,187.0	7.93	252.7	16.2	7.74	1,608.1	6.55	105.3	14.3
55–64 y	21,890	21.85	4,783.0	8.15	389.8	25.0	9.29	2,033.6	6.37	129.5	17.6
65–74 y	16,598	13.85	2,298.8	6.38	146.7	9.4	8.00	1,327.8	6.40	85.0	11.5
75–84 y	8,656	10.96	948.7	5.63	53.4	3.4	5.58	483.0	5.82	28.1	3.8
85+ y	3,611	7.52	271.5	3.85	10.5	0.7	2.98	107.6	3.89	4.2	0.6
Female total	129,262	12.15	15,701.1	7.53	1,181.9	75.7	6.95	8,977.7	6.30	565.3	76.6
Total	250,562	9.22	23,095.6	6.76[c]	1,560.7	100.0	5.04	12,634.9	5.84[c]	737.9	100.0

[a]In thousands.
[b]Data from https://www.census.gov/data/tables/2019/demo/age-and-sex/2019-age-sex-composition.html.
[c]Standardized prevalence of TRD is the expected TRD/expected PTD; 6.8% for Humana, and 5.8% for Optum.
Abbreviations: PTD = pharmaceutically treated depression, TRD = treatment-resistant depression.

CI, 5.7%–5.9%) in Optum. Based on the standardization results, females represented the majority of the TRD patients (Humana 1,182/1,561 = 75.7%, Optum 565/738 = 76.6%; both > 75%), and female patients aged 45–64 years were the largest patient group in the TRD population (Table 2).

The results from the multivariable logistic regression were similar between Humana and Optum. Age 65+ years was associated with lower risk of TRD compared to age 45–64 years; female sex was associated with higher risk of TRD than male sex; Black patients had lower TRD risk than White patients, and patients in the South had the highest TRD risk among all regions (Table 3).

Sensitivity Analyses by Varying TRD Definition

We found that the longer the requirement of adequate antidepressant treatment duration to define TRD, the lower the prevalence of TRD. The raw prevalence of TRD in PTD was about 4% (Humana: 4.1%, Optum: 3.9%) if the adequate antidepressant treatment was 6 weeks. The raw prevalence of TRD in PTD was 6.4%–6.5% (Humana: 6.5%, Optum: 6.4%) if the adequate antidepressant treatment was 3 weeks (main analysis used 4 weeks).

TRD Development Timeline in Incident PTD Patients

In Humana and Optum incident PTD patients, the event rate of TRD (based on 28-day definition) during the follow-up period was 3.1 (95% CI, 2.9–3.2) and 3.6 (95% CI, 3.4–3.8) per 100 patient-years, respectively. The Kaplan-Meier curves showing the development of TRD in patients with incident PTD based on 3 TRD definitions (21-day, 28-day, and 42-day) for Humana and Optum databases are shown in Figure 1.

Table 3. Associations of Age, Sex, Race, and Region With the Risk of TRD in Patients With PTD[a]

	Humana			Optum		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Sex (ref: male)						
Female	1.49	1.44–1.55	<.0001	1.35	1.30–1.40	<.0001
Age (ref: 45–64 y)						
18–44 y	1.04	0.95–1.13	.4144	0.98	0.94–1.02	.2902
65+ y	0.71	0.69–0.74	<.0001	0.95	0.92–0.99	.0102
Race (ref: White)						
Black	0.76	0.72–0.81	<.0001	0.90	0.84–0.96	.0007
Others	0.81	0.77–0.85	<.0001	0.86	0.83–0.90	<.0001
Region (ref: South)						
Midwest	0.98	0.94–1.01	.1973	0.89	0.85–0.92	<.0001
Northeast	0.76	0.68–0.86	<.0001	0.74	0.69–0.79	<.0001
West	0.85	0.81–0.90	<.0001	0.85	0.81–0.89	<.0001

[a]All variables were included in the logistic regression model.
Abbreviations: OR = odds ratio, PTD = pharmaceutically treated depression, ref = reference, TRD = treatment resistant depression.

As the follow-up time to identify a TRD event for incident PTD patients in this study was shorter than 1 year, we should be cautious when interpreting this finding. Other studies showed that if the follow-up time was longer, the median number of days from index antidepressant to TRD identification would be longer accordingly.[12]

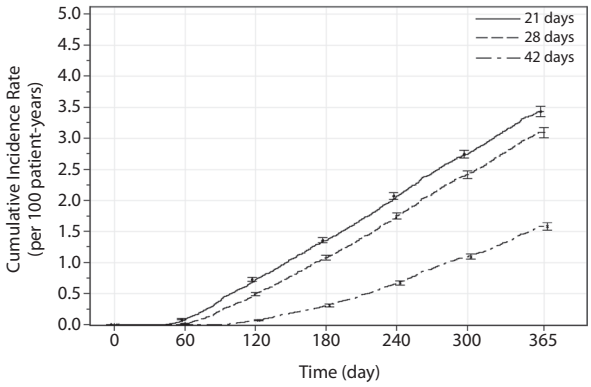
DISCUSSION

In this study, we found that in 2018 the standardized prevalence of TRD in PTD patients in the Humana and Optum databases was about 6%–7% based on the definition of at least 2 failed antidepressants after at least 4 weeks of treatment at adequate dose. The prevalence of TRD in PTD patients varied by age, sex, race, and geographic region.

Figure 1. Development of TRD in Patients With Incident PTD (Product-Limit Failure Estimates With Standard Error)

A. Humana

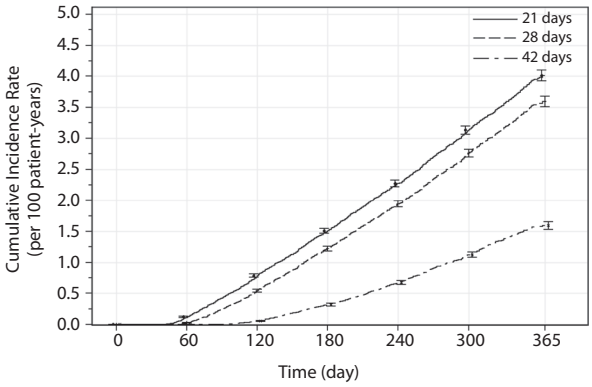
	21 days	28 days	42 days
No. of Events	2,036	1,774	805
% of Events (95% CI)	3.4 (3.3–3.6)	3.1 (2.9–3.2)	1.6 (1.5–1.7)
Survival Mean Time (SE)	354.8 (0.1)	355.7 (0.1)	358.3 (0.1)



No. of participants at risk							
21 days	90,361	84,105	75,656	66,737	56,136	41,770	569
28 days	90,361	84,157	75,835	66,931	56,334	41,929	572
42 days	90,361	84,168	76,152	67,469	56,979	42,513	580
No. of events inside period							
21 days	63	508	462	444	352	207	0
28 days	11	371	426	419	345	202	0
42 days	0	52	170	226	221	136	0

B. Optum

	21 days	28 days	42 days
No. of Events	2,497	2,172	868
% of Events (95% CI)	4.0 (3.8–4.2)	3.6 (3.4–3.8)	1.6 (1.5–1.7)
Survival Mean Time (SE)	357.1 (0.1)	358.0 (0.1)	361.2 (0.1)



No. of participants at risk							
21 days	104,658	95,691	83,133	71,383	58,614	42,648	861
28 days	104,658	95,776	83,321	71,577	58,796	42,801	866
42 days	104,658	95,796	83,724	72,212	59,520	43,470	870
No. of events inside period							
21 days	105	585	575	517	447	268	0
28 days	20	450	536	487	421	258	0
42 days	0	44	208	231	238	147	0

Abbreviations: PTD = pharmaceutically treated depression, TRD = treatment-resistant depression.

Prior publications reported wide variation in adult TRD prevalence (6%–55%)[3,5] due to different study populations and definitions of TRD. In particular, the more sensitive the TRD definition is, the higher the TRD prevalence. For example, the prevalence of TRD was as high as 55% if patients were identified as having TRD if they scored ≥ 14 on the BDI-II (the presence of at least mild depressive symptoms) and had been taking antidepressant medication at an adequate dose for at least 6 weeks. Our study result is similar to studies with comparable methodologies.[5]

In addition, prior studies showed that the incidence/prevalence of TRD depends strongly on the details of the operating definition,[5,13] so we considered several important factors when estimating the prevalence of TRD. First, we used PTD patients as the denominator. The definition of PTD requires both MDD diagnosis and antidepressant prescription. Using PTD instead of MDD rendered the population in the denominator one with confirmed MDD; thus, the calculation of TRD prevalence was more stable and less subject to diagnosis variation across different practices.[14] Second, we defined the follow-up time as limited to the duration of 1 typical depressive episode (6–12 months).[15] The 1-episode-based definition of TRD is recommended by existing studies.[16] In our study, for non-incident PTD patients, the follow-up time was about 12–24 months, and for incident PTD patients, the follow-up time was less than 12 months. It is not unusual for health care practitioners to prescribe a different antidepressant or add an augmentation therapy in a recurrent depressive episode.[17] Therefore, a study with long follow-up time including multiple depressive episodes may report a higher prevalence of TRD. Third, we used a moderate length of adequate treatment (4 weeks) to define TRD. The average time for onset of response to an antidepressant is about 2 weeks, and the average time to full response is about 3 weeks.[18] We used 4 weeks to make reasonably certain that patients were on antidepressants long enough to observe a response, but not too long to result in an underestimated TRD prevalence. Lastly, because the prevalence of TRD in PTD patients varied by age and sex, and the Humana population was older than the Optum population, we standardized the prevalence estimates when comparing TRD prevalence in Humana and Optum.

Additionally, the variation of TRD prevalence might be in part explained by practice differences related to diagnosis and treatment. Primary care providers often are hesitant to increase the dose of commonly prescribed antidepressants to high enough levels to be effective[19] and may misdiagnose other mental health disorders (eg, bipolar disorder) as unipolar depression.[20] Therefore, the prevalence of TRD in patients cared for by primary care providers may differ from that in patients under the care of psychiatrists.

One interesting finding in our study was that the Humana population had a much higher PTD prevalence even after stratification by age. Database heterogeneity is a recognized problem for observational studies.[21] Drug utilization can vary greatly among different data sources. Factors determining the use of antidepressants are multiple, eg, clinical symptoms, adverse effects, and other psychiatric comorbidities.[22] Further research needs to be done to

evaluate why Humana has higher PTD prevalence than Optum. One may be tempted to use the prevalence of PTD and TRD in this study to estimate the TRD population size in the US; however, because of the large difference in PTD prevalence between the 2 databases, using these claims database populations to determine the magnitude of TRD in the entire US population is not warranted.

Regarding TRD patient subgroups, we found that in both Humana and Optum databases, middle-aged adults (45–64 years) had the highest TRD prevalence compared to the younger adults (18–44 years) and older adults (65+ years), though the absolute differences were small (< 2%). One study conducted in Taiwan used different age cutoff points and reported a similar trend in females. The authors found that TRD incidence among females aged ≥ 60 was slightly lower than among females aged 50–59.[12] One systematic review investigated sociodemographic and clinical predictors for non-response/non-remission in patients with TRD. It found 3 studies showing that older age was associated with nonresponse of antidepressants in patients with TRD,[23] but after carefully examining the 3 studies included in the systematic review, we identified several methodological concerns. First, the 3 studies included in the systematic review did not aim to evaluate TRD prevalence in subgroups; rather, they aimed to evaluate comorbidities[24,25] or efficacy of antidepressants.[26] Second, the TRD populations of the 3 studies in the systematic review were selected from clinical trials or case series, with small sample sizes (TRD populations of 53,[24] 53,[25] and 13[26]) and no comparison groups, and thus were subject to selection bias and not representative of the general TRD population.

Our study shows that females had higher TRD prevalence than males. This finding is similar to that of the epidemiologic study conducted in Taiwan.[12] But between males and females, the absolute TRD prevalence values were smaller while the magnitude of TRD prevalence difference was larger in our study (standardized Humana males: 5.1% vs females: 7.6%; standardized Optum males: 4.7% vs females: 6.3%) than the Taiwan study (males: 20.06% vs females: 21.44%). Longer follow-up (maximum follow-up time was 8 years) may partially explain higher TRD prevalence in the Taiwan study, but the gender difference may require further investigation. We found 1 study that reported that males (11.5%) had a higher risk of TRD than females (9.7%).[27] This study used a different algorithm from ours; it defined TRD as having at least 3 distinct antidepressants or 1 antidepressant and 1 antipsychotic within 1 year after the index date. This algorithm, especially the inclusion of 1 antidepressant and 1 antipsychotic (instead of using a comprehensive augmentation drug list as in our study), may be too sensitive to identify TRD and may classify more males than females as having TRD, because drug utilization studies showed that more males with depression initiated antipsychotics than females.[28]

While some publications reported inconclusive evidence about the association of race and TRD prevalence,[23] our study found slightly higher TRD prevalence among White individuals than Black individuals. Similarly, the absolute difference was small in both databases. In Optum, the results also suggested that Hispanics had the lowest TRD prevalence compared to other races; however, this result should be interpreted with caution because Hispanic information was likely underreported in these claims data.[10,11]

It should be noted that patients who were identified as having higher risks for TRD, ie, females, middle-aged patients, and White patients, might advocate more strongly for treatment to remission,[29] be more optimistic about next courses of medication/treatment,[30] and have more supportive people in their lives urge them to get help.[31] These patients' treatment acceptance factors were not accounted for in the analysis because they were difficult to measure in claims databases. Also, health care access plays a role in the variation of TRD prevalence.[32] Health care providers may be biased in following up on treatment and aiming toward remission in some patient groups compared to others.

Our study found that the TRD prevalence was slightly higher in the South and the Midwest. Regional variation in medical care of MDD has been extensively documented in publications,[33–35] and many factors could contribute to the variation. That this geographic variation in TRD prevalence was still significant after accounting for age, sex, and race differences in the logistic regression suggests that other factors, such as medical practice variations, could also have contributed to this small regional difference.

We found the median time from antidepressant use to TRD was about 6 months in incident PTD patients. This finding should be interpreted as exploratory because the maximum follow-up time for incident PTD patients was only 1 year. The time from antidepressant use to TRD could change with longer follow-up time.

This study had limitations that were inherently associated with secondary database analysis. First, neither database was nationally representative because only patients with health insurance (commercial or Medicare in Humana, commercial or Medicare Advantage in Optum) were included in these populations. Second, claims data did not provide reasons for regimen changes, and assumptions were made in the TRD definition because a switch of antidepressant or an add-on of an augmentation could be due to many reasons other than inadequate response, such as personal preference and adverse events.

CONCLUSION

The overall TRD prevalence among PTD patients was about 6%–7% in the Humana and Optum databases in 2018. The prevalence of TRD varied by age, sex, race, and geographic region, but the absolute differences were small. The TRD patients were predominantly female and were between ages 45–64 years. Given the vast variation of TRD prevalence in publications, further efforts should be taken to standardize TRD definition.

Submitted: February 26, 2021; accepted July 1, 2021.

Published online: November 30, 2021.

Potential conflicts of interest: All authors are current employees of Merck & Co., Inc and may hold stocks in the company.

Funding/support: This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Role of the sponsor: The sponsor was involved in the design and conduct of the study; collection, analysis, and interpretation of data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication.

Acknowledgment: The authors acknowledge the contributions of Weifeng Xu, Merck & Co., Inc., Upper Gwynedd, PA, for programming support.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary material: Available at PSYCHIATRIST.COM

REFERENCES

1. Brody DJ, Pratt LA, Hughes JP. Prevalence of depression among adults aged 20 and over: United States, 2013–2016. *NCHS Data Brief*. 2018;303:1–8.
2. Ionescu DF, Rosenbaum JF, Alpert JE. Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues Clin Neurosci*. 2015;17(2):111–126.
3. Thomas L, Kessler D, Campbell J, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. *Br J Gen Pract*. 2013;63(617):e852–e858.
4. Preskorn SH. Prediction of individual response to antidepressants and antipsychotics: an integrated concept. *Dialogues Clin Neurosci*. 2014;16(4):545–554.
5. Fife D, Reps J, Cepeda MS, et al. Treatment resistant depression incidence estimates from studies of health insurance databases depend strongly on the details of the operating definition. *Heliyon*. 2018;4(7):e00707.
6. Olfson M, Amos TB, Benson C, et al. Prospective service use and health care costs of Medicaid beneficiaries with treatment-resistant depression. *J Manag Care Spec Pharm*. 2018;24(3):226–236.
7. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry*. 2007;68(suppl 8):17–25.
8. Gaynes BN, Gartlehner G, Hoffman V, et al. *Definition of Treatment-Resistant Depression in the Medicare Population. Technology Assessment Program*. Rockville, MD: Agency for Healthcare Research and Quality; 2018.
9. Li G, Fife D, Wang G, et al. All-cause mortality in patients with treatment-resistant depression: a cohort study in the US population. *Ann Gen Psychiatry*. 2019;18(1):23.
10. Waldo DR. Accuracy and bias of race/ethnicity codes in the Medicare enrollment database. *Health Care Financ Rev*. 2004;26(2):61–72.
11. Polubriaginof FCG, Ryan P, Salmasian H, et al. Challenges with quality of race and ethnicity data in observational databases. *J Am Med Inform Assoc*. 2019;26(8-9):730–736.
12. Fife D, Feng Y, Wang MY, et al. Epidemiology of pharmaceutically treated depression and treatment resistant depression in Taiwan. *Psychiatry Res*. 2017;252:277–283.
13. Trevino K, McClintock SM, McDonald Fischer N, et al. Defining treatment-resistant depression: a comprehensive review of the literature. *Ann Clin Psychiatry*. 2014;26(3):222–232.
14. Demyttenaere K, Van Duppen Z. The impact of (the concept of) treatment-resistant depression: an opinion review. *Int J Neuropsychopharmacol*. 2019;22(2):85–92.
15. Bains NAS. Major Depressive Disorder. NCBI. https://www.ncbi.nlm.nih.gov/books/NBK559078/. Accessed Oct 19, 2020.
16. Kubitz N, Mehra M, Potluri RC, et al. Characterization of treatment resistant depression episodes in a cohort of patients from a US commercial claims database. *PLoS One*. 2013;8(10):e76882.
17. Nuggerud-Galeas S, Sáez-Benito Suescun L, Berenguer Torrijo N, et al. Analysis of depressive episodes, their recurrence and pharmacologic treatment in primary care patients: a retrospective descriptive study. *PLoS One*. 2020;15(5):e0233454.
18. Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals (Basel)*. 2010;3(1):19–41.
19. Katon W. Collaborative depression care models: from development to dissemination. *Am J Prev Med*. 2012;42(5):550–552.
20. Culpepper L. Misdiagnosis of bipolar depression in primary care practices. *J Clin Psychiatry*. 2014;75(3):e05.
21. Madigan D, Ryan PB, Schuemie M, et al. Evaluating the impact of database heterogeneity on observational study results. *Am J Epidemiol*. 2013;178(4):645–651.
22. Zimmerman M, Posternak M, Friedman M, et al. Which factors influence psychiatrists' selection of antidepressants? *Am J Psychiatry*. 2004;161(7):1285–1289.
23. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: a systematic review. *Psychiatry Res*. 2016;240:421–430.
24. Petersen T, Hughes M, Papakostas GI, et al. Treatment-resistant depression and Axis II comorbidity. *Psychother Psychosom*. 2002;71(5):269–274.
25. Sagud M, Mihaljevic-Peles A, Uzun S, et al. The lack of association between components of metabolic syndrome and treatment resistance in depression. *Psychopharmacology (Berl)*. 2013;230(1):15–21.
26. Bergman J, Miodownik C, Palatnik A, et al. Efficacy of bupropion XR in treatment-resistant elderly patients: a case series study. *Clin Neuropharmacol*. 2011;34(1):17–20.
27. Cepeda MS, Reps J, Ryan P. Finding factors that predict treatment-resistant depression: results of a cohort study. *Depress Anxiety*. 2018;35(7):668–673.
28. Gerhard T, Stroup TS, Correll CU, et al. Antipsychotic medication treatment patterns in adult depression. *J Clin Psychiatry*. 2018;79(2):55–61.
29. Hinton L, Zweifach M, Oishi S, et al. Gender disparities in the treatment of late-life depression: qualitative and quantitative findings from the IMPACT trial. *Am J Geriatr Psychiatry*. 2006;14(10):884–892.
30. Burnett-Zeigler I, Kim HM, Chiang C, et al. The association between race and gender, treatment attitudes, and antidepressant treatment adherence. *Int J Geriatr Psychiatry*. 2014;29(2):169–177.
31. Bogner H, Dobransky LN, Wittink MN. Patient ethnicity and perceptions of families and friends regarding depression treatment. *Ethn Health*. 2008;13(5):465–478.
32. Alegría M, Chatterji P, Wells K, et al. Disparity in depression treatment among racial and ethnic minority populations in the United States. *Psychiatr Serv*. 2008;59(11):1264–1272.
33. King M, Essick C. The geography of antidepressant, antipsychotic, and stimulant utilization in the United States. *Health Place*. 2013;20:32–38.
34. Columbo JA, Stone DH, Goodney PP, et al. The prevalence and regional variation of major depressive disorder among patients with peripheral arterial disease in the Medicare population. *Vasc Endovascular Surg*. 2016;50(4):235–240.
35. Wang J, Wu X, Lai W, et al. Prevalence of depression and depressive symptoms among outpatients: a systematic review and meta-analysis. *BMJ Open*. 2017;7(8):e017173.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Epidemiology of Treatment-Resistant Depression in the United States

Authors: Xinyue Liu, PhD; Yuki Mukai, MD; Christine I. Furtek, BS; Edward A. Bortnichak, PhD; Kai-Li Liaw, PhD; and Wenjun Zhong, PhD

DOI Number: 10.4088/JCP.21m13964

List of Supplementary Material for the article

1. Table 1 — List of Antidepressants and Their Adequate Dose (Minimum Daily Adequate Dose), and Augmentation Medications
2. Table 2 — US Regions

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. List of antidepressants and their adequate dose (minimum daily adequate dose), and augmentation medications

Antidepressant medication		
Name	**Minimum daily adequate dose1**	**Augmentation medications**
SSRIs		Aripiprazole
Citalopram	20 mg	Cariprazine
Escitalopram	10 mg	Clozapine
Fluvoxamine	50 mg	Iloperidone
Fluvoxamine, continuous release	100 mg	Olanzapine
Fluoxetine	20 mg	Paliperidone
Paroxetine	20 mg	Quetiapine
Paroxetine, extended release	12.5 mg	Risperidone
Sertraline	50 mg	Ziprasidone
Vilazodone	10 mg	Lithium
DNRI		Thyroid hormone (T3 and T4)
Bupropion	150 mg	Esketamine
SNRIs		Gabapentin
Desvenlafaxine	50 mg	Lamotrigine
Duloxetine	60 mg	Topiramate
Levomilnacipran	20 mg	
Milnacipran	12.5 mg	
Venlafaxine	37.5 mg	
Serotonin modulators		
Nefazodone	50 mg	
Trazodone	150 mg	
Vortioxetine	10 mg	
Norepinephrine-serotonin modulator		
Mirtazapine	15 mg	
Tricyclics and tetracyclics		
Amitriptyline	25 mg	
Amoxapine	50 mg	
Clomipramine	25 mg	
Doxepin	25 mg	
Desipramine	25 mg	
Imipramine	25 mg	
Maprotiline	75 mg	
Nortriptyline	25 mg	
Protriptyline	10 mg	
Trimipramine	25 mg	
MAOIs		
Isocarboxazid	10 mg	
Moclobemide	150 mg	
Opipramol	x	
Phenelzine	15 mg	
Selegiline transdermal	6 mg	
Tranylcypromine	10 mg	
Other selected medications		
Agomelatine	x	
Mianserin	30 mg	
Nefazadone	x	

Noxiptiline	x	
Olanzapine-fluoxetine[2]	20 mg	
Pipofezine	x	
Reboxetine	x	
Tianeptine	x	

MAOIs = monoamine oxidase inhibitors; NDRIs = norepinephrine-dopamine reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

1. Minimum adequate doses based on APA practice guideline or FDA package inserts.
2. For this combination, we only look at fluoxetine dose
3. X: since these medications are rarely used, we assume any dose is therapeutic.

Supplementary Table 2. US regions

Regions	**State**
Midwest	IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI
Northeast	CT, MA, ME, NH, NJ, NY, PA, RI, VT
South	AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV
West	AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY