Prevalence of Residual Symptoms in Adults With Depression or Major Depressive Disorder on Antidepressant Monotherapy: A Retrospective, Longitudinal Analysis of US Health Insurance Claims and Electronic Health Record Data

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BACKGROUND

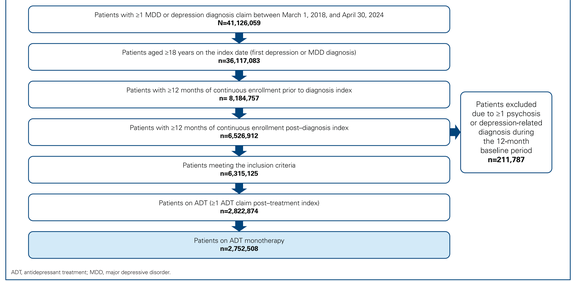
- Major depressive disorder (MDD) is a common, disabling psychiatric illness characterized by cognitive, emotional, and physical symptoms, with high rates of recurrence, disability, and suicide[1]
- The primary goal of antidepressant treatment (ADT) is complete symptom remission and restoration of function; however, many patients continue to experience residual symptoms despite apparent remission[1,2]
  - Residual symptoms are defined as subclinical depressive symptoms that persist post-treatment[1]
  - These symptoms are associated with significant psychosocial dysfunction, reduced quality of life, and increased risk of clinical relapse[1-3]
- Early detection and appropriate management of residual symptoms are essential to guide treatment decisions (ie, whether to continue, modify, or switch therapies), reduce treatment inertia, and improve long-term outcomes and functional recovery[1,2]
- This retrospective, observational study assessed the prevalence of residual symptoms in adults with depression or MDD receiving ADT

METHODS

Study Design and Population

- The study employed a retrospective, observational cohort design that analyzed de-identified health insurance claims and electronic health records from the HealthVerity database
- Inclusion criteria:
  - Age ≥18 years
  - At least 1 inpatient or outpatient diagnosis of depression or MDD between March 1, 2019, and April 30, 2024
  - At least 12 months of continuous health plan enrollment before the diagnosis index (baseline period), and ≥12 months after the diagnosis index (follow-up period) (**Figure 1**). Diagnosis index is defined as date of first observed diagnosis of depression or MDD during the study period
- Patients with psychosis or depression-related diagnosis during the 12-month baseline period were excluded

Figure 1. Patient Disposition and Selection of Analysis Set



ADT, antidepressant treatment; MDD, major depressive disorder.

Study Endpoints and Assessments

- Demographic characteristics were recorded at the diagnosis index date and comorbidities were evaluated during the baseline period
- The annualized residual symptom count per patient was calculated by summing the total number of residual symptoms reported during the follow-up period and dividing by the duration of follow-up in years
- Primary analysis of residual symptoms was conducted on the patient population receiving monotherapy during the post–treatment index period, defined from the first medication claim on or after the index diagnosis date
- Three representative categories of residual symptoms—sleep disturbance, cognitive impairment, and sexual dysfunction—were assessed in up to 4 lines of therapy (LOTs), overall and by ADT class
  - LOT was defined as continuous treatment with a consistent set of oral ADT, and the initiation of a new ADT class was considered as the next LOT initiation
  - Residual symptoms at ADT class level were evaluated for 6 drug classes: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), other ADTs (may include individual antidepressants such as bupropion, fluoxetine, and vortioxetine or ADT combinations), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antipsychotics (AAs)

Statistical Analysis

- Results were analyzed using descriptive statistics
- Continuous variables (eg, age) were summarized using means, medians, SDs, and IQRs, while categorical variables (eg, sex and race) were presented as frequency distributions
- Sample selection and creation of analytic variables were performed using the Instant Health Data software (Panalgo). Statistical analyses were performed using SAS Studio version 9.04 (SAS Institute)

RESULTS

Baseline Demographics

- Of 41,126,059 patients with a medical claim for depression or MDD, 6,315,125 met the inclusion criteria (see **Supplementary Table** for demographics and clinical characteristics)
- Of the patients meeting study inclusion criteria, 2,822,874 (44.7%) received antidepressant pharmacotherapy (≥1 ADT claim post–treatment index); of these, 2,752,508 (97.5%) were treated with monotherapy. These individuals are the focus of the analyses presented herein
- The mean participant age was 43.7 years (SD 16.9), 69.6% were female, 52.1% had commercial insurance, and 37.0% had Medicaid (**Table 1**)

Table 1. Demographics and Clinical Characteristics

Criteria	Patients on ADT monotherapy (n=2,752,508)
Age at index (years)	
Mean (SD)	43.7 (16.9)
Median (IQR)	42.0 (30.0-56.0)
Sex, n (%)	
Male	836,316 (30.4)
Female	1,916,188 (69.6)
Missing/unknown	4 (<0.1)
Region, n (%)	
Northeast	446,016 (16.2)
Midwest	755,914 (27.5)
South	935,142 (34.0)
West	607,684 (22.1)
Missing/unknown	7752 (0.3)
Race, n (%)	
Asian	49,123 (1.8)
Black	201,348 (7.3)
Hispanic	217,696 (7.9)
White	1,116,673 (40.6)
Other	91,425 (3.3)
Missing/unknown	1,076,243 (39.1)
Payer Type, n (%)	
Commercial	1,434,979 (52.1)
Medicaid	1,017,864 (37.0)
Medicare Advantage	212,179 (7.7)
Multiple payers	87,486 (3.2)
Comorbidities, n (%)	
Anhedonia	650 (<0.1)
Bipolar disorder	80,362 (2.9)
Other anxiety disorders	648,089 (23.5)
Attention-deficit/hyperactivity disorder	95,363 (3.5)
Substance use disorder	456,037 (16.6)

ADT, antidepressant treatment.

Treatment With ADT Monotherapy

- Patients were followed from the start of LOT1 to the end of LOT4, with a median treatment duration of 334.0 days (IQR, 151.0-649.0)
- Median treatment durations in days for each LOT were as follows: 215.0 (IQR, 116.0-459.0) for LOT1, 157.0 (IQR, 91.0-305.0) for LOT2, 121.0 (IQR, 71.0-257.0) for LOT3, and 102.0 (IQR, 64.0-214.0) for LOT4

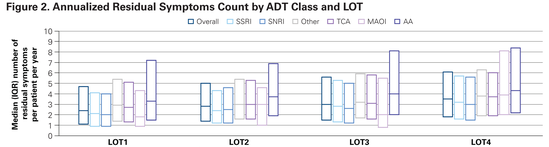
Residual Symptom Prevalence

- Among patients receiving monotherapy, 445,399 (16.2%) reported ≥1 residual symptom (of the 3 symptom categories of interest) post–treatment index
- Residual symptom prevalence was highest in LOT1 (13.1%) and slightly lower in LOT2-LOT4 (~10.5%)
- Overall, residual symptoms were common among all ADT classes and ranged from 11.8% to 21.4%

Annualized Residual Symptom Burden

- Among all patients receiving monotherapy, the mean annualized number of residual symptoms was 3.9 per patient (SD, 13.1) with a median of 1.7 (IQR, 0.8-3.7)
- Residual symptom burden increased over each successive LOT, as both the mean (6.0-7.5) and median (2.4-3.5) annualized counts per patient increased from LOT1 to LOT4
- Across ADT classes, mean annualized residual symptom counts per patient were similar and ranged from 4.1 to 8.0, with a median range of 1.5-3.1 and relatively higher counts in those receiving AAs (**Figure 2**)
  - Annualized symptom count per patient increased with each LOT across all treatments, with median ranges of 1.8-3.3 in LOT1, 2.4-3.7 in LOT2, 2.0-4.0 in LOT3, and 3.0-4.3 in LOT4

Figure 2. Annualized Residual Symptoms Count by ADT Class and LOT



Box shows Q1 (bottom), Q3 (top); line inside is median (Q2).

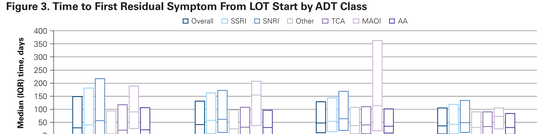
	LOT1			LOT2			LOT3			LOT4		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Overall	338,242	6.0 (22.0)	2.4 (1.1-4.7)	80,403	5.8 (18.6)	2.8 (1.4-5.0)	58,059	6.5 (20.1)	3.0 (1.5-5.6)	25,785	7.5 (23.5)	3.5 (1.8-6.1)
SSRI	161,973	5.2 (16.3)	2.1 (0.9-4.1)	36,898	5.0 (15.5)	2.4 (1.2-4.3)	21,361	6.0 (16.6)	2.6 (1.3-5.3)	8935	7.1 (22.4)	3.2 (1.6-5.7)
SNRI	36,667	5.1 (19.0)	2.0 (0.9-4.0)	10,430	5.5 (19.3)	2.5 (1.2-4.6)	8634	5.5 (16.5)	2.6 (1.2-5.0)	3827	6.7 (22.6)	3.0 (1.5-5.6)
Other*	106,965	7.0 (24.7)	2.9 (1.4-5.4)	32,359	6.3 (20.1)	3.0 (1.6-5.4)	20,299	6.9 (21.3)	3.2 (1.7-5.9)	9140	7.7 (24.2)	3.8 (1.9-6.3)
TCA	17,038	6.6 (24.6)	2.7 (1.3-5.1)	5277	5.7 (16.2)	3.0 (1.6-5.3)	3286	6.5 (18.9)	3.1 (1.6-5.8)	1525	7.3 (21.2)	3.7 (1.9-6.0)
MAOI	65	4.2 (7.2)	1.8 (0.9-4.3)	17	8.1 (18.3)	3.0 (1.0-4.6)	12	3.0 (2.7)	2.0 (0.8-5.5)	8	5.4 (4.6)	3.9 (2.0-8.1)
AA	15,534	9.5 (36.0)	3.3 (1.5-7.2)	5422	9.0 (27.7)	3.7 (1.9-6.9)	4467	9.5 (27.6)	4.0 (2.0-8.1)	2350	10.0 (27.2)	4.3 (2.2-8.4)

*May include individual ADTs such as bupropion, fluoxetine, and vortioxetine or ADT combinations.
AA, atypical antipsychotics; ADT, antidepressant therapy; LOT, line of therapy; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Time to First Residual Symptom

- Mean time to first residual symptom following the start of each LOT (across LOT1 to LOT4) was 128.4 days (SD, 220.4) with a median of 39.0 days (IQR, 1.0-149.0)
- Median time to first residual symptoms increased from LOT1 to LOT3 with a reduction noted in LOT4, across all ADTs (**Figure 3**)
- Overall, median time to first residual symptoms across all ADTs ranged between 20.8 and 93.5 days, with the shortest duration for "Other" ADTs

Figure 3. Time to First Residual Symptom From LOT Start by ADT Class



Box shows Q1 (bottom), Q3 (top); line inside is median (Q2).

	LOT1			LOT2			LOT3			LOT4		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Overall	338,242	136.4 (254.8)	29.0 (1.0-149.0)	90,403	107.8 (174.6)	41.0 (1.0-131.0)	58,059	107.1 (164.0)	48.0 (10.0-129.0)	25,785	86.6 (136.4)	27.0 (5.0-105.0)
SSRI	161,973	149.1 (293.9)	40.0 (1.0-181.0)	36,898	127.0 (188.4)	57.0 (6.0-162.0)	21,361	116.0 (169.4)	54.0 (14.0-143.0)	8935	93.6 (140.5)	43.0 (7.0-119.0)
SNRI	36,667	171.4 (272.0)	56.0 (1.0-217.0)	10,430	136.2 (202.7)	81.5 (1.0-172.0)	8634	136.0 (193.7)	84.0 (10.0-198.0)	3827	108.7 (160.9)	49.0 (12.0-134.0)
Other*	106,965	95.0 (195.3)	7.0 (1.0-94.0)	32,359	83.3 (149.0)	25.0 (1.0-98.0)	20,299	92.6 (150.3)	38.0 (6.0-108.5)	9140	75.9 (126.4)	30.0 (1.0-90.0)
TCA	17,038	308.7 (411.0)	20.0 (1.0-113.0)	5277	90.2 (157.5)	31.0 (1.0-107.0)	3286	90.7 (140.1)	40.0 (10.0-102.0)	1525	76.4 (122.4)	34.0 (3.0-90.0)
MAOI	65	172.6 (268.7)	90.0 (26.0-188.0)	17	148.5 (112.1)	155.0 (38.0-207.0)	12	213.9 (270.5)	113.5 (18.0-362.5)	8	84.9 (82.1)	72.0 (25.0- 105.5)
AA	15,534	104.6 (201.4)	22.0 (1.0-106.0)	5422	86.6 (151.5)	30.0 (1.0-96.0)	4467	86.4 (138.9)	35.0 (9.0-101.0)	2350	71.6 (115.7)	30.0 (4.0-84.0)

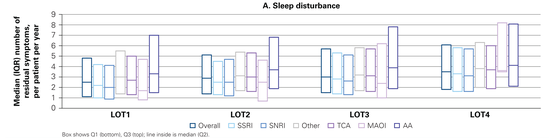
*May include individual ADTs such as bupropion, fluoxetine, and vortioxetine or ADT combinations.
AA, atypical antipsychotics; ADT, antidepressant therapy; LOT, line of therapy; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Residual Symptoms: Categories of Interest

- Of those patients with residual symptoms, 82.0% reported sleep disturbance, 14.1% reported cognitive impairment, and 9.2% reported sexual dysfunction
- Through each LOT and across all ADT classes, the frequency rates reported for these categories of symptoms were similar to those reported for the overall population (**Figure 4**)

Figure 4. Annualized Count of Residual Symptoms by ADT Class and LOT: A) Sleep Disturbance; B) Cognitive Impairment/Concentration Issues; C) Sexual Dysfunction

A. Sleep disturbance

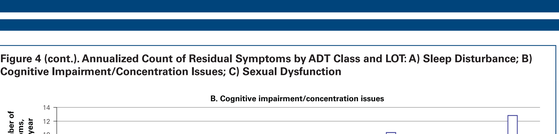


Box shows Q1 (bottom), Q3 (top); line inside is median (Q2).

	LOT1			LOT2			LOT3			LOT4		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Overall	276,705	6.2 (22.3)	2.5 (1.1-4.8)	74,827	5.8 (16.9)	2.5 (1.3-4.5)	48,460	6.4 (20.4)	3.0 (1.5-5.7)	21,964	7.9 (24.0)	3.5 (1.8-6.1)
SSRI	125,404	5.4 (20.3)	2.2 (1.0-4.2)	28,607	5.0 (15.2)	2.5 (1.3-4.5)	13,191	5.9 (18.9)	2.8 (1.4-5.3)	7315	7.3 (23.9)	3.3 (1.6-5.8)
SNRI	29,463	5.2 (20.2)	2.0 (0.9-4.1)	8350	5.7 (20.9)	2.5 (1.2-4.7)	6960	5.5 (17.1)	2.8 (1.3-5.1)	3156	6.6 (23.0)	3.1 (1.6-5.7)
Other*	92,362	7.1 (25.4)	3.0 (1.4-5.5)	28,227	6.2 (20.0)	3.1 (1.7-5.4)	17,398	6.7 (21.4)	3.2 (1.7-5.8)	7992	7.7 (24.5)	3.8 (2.0-6.3)
TCA	15,689	6.4 (24.7)	2.7 (1.3-5.0)	4867	5.6 (16.2)	3.0 (1.6-5.3)	3018	6.4 (19.2)	3.1 (1.6-5.7)	1414	6.8 (18.5)	3.7 (1.9-6.0)
MAOI	58	4.2 (7.1)	1.7 (0.8-4.7)	14	8.4 (20.0)	2.6 (0.7-4.6)	10	3.4 (2.7)	2.4 (1.0-6.2)	5	6.2 (6.3)	3.6 (3.5-8.2)
AA	13,729	9.2 (29.2)	3.3 (1.5-7.0)	4762	8.9 (27.8)	3.7 (1.9-6.6)	3923	9.2 (27.4)	3.9 (1.9-7.9)	2092	9.7 (26.9)	4.1 (2.1-8.1)

Figure 4 (cont.). Annualized Count of Residual Symptoms by ADT Class and LOT: A) Sleep Disturbance; B) Cognitive Impairment/Concentration Issues; C) Sexual Dysfunction

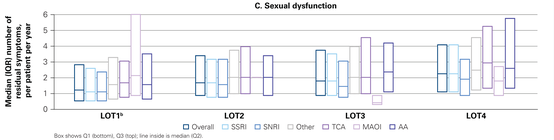
B. Cognitive impairment/concentration issues



Box shows Q1 (bottom), Q3 (top); line inside is median (Q2).

	LOT1			LOT2			LOT3			LOT4		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Overall	46,244	5.7 (16.4)	2.1 (0.9-4.4)	11,476	6.4 (19.7)	2.5 (1.2-5.0)	7309	7.5 (21.0)	2.9 (1.3-5.9)	3025	7.9 (21.4)	3.3 (1.5-6.3)
SSRI	26,519	5.0 (16.4)	1.8 (0.8-4.0)	5866	5.7 (18.1)	2.2 (1.1-4.3)	3082	6.9 (19.5)	2.7 (1.2-5.4)	1210	6.8 (16.2)	3.1 (1.4-5.9)
SNRI	5083	4.9 (14.3)	1.8 (0.7-4.0)	1481	5.5 (13.6)	2.4 (1.1-4.9)	1226	5.8 (14.7)	2.4 (1.1-4.7)	520	7.2 (16.9)	2.7 (1.3-5.6)
Other*	11,716	6.6 (19.4)	2.7 (1.1-5.4)	3238	7.4 (22.5)	3.0 (1.4-5.6)	2289	8.3 (23.6)	3.1 (1.4-6.5)	941	8.0 (22.6)	3.5 (1.6-6.3)
TCA	1144	8.7 (25.4)	2.7 (1.1-6.2)	290	7.8 (17.1)	3.1 (1.4-6.0)	203	7.5 (16.2)	3.3 (1.7-5.7)	93	13.2 (45.6)	3.4 (1.9-8.1)
MAOI	7	3.3 (3.6)	2.3 (0.9-4.3)	3	5.9 (2.3)	5.7 (3.7-8.2)	0	0.0 (0.0)	0.0 (0-0)	2	4.4 (6.2)	4.4 (0.7-8.0)
AA	1775	11.7 (35.2)	3.5 (1.5-8.1)	598	10.2 (29.2)	3.7 (1.8-8.9)	509	12.1 (29.5)	4.6 (2.0-10.3)	259	12.1 (30.2)	4.9 (2.6-12.8)

C. Sexual dysfunction



Box shows Q1 (bottom), Q3 (top); line inside is median (Q2).

	LOT1			LOT2			LOT3			LOT4		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Overall	29,684	3.0 (12.5)	1.3 (0.6-2.8)	7626	3.3 (10.7)	1.7 (0.9-3.4)	4743	3.8 (9.9)	1.8 (0.9-3.7)	1844	4.6 (12.1)	2.3 (1.2-4.1)
SSRI	16,810	2.8 (11.6)	1.2 (0.6-2.6)	3954	3.2 (10.2)	1.7 (0.8-3.2)	1959	3.8 (11.1)	1.8 (0.9-3.5)	772	4.4 (8.5)	2.3 (1.2-4.1)
SNRI	3845	2.5 (6.3)	1.1 (0.6-2.4)	1058	3.0 (5.3)	1.6 (0.8-3.2)	856	3.2 (8.5)	1.5 (0.8-3.1)	325	4.7 (21.5)	1.9 (0.9-3.2)
Other*	7649	3.6 (15.2)	1.6 (0.7-3.3)	2208	3.7 (13.9)	2.0 (1.0-3.7)	1563	4.0 (9.0)	2.0 (1.0-4.0)	588	4.4 (9.4)	2.5 (1.3-4.6)
TCA	745	3.0 (5.3)	1.7 (0.8-3.1)	256	3.7 (6.3)	2.1 (1.0-4.0)	154	4.2 (7.6)	2.0 (1.0-4.5)	53	5.8 (10.7)	3.0 (1.4-5.2)
MAOI	4	14.3 (25.2)	2.2 (0.9-27.8)	1	2.0 (0.0)	2.0 (2.0-2.0)	3	0.6 (0.3)	0.5 (0.4-0.9)	2	1.8 (1.2)	1.8 (0.9-2.7)
AA	631	4.9 (24.8)	1.6 (0.7-3.5)	239	3.2 (13.7)	1.2 (0.9-3.4)	208	4.7 (10.9)	2.4 (1.1-4.2)	104	6.0 (8.7)	2.6 (1.4-5.7)

*May include individual ADTs such as bupropion, fluoxetine, and vortioxetine or ADT combinations.
b2QR of the annualized number of sexual dysfunction symptoms per patient receiving MAOIs in LOT1 extends above axis.
AA, atypical antipsychotics; ADT, antidepressant therapy; LOT, line of therapy; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

LIMITATIONS

- The study population may not represent the broader population with depression, particularly uninsured individuals, those from diverse socioeconomic backgrounds, or those receiving care in nontraditional settings (eg, community clinics)
- Residual symptoms and outcomes were identified via diagnostic codes and clinician notes, which may lead to underreporting and underestimation of symptom prevalence and treatment outcomes, potentially biasing the study findings

CONCLUSIONS

- Findings from this real-world study highlight the persistent burden of residual symptoms among patients with depression or MDD treated with antidepressant monotherapy
- Despite receiving multiple LOTs, approximately 16% of the patients continued to experience residual symptoms
- Higher annualized per-patient counts of residual symptoms in later LOTs may reflect the unmet needs of a patient population that is treatment-resistant and more prone to relapse
- The prevalence of sleep disturbance, cognitive impairment, and sexual dysfunction was similar across all LOTs and ADT classes
- These findings underscore the need for individualized treatment strategies and may inform clinical decision-making to improve patient outcomes

ACKNOWLEDGMENTS

Under the direction of the authors, medical writing assistance was provided by Syneos Health and supported by Takeda Pharmaceuticals U.S.A., Inc. Presented at Psych Congress 2025, September 17-21, 2025, San Diego, CA

FUNDING

This study was funded by Takeda Pharmaceuticals U.S.A., Inc.

DISCLOSURES

Y Liu, M Lu, and **M Martin** are employees of Takeda Pharmaceuticals U.S.A., Inc. **S Manne** and **V Gandhi** are employees of Takeda Development Center Americas, Inc. **M Kim** and **B de los Santos** were employees of Takeda Pharmaceuticals U.S.A., Inc., at the time of study. **YL, ML, MM,** and **SM** are stockholders of Takeda Pharmaceuticals.

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