Remission and Treatment Augmentation of Depression in the United States

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ABSTRACT

Objective: To determine the proportion of adults treated for depression in the US who achieve remission and, among those not achieving remission, the proportion receiving augmentation treatment.

Methods: Using data from the US National Health and Nutrition Examination Survey (NHANES) for years 2013–2014, 2015–2016, and 2017–2018, we identified 869 adults who reported using antidepressant medications for depression for at least 3 months. This sample was partitioned into remitted (score < 5) and non-remitted (score ≥ 5) respondents based on 9-item Patient Health Questionnaire (PHQ-9) score—a questionnaire based on the *DSM-IV* criteria for major depressive disorder. Among the non-remitted group, the proportion receiving antidepressant augmentation with another antidepressant medication of a different class or other medications was also assessed.

Results: An estimated 43.5% of adults receiving antidepressant medications for depression were in remission when assessed. Among those not in remission, 28.1% were using augmentation treatment, which in most cases was another antidepressant medication from a different class. As compared to depressed adults without any mental health contact in the past year, those with such contact had significantly higher odds of using augmentation treatment (adjusted odds ratio = 2.72; 95% CI, 1.56–4.76; *P* = .001)

Conclusions: The low percentage of US adults treated with antidepressants for depression that achieves remission represents a missed clinical and public health opportunity to optimize depression treatment. Closer monitoring of symptoms through measurement-based care and setting symptom remission as a goal can help improve outcomes for adults with depression.

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- Try evidence-based strategies such as augmentation when measurement-based care for depression indicates that patients have not achieved symptom remission

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Clinical Points

- Only 43.5% of US adults receiving antidepressant medications for depression are in remission at any time.
- Only 28.1% of US adults with non-remitted depression receiving antidepressant medications are using augmentation treatment, which in most cases is another antidepressant medication from a different class.

Many patients treated for major depressive disorder (MDD) continue to experience depressive symptoms after weeks of antidepressant treatment.[1–5] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[4] for example, only 28% of patients achieved remission after up to 14 weeks of citalopram monotherapy. Because not achieving remission is associated with increased risk of recurrence and worse outcomes,[6–8] full remission of depressive symptoms—usually, within 6–12 weeks of treatment initiation for acute MDD[9]—is a widely accepted treatment goal.[1,9,10]

Remission can be achieved in specialty mental health or primary care treatment settings.[11] Several strategies to enhance antidepressant treatment response have evidence-based support, including dose optimization,[12] switching antidepressants within or across classes, augmentation with an antidepressant from a different class,[13] or augmentation with other medications.[14,15] While most guidelines support reviewing diagnosis, assessing treatment adherence, and optimizing antidepressant dose as first steps in managing partial response or nonresponse to antidepressant treatment,[9,16,17] there is little agreement regarding the superiority of medication switching compared to medication augmentation strategies.[18–21] Reviewing the available evidence, the 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines[16] recommended that the choice between switching and augmentation strategies should be individualized based on clinical factors, including level of initial treatment response. There appears to be a consensus that augmentation is the preferred strategy when there is an initial partial response to treatment, whereas switching within or across antidepressant classes is preferred for nonresponse to initial treatment.[17,22]

The 2010 American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*[9] recommended 3 augmentation strategies "with moderate clinical confidence": atypical antipsychotic medications, lithium, and thyroid hormone. In the intervening years, evidence has grown supporting use of these medications[23] and other medications for augmentation treatment, including the anticonvulsant lamotrigine,[24] stimulant medications, and the dopamine agonist pramipexole.[25,26] However, the extent to which these augmentation strategies are used in the US is not known. One European study[27] suggested that few of these strategies are used in day-to-day practice and that patients with residual depressive symptoms often continue taking the same medications for months.

In the present study, we use data from a nationally representative general population survey to examine the prevalence of non-remission and use of medication augmentation in adults currently receiving antidepressant treatment for depression. While past general population surveys in the US have provided estimates of prevalence and treatment of depression,[28–30] and depression remission,[31,32] they have not examined the prevalence of augmentation treatment. These new findings can potentially inform efforts to improve the care of adult depression.

METHODS

Sample

Data were drawn from 3 successive cycles of the National Health and Nutrition Examination Survey (NHANES): 2013–2014, 2015–2016, and 2017–2018. NHANES is a nationally representative survey of the general population conducted by the National Center for Health Statistics.[33] Starting in 1999, the NHANES has been conducted biennially. Completed interviews were obtained from 17,961 adults aged 18 years and over. Response rates for the NHANES, as defined by the proportion with completed interviews among screened potential respondents, ranged from 71.0% in 2013–2014 to 57.1% in 2017–2018. Computerized interviews were conducted in the respondents' homes. The NHANES data are deidentified, publicly available, and exempted from institutional ethical review. Further details on study design and sample description are provided elsewhere.[34] The study sample was limited to 869 adult respondents of the 3 NHANES cycles who reported using antidepressant medications for at least 3 months for depression and whose remission status could be ascertained (see the next section), representing 6.9% (weighted) of the US adult population.

Assessments

Antidepressant treatment for depression was defined by self-reported past-month use of these medications for depression. Antidepressants comprised serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, and vortioxetine; serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran; tricyclic antidepressants (TCAs), including amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, protriptyline, trimipramine, and amoxapine; monoamine oxidase inhibitors (MAOIs), including isocarboxazid, phenelzine, tranylcypromine, and selegiline transdermal; and other antidepressants, including bupropion, agomelatine, maprotiline, mirtazapine, and nefazodone.

The interviewers inspected and confirmed medication packages for 87.7%–89.4% of medications across the survey cycles. The length of time the respondent had been taking each medication was also recorded. For respondents taking more than one antidepressant, the length of medication use was based on the longest used medication. To help

ensure that respondents were in the maintenance phase of treatment, the analyses were limited to respondents using at least one antidepressant for at least 3 months.

Respondents were also asked about the "main reason" for taking each medication. These reasons were translated into the *International Classification of Diseases, 10th Edition, Clinical Modification* (*ICD-10*-CM) categories (https://www.icd10data.com/ICD10CM/Codes) by the National Center for Health Statistics using explicit guidelines. Analyses were restricted to respondents who reported taking antidepressants for MDD coded as "major depressive disorder, single episode, unspecified" (F32.9) and "major depressive disorder, recurrent, unspecified" (F33.9). The details of the coding strategy are available elsewhere (https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/RXQ_RX_J.htm).

Remission was ascertained by the 9-item Patient Health Questionnaire (PHQ-9),[35] a commonly used measure that assesses the frequency of 9 *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) symptom criteria for major depressive episodes in the past 2 weeks. Frequency of each symptom ranges from "not at all" (0) to "nearly every day" (3). Total scores, computed by summing the symptom scores, can range from 0 to 27. PHQ-9 scores of < 5 indicate remission of depression.[35,36] In sensitivity analyses, an alternative cutoff PHQ-9 score of < 10 was also assessed. The validity of PHQ-9 ratings has been established in past research.[35,37]

Following questions about specific depressive symptoms, respondents who reported any symptoms were asked, "How difficult have these problems made it for you to do your work, take care of things at home, or get along with people?" Responses included "not at all difficult" (0), "somewhat difficult" (1), "very difficult" (2), and "extremely difficult" (3).

Antidepressant augmentation strategies were limited to use of another antidepressant from a different class, an atypical antipsychotic medication, thyroid hormone, lithium, lamotrigine, modafinil, lisdexamfetamine, and pramipexole.[9,24–26]

MAOIs (with the exception of transdermal selegiline) and trazodone were not considered as augmentation treatments because of limited evidence supporting their efficacy for this purpose and because trazodone is commonly prescribed as a sleep aid medication.[38]

Atypical antipsychotic medications included aripiprazole, asenapine, brexpiprazole, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

No specific *ICD-10-CM* categories exist for augmentation treatment. Therefore, we developed an algorithm to identify uses of these medications that are more likely to be for antidepressant augmentation than other clinical indications (Supplementary Appendix 1).

Other variables in the analyses included sex, age, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), income compared to Federal Poverty Level (FPL), education, common chronic medical conditions, use of health services, any mental health visits in the past year, and health insurance (private, Medicaid, Medicare, other types of health insurance). Chronic health conditions included arthritis, lung disease (asthma, chronic obstructive pulmonary disease, and bronchitis), diabetes mellitus, hypertension, and heart disease (coronary heart disease or history of heart attacks). Health services were assessed as the number of times respondents reported seeing a doctor or other health care professional during the past 12 months.

Table 1. Characteristics of 869 Respondents Taking Antidepressant Medication for Depression, 2013–2018[a]

Characteristic	n	%[b]
Sex		
Women	594	70.9
Men	275	29.1
Age, y		
18–29	68	7.6
30–39	96	12.7
40–49	143	17.0
50–64	317	36.4
≥65	245	26.3
Race/ethnicity		
Non-Hispanic White	534	81.8
Non-Hispanic Black	120	5.9
Hispanic	141	6.8
Other	74	5.5
Income, compared to FPL (%)		
<100	184	15.0
100–199	250	22.2
≥200	365	62.7
Education		
Less than high school	146	10.5
High school/GED	194	20.6
Some college or more	528	68.9
Medical conditions		
Arthritis	478	52.6
Lung disease	317	34.8
Diabetes mellitus	208	18.8
Hypertension	487	50.1
Heart disease	102	9.0
No. of health care visits in the past year		
0–3	290	36.7
4–9	332	35.5
≥10	246	27.8
Any mental health provider contacts in the past year		
No	519	62.9
Yes	348	37.1
Health insurance		
Private insurance	396	58.0
Medicaid	186	13.5
Medicare	330	34.0
Other insurance	215	27.0
Type of antidepressant		
SSRI	604	67.7
Non-SSRI	265	32.3
Length of antidepressant medication treatment		
>3 mo–1 y	177	18.2
>1 y–2 y	128	11.8
>2 y	556	70.0

[a]Data from 2013 to 2018 National Health and Nutrition Examination Survey.
[b]Percentages are weighted.
Abbreviations: FPL = Federal Poverty Level, GED = General Educational Development, SSRI = selective serotonin reuptake inhibitor.

Statistical Analyses

Analyses were conducted in 3 stages. First, the prevalence of remission among respondents using antidepressants for depression was assessed. The prevalence of different PHQ-9 symptoms and the level of difficulty caused by symptoms

were also compared among respondents whose depression had and had not remitted.

Second, factors associated with non-remission were assessed using multivariable logistic regression models. Models were adjusted for sociodemographic characteristics, chronic medical conditions, use of health services, health insurance, length of antidepressant treatment, and type of antidepressants (SSRI vs other types of antidepressants).

Third, the prevalence of antidepressant augmentation and factors associated with augmentation among respondents whose depression had not remitted were examined using multivariable logistic regression models adjusting for the same variables noted above.

In sensitivity analyses, correlates were assessed for remission defined as PHQ-9 score < 10 and for augmentation treatment among those not remitted based on this definition.

Svy routines of STATA 16 software (StataCorp, 2020; College Station, Texas) were used for analyses to account for the complex survey design of NHANES. All percentages reported are weighted. The weighted percentages may not match the actual numbers of respondents. A $P < .05$ (2-tailed) significance level was used.

RESULTS

Table 1 presents characteristics of respondents using antidepressants for depression. A majority were female, aged 50 years or older, non-Hispanic White, with family income ≥ 200% FPL, college education, private insurance, and at least one medical condition. SSRIs were the most common class of antidepressants used for depression. More than two-thirds had been using the same medication for more than 2 years (Table 1).

Remission

Among the 869 respondents using antidepressants for depression for at least 3 months, 43.5% (n = 329) were in remission; 56.5% (n = 540) experienced residual symptoms (PHQ-9 score ≥ 5). The most frequent residual symptoms were "feeling tired or having little energy" and "trouble falling or staying asleep or sleeping too much" (Figure 1). A total of 41.5% (n = 227) of non-remitted respondents reported feeling tired or having little energy and 36.7% (n = 197) reported sleep problems nearly every day in the past 2 weeks (data not shown).

Compared to respondents not in remission, those in remission reported much less difficulty in work, taking care of things at home, and getting along with people (mean difficulty score = 1.01 vs 0.18, regression coefficient = −0.84, SE = 0.05, $P < .001$). While 22.7% of respondents not in remission reported that the depression had made it very or extremely difficult to complete these tasks, less than 0.01% of those whose depression had remitted reported this level of difficulty.

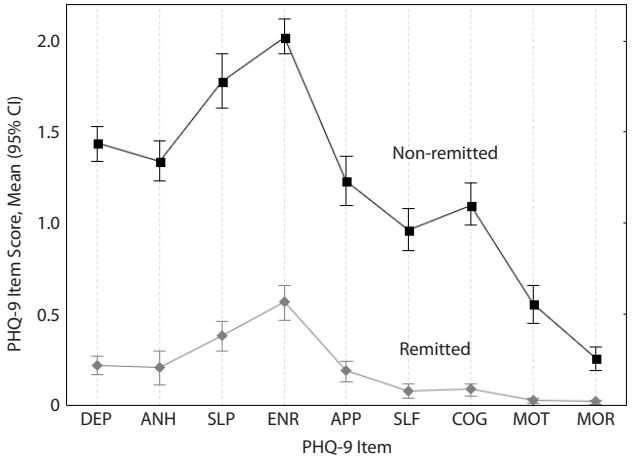
In adjusted analyses, adults in the ≥ 65 years age group had higher odds of remitting than respondents aged 18–29 years (51.3% vs 41.6%; adjusted odds ratio [AOR] = 4.04; 95% CI, = 1.04–15.76, $P = .044$), as did respondents with family incomes in the ≥ 200% FPL compared to those with family income < 100% FPL (50.2% vs 20.7%; AOR = 1.99; 95% CI, 1.00–3.95; $P = .049$) (Table 2).

Among physical health comorbidities, only heart disease was significantly associated with lower adjusted odds of remission compared to no heart disease (26.1% vs 45.1%; AOR = 0.35; 95% CI; 0.18%–0.67%; $P = .002$). A larger number of health care visits in the past year was also associated with lower odds of remission compared to 0–3 visits (38.1% vs 59.4%; AOR = 0.50; 95% CI, 0.27–0.92; $P = .029$ for 4–9 visits; 29.4% vs 59.4%; AOR = 0.45; 95% CI, 0.24–0.85; $P = .015$ for ≥ 10 visits), as was any mental health contact in the past year compared to no contact (31.5% vs 50.6%; AOR = 0.45; 95% CI, 0.29–0.69; $P = .001$) (Table 2).

Of different types of insurance, private insurance was significantly associated with higher odds of remission compared to not having this coverage (51.7% vs 32.2%; AOR = 1.72; 95% CI, 1.01–2.95; $P = .047$) and Medicare with lower odds of remission (40.8% vs 44.9%; AOR = 0.47; 95% CI, 0.24–0.93; $P = .030$). The length of antidepressant treatment was not significantly associated with remission (Table 2).

In sensitivity analyses, 28.3% (n = 296) of the 869 respondents scored ≥ 10 on PHQ-9 and 71.8% (n = 573) scored < 10. The results of multivariable analyses for

Figure 1. Mean PHQ-9 Symptoms Among 869 Respondents With Remitted or Non-Remitted Depression[a]



[a]Individuals were asked the following question: "Over the last 2 weeks, how often have you been bothered by the following problems?" The 9 queried problems included feeling down, depressed, or hopeless (DEP); little interest or pleasure in doing things (ANH); trouble falling or staying asleep or sleeping too much (SLP); feeling tired or having little energy (ENR); poor appetite or overeating (APP); feeling bad about yourself, or that you are a failure or have let yourself or your family down (SLF); trouble concentrating on things, such as reading the newspaper or watching TV (COG); moving or speaking so slowly that other people could have noticed, or the opposite—being so fidgety or restless that you have been moving around a lot more than usual (MOT); thoughts that you would be better off dead or of hurting yourself in some way (MOR). Response options were scored as "not at all" (0), "several days" (1), "more than half the days" (2), and "nearly every day" (3).
Abbreviation: PHQ-9 = 9-item Patient Health Questionnaire.

Table 2. Depression Remission in 869 Respondents Taking Antidepressant Medication for Depression, 2013–2018[a]

Characteristic	Remitted (n = 329) Row %[c]	Non-Remitted (n = 540) Row %[c]	Unadjusted Comparison (Non-Remitted, Reference) OR	95% CI	*P*	Adjusted Comparison[b] (Non-Remitted, Reference) AOR	95% CI	*P*
Sex								
Women	43.4	56.6	1.00	…		1.00	…	
Men	42.8	57.2	0.96	0.67–1.38	.830	1.23	0.79–1.92	.341
Age, y								
18–29	41.6	58.4	1.00	…		1.00	…	
30–39	34.3	65.7	0.73	0.27–2.01	.536	0.76	0.25–2.29	.621
40–49	45.4	54.6	1.17	0.55–2.47	.684	1.20	0.46–3.15	.704
50–64	40.6	59.4	0.96	0.43–2.14	.916	1.27	0.46–3.48	.636
≥ 65	51.3	48.7	1.48	0.65–3.39	.345	4.04	1.04–15.76	.044
Race/ethnicity								
Non-Hispanic White	45.5	54.5	1.00	…		1.00	…	
Non-Hispanic Black	32.1	67.9	0.57	0.35–0.92	.024	0.99	0.51–1.91	.970
Hispanic	28.3	71.7	0.47	0.31–0.71	.001	0.60	0.30–1.21	.151
Other	44.7	55.3	0.97	0.43–2.19	.938	1.27	0.55–2.93	.566
Income, compared to Federal Poverty Level (%)								
< 100	20.7	79.3	1.00	…		1.00	…	
100–199	38.9	61.1	2.44	1.38–4.33	.003	1.68	0.88–3.20	.114
≥ 200	50.2	49.8	3.87	2.47–6.09	< .001	1.99	1.00–3.95	.049
Education								
Less than high school	28.6	71.4	1.00	…		1.00	…	
High school/GED	44.4	55.6	1.99	0.99–3.98	.052	1.44	0.56–3.71	.442
Some college or more	45.5	54.5	2.08	1.25–3.47	.006	1.65	0.83–3.30	.149
Medical conditions[d]								
Arthritis	36.9	63.1	0.57	0.40–0.80	.002	0.70	0.42–1.15	.154
Lung disease	39.5	60.5	0.78	0.47–1.30	.331	1.17	0.66–2.09	.575
Diabetes mellitus	34.1	65.9	0.62	0.39–0.96	.035	0.69	0.42–1.14	.145
Hypertension	41.1	58.9	0.82	0.55–1.22	.320	0.98	0.61–1.57	.939
Heart disease	26.1	73.9	0.43	0.24–0.78	.006	0.35	0.18–0.67	.002
No. of health care visits in the past year								
0–3	59.4	40.6	1.00	…		1.00	…	
4–9	38.1	61.9	0.42	0.25–0.70	.001	0.50	0.27–0.92	.029
≥ 10	29.4	70.6	0.28	0.17–0.48	< .001	0.45	0.24–0.85	.015
Any mental health provider contacts in the past year								
No	50.6	49.4	1.00	…		1.00	…	
Yes	31.5	68.5	0.45	0.29–0.69	.001	0.45	0.29–0.69	.001
Health insurance[e]								
Private insurance	51.7	48.3	2.25	1.55–3.28	< .001	1.72	1.01–2.95	.047
Medicaid	25.6	74.4	0.40	0.25–0.64	< .001	1.53	0.77–3.05	.223
Medicare	40.8	59.2	0.84	0.60–1.19	.328	0.47	0.24–0.93	.030
Other insurance	43.9	56.1	1.02	0.63–1.66	.932	1.20	0.66–2.16	.545
Type of antidepressant								
SSRI	46.2	53.8	1.00	…		1.00	…	
Non-SSRI	37.9	62.1	0.71	0.45–1.13	.146	0.71	0.44–1.16	.164
Length of antidepressant medication treatment								
> 3 mo–1 y	39.1	60.9	1.00	…		1.00	…	
> 1 y–2 y	42.2	57.8	1.14	0.59–2.19	.975	1.46	0.71–2.97	.295
> 2 y	44.9	55.1	1.27	0.80–2.03	.307	0.95	0.51–1.69	.871

[a]Data from 2013 to 2018 National Health and Nutrition Examination Survey.
[b]Model adjusted for all variables in the table.
[c]All percentages are weighted.
[d]Respondents with each condition were compared to all other respondents.
[e]Respondents with each type of health insurance were compared to all other respondents.
Abbreviations: AOR = adjusted odds ratio, GED = General Educational Development, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

correlates of a PHQ-9 score < 10 were similar to those of the main analyses (Supplementary Appendix 2). Adults in the ≥ 65 years age range had higher odds compared to the 18–29 years age group, as did those with college education compared to less than high school education and those with private insurance compared to those without such insurance. In contrast, respondents with heart disease had lower odds of scoring in this range compared to those without heart disease, as did respondents with more health care visits, and those with mental health care provider contacts compared to those without such contacts.

Antidepressant Augmentation

A total of 28.1% (n = 144) of the 540 respondents whose depression had not remitted were using augmentation medication. A list of various augmentation regimens is provided in Supplementary Appendix 3. The most common augmentation treatments were antidepressants from a different class (n = 104, 71.7% of respondents using augmentation), followed by atypical antipsychotics (n = 38, 25.7%).

In adjusted analyses, adults aged 40–49 years had significantly higher odds of using augmentation than those aged 18–29 years (32.5% vs 16.5%; AOR = 3.34; 95%

Table 3. Augmentation Treatment Among 540 Respondents Taking Antidepressant Medications for Depression Whose Depression Had Not Remitted at the Time of the Interview, 2013–2018[a]

Characteristic	Receiving Augmentation (n = 144), Row %[c]	Not Receiving Augmentation (n = 396), Row %[c]	Unadjusted Comparisons (Not Receiving Augmentation, Reference) OR	95% CI	*P*	Adjusted Comparison[b] (Not Receiving Augmentation, Reference) AOR	95% CI	*P*
Sex								
Women	27.5	72.5	1.00	…		1.00	…	
Men	29.7	70.3	1.11	0.60–2.06	.728	0.95	0.46–1.95	.878
Age, y								
18–29	16.5	83.5	1.00	…		1.00	…	
30–39	33.9	66.1	2.59	0.86–7.83	.090	3.21	0.97–10.68	.057
40–49	32.5	67.5	2.43	0.86–6.86	.092	3.34	1.01–10.97	.048
50–64	35.3	64.7	2.76	1.07–7.06	.035	2.80	0.92–8.51	.069
≥ 65	13.1	86.9	0.76	0.25–2.30	.622	0.79	0.17–3.71	.765
Race/ethnicity								
Non-Hispanic White	29.8	70.2	1.00	…		1.00	…	
Non-Hispanic Black	20.9	79.1	0.62	0.30–1.27	.188	0.51	0.19–1.37	.174
Hispanic	22.6	77.4	0.69	0.34–1.40	.294	0.72	0.34–1.52	.379
Other	21.8	78.2	0.66	0.29–1.49	.306	0.21	0.07–0.65	.008
Income, compared to Federal Poverty Level (%)								
< 100	31.4	68.6	1.00	…		1.00	…	
100–199	21.9	78.1	0.61	0.29–1.27	.179	0.79	0.35–1.80	.573
≥ 200	30.7	69.3	0.97	0.52–1.79	.913	1.56	0.70–3.46	.271
Education								
Less than high school	18.2	81.8	1.00	…		1.00	…	
High school/GED	36.9	63.1	2.62	1.17–5.90	.021	3.25	1.22–8.63	.019
Some college or more	27.5	72.5	1.70	0.81–3.59	.158	1.38	0.55–3.46	.484
Medical conditions[d]								
Arthritis	30.4	69.6	1.32	0.78–2.21	.290	1.33	0.73–2.42	.352
Lung disease	34.5	65.5	1.63	1.09–2.43	.018	1.43	0.83–2.48	.191
Diabetes mellitus	23.8	76.2	0.75	0.41–1.38	.348	0.77	0.38–1.59	.474
Hypertension	27.3	72.7	0.91	0.56–1.48	.711	1.24	0.71–2.15	.445
Heart disease	33.7	66.3	1.34	0.78–2.30	.280	1.52	0.68–3.40	.306
No. of health care visits in the past year								
0–3	23.6	76.4	1.00	…		1.00	…	
4–9	25.9	74.1	1.13	0.63–2.05	.668	1.14	0.58–2.23	.694
≥ 10	34.1	65.9	1.68	0.86–3.28	.129	1.79	0.83–3.88	.137
Any mental health provider contacts in the past year								
No	21.7	78.3	1.00	…		1.00	…	
Yes	36.0	64.0	2.02	1.32–3.11	.002	2.72	1.56–4.76	.001
Health insurance[e]								
Private insurance	28.2	71.8	1.01	0.60–1.70	.977	1.09	0.50–2.40	.821
Medicaid	34.5	65.5	1.45	0.84–2.49	.177	1.13	0.52–2.47	.756
Medicare	22.9	77.1	0.66	0.38–1.17	.154	0.82	0.38–1.74	.592
Other insurance	28.4	71.6	1.02	0.53–1.96	.945	0.86	0.45–1.64	.640
Type of antidepressant								
SSRI	28.8	71.2	1.00	…		1.00	…	
Non-SSRI	26.9	73.1	0.91	0.35–2.36	.840	0.92	0.51–1.64	.773
Length of antidepressant medication treatment								
> 3 mo–1 y	22.5	77.5	1.00	…		1.00	…	
> 1 y–2 y	20.8	79.2	0.91	0.35–2.36	.840	0.95	0.36–2.51	.914
> 2 y	31.0	69.0	1.55	0.78–3.07	.203	1.56	0.72–3.38	.249

[a]Data from 2013 to 2018 National Health and Nutrition Examination Survey.
[b]Model adjusted for all variables in the table.
[c]All percentages are weighted.
[d]Respondents with each condition were compared to all other respondents.
[e]Respondents with each type of health insurance were compared to all other respondents.
Abbreviations: AOR = adjusted odds ratio, GED = General Educational Development, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

CI, 1.01–10.97; *P* = .048), as did respondents with high school or GED education compared to those with less education (36.9% vs 18.2%; AOR = 3.25; 95% CI, 1.22–8.63; *P* = .019) and respondents who had mental health provider contact compared to those who did not (36.0% vs 21.7%; AOR = 2.72; 95% CI, 1.56–4.76; *P* = .001) (Table 3). In contrast, adults from the Other racial/ethnic group had lower odds of using augmentation treatment compared to non-Hispanic White respondents (21.8% vs 29.8%; AOR = 0.21; 95% CI, 0.07–0.65; *P* = .008).

In sensitivity analyses, 32.6% of respondents who scored ≥ 10 on PHQ-9 reported using augmentation treatment. The results of multivariate analyses of augmentation treatment among these respondents were similar to results of the main analyses (Supplementary Appendix 4). Adults aged 30–39 years had higher odds of using augmentation treatment compared to those aged 18–29 years, as did those with income ≥ 200 FPL compared to those with FPL < 100, respondents with high school/GED compared to respondents with less education, respondents

with heart disease compared to those without, and those who had mental health provider contacts compared to those without such contacts. In contrast, respondents from the Other racial/ethnic groups had lower odds of using augmentation treatment compared to non-Hispanic White respondents.

DISCUSSION

This study presents a broad overview of the prevalence and correlates of depression non-remission and antidepressant augmentation treatment use among US adults. There were two main findings. First, most respondents currently on antidepressant treatment for depression for 3 months or longer experienced residual depressive symptoms and were not in remission based on a PHQ-9 cutoff score ≥ 5. They also experienced difficulties in daily living associated with these symptoms. These findings in a nationally representative sample are consistent with results from past clinical studies.[1–5,39] In the STAR*D study,[4] for example, most patients did not achieve remission by the end of a 14-week citalopram trial.

Persisting depressive symptoms put patients at increased risk of relapse and are associated with other adverse outcomes.[6–8] A lower prevalence of remission among adults with lower income and heart disease highlights the importance of socioeconomic and health factors in depression remission. By contrast, lower remission rates among respondents with more health care contacts and with any mental health contact likely represent greater service use and greater likelihood of receiving care from mental health providers in those with more severe and persistent depression.[40]

In previous clinical and general population studies,[2,5,41,42] poor physical health and lower socioeconomic status have been consistent predictors of poor response to treatment and course of depression, highlighting the role of social and health adversities in the course of depression. The association between heart disease and depression non-remission underscores the need for coordinated mental and physical health care. Collaborative care interventions have been shown to improve care and outcomes in patients with depression[43] and provide opportunities to address both physical and mental health needs. The greater likelihood of augmentation treatment in respondents who had contact with mental health providers also points to potential benefits of collaborative care.[43]

A second finding was that augmentation was received by only a small fraction of antidepressant-treated adults with non-remitted depression. Low use of proven augmentation strategies, such as lithium, is especially noteworthy and consistent with past research.[44,45] Augmentation strategies, along with optimizing the antidepressant dose or medication switching, can help increase the likelihood of remission.[46] In the STAR*D program,[2,47] most patients who completed the different stages of treatment finally achieved remission, sometimes after a series of medication switches and augmentation attempts. In contrast, most respondents taking antidepressant medications in the present study had not achieved remission, even though a majority stayed on the same medication for more than 2 years. This finding suggests missed opportunities to optimize medication regimens to improve chances of full remission.

Few past studies have examined the prevalence of depression augmentation treatment in the general population.[27,40] A European study of patients hospitalized for depression[27] reported that over 84% of these patients had continued to receive the same medication for many weeks. Only about 14% received augmentation treatment. Another study based on the US National Ambulatory Medical Care Survey[40] reported that prescription of atypical antipsychotic medications among patients with non-psychotic depression increased from 4.6% in 1999–2000 to 12.5% in 2009–2010. Other forms of augmentation treatment were not assessed. Furthermore, the remission status of patients could not be assessed in either study.

Non-recognition of residual symptoms of depression may contribute to low uptake of antidepressant augmentation. Monitoring treatment response with validated measures and adjusting treatment accordingly—generally known as "measurement-based care"—can potentially improve recognition of residual symptoms and their management.[36,48]

In interpreting these results, several limitations should be considered. First, the NHANES did not capture symptom ratings at the start of antidepressant treatment. Second, other strategies such as antidepressant dose change or medication switching, as well as possible previous augmentation attempts, could not be assessed because NHANES does not collect dose information or history of previous medication use. Also, information on psychotherapy was not collected. However, a sizeable proportion of the sample, especially those with non-remitted depression, had contact with mental health providers. Third, the most common residual depressive symptoms were fatigue and sleep problems, which are difficult to distinguish from similar complaints in physical conditions. Fourth, many patients who start antidepressants remit and stop the medication shortly thereafter.[49] These patients would be undercounted in a cross-sectional sample of patients currently on antidepressant treatment, whereas long-term users of medications would be overrepresented.[50] Fifth, a causal relationship between physical health conditions and non-remission of depression cannot be established in this cross-sectional study. The relationship between physical health conditions and depression is thought to be bidirectional.[51–55] Finally, depression diagnoses were based on self-reported symptoms for which respondents were prescribed antidepressants rather than research diagnoses.

In the context of these limitations, this study offers an overview of the prevalence of non-remission and medication augmentation treatment in individuals receiving antidepressant treatment for depression in the US. The high prevalence of residual symptoms in individuals who had stayed on the same antidepressant medications for extended periods is concerning and calls for greater attention to evidence-based strategies to improve the pharmacologic management of adult depression.

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Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, fluvoxamine, milnacipran, levomilnacipran, clomipramine, agomelatine, asenapine, lurasidone, olanzapine, paliperidone, risperidone, ziprasidone, thyroid hormone, lithium, lamotrigine, modafinil, lisdexamfetamine, and pramipexole are not approved by the US Food and Drug Administration for the treatment of major depressive disorder.

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Supplementary material: Available at PSYCHIATRIST.COM

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1. **Among practice guidelines for the treatment of major depressive disorder, there appears to be a consensus that:**
   a. Treatment augmentation is the preferred strategy for patients who have partially responded to treatment, but medication switching is preferred for those who have not responded at all.
   b. Treatment augmentation is the preferred strategy for patients who have not responded to treatment at all, but medication switching is preferred for those who have responded only partially.
   c. Treatment augmentation is the preferred strategy if the patient has either responded to treatment only partially or not responded at all.
   d. Medication switching is the preferred strategy if the patient has either responded to treatment only partially or not responded at all.
2. **Which three medication augmentation strategies were recommended by the American Psychiatric Association's 2010 *Practice Guideline for the Treatment of Patients With Major Depressive Disorder* "with moderate clinical confidence"?**
   a. Lamotrigine, lithium, and thyroid hormone
   b. Atypical antipsychotic medications, modafinil, and thyroid hormone
   c. Atypical antipsychotic medications, lithium, and thyroid hormone
   d. Atypical antipsychotic medications, lithium, and pramipexole
3. **Keisha is a 45-year-old woman who has been treated with an antidepressant for depression for 3 months. Although she has had some improvement in mood, she continues to experience poor sleep, low energy, diminished interest in daily activities, feelings of hopelessness, and difficulty at work and in completing daily chores. To address Keisha's poor response, what would be the first step, according to most guidelines?**
   a. Augment the current medication regimen with a second antidepressant or another medication.
   b. Switch to another antidepressant medication from a different class.
   c. Refer her for psychotherapy while continuing the current medication regimen.
   d. Review her diagnosis, assess treatment adherence, and optimize the antidepressant dose.

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Supplementary Material

Article Title: Remission and Treatment Augmentation of Depression in the United States

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Appendix 1:

Algorithm for identifying medication use for antidepressant augmentation in the treatment of major depressive disorder.

If the respondent reported using an atypical antipsychotic medication, lithium, lamotrigine, modafinil, pramipexole, lisdexamfetamine or thyroid hormone for major depressive disorder (F32.9, F33.9), “unspecified mood disorder” (F39), or complaints related to depressive symptoms (e.g., insomnia, G47.0), their use was categorized as augmentation. Additionally, atypical antipsychotic medications were considered as augmentations if not used for schizophrenia (F20), other psychotic disorders (e.g., F29), bipolar disorder (F31.9), anxiety disorders (F41.0, F41.9), and other psychiatric disorders such as attention-deficit/hyperactivity disorder (F90), post-traumatic stress disorder (F43.1) and pervasive developmental disorder (F84). Lithium and lamotrigine used for bipolar disorder (F31.9); lamotrigine used for epilepsy (G40); modafinil used for narcolepsy (47.4) and sleep apnea (47.3); pramipexole for Parkinson disease (G20, G21), restless leg syndrome (G25.81) and essential tremor (G25.0); and lisdexamfetamine used for the treatment of attention deficit hyperactivity disorder (F90) were not considered antidepressant augmentation treatment. Thyroid hormone use was not considered as augmentation if the reason for use was related to hypothyroidism (E03.9), another thyroid disease (E06, E07.9, E04, E05, C73), or a related physical health complaint, such as edema (R60.9).

Appendix 2: Adjusted analyses for the alternative definition of depression remission (PHQ-9 score<10) in 869 respondents taking antidepressant medication for depression, 2013-2018.[a]

	AOR[b]	95% CI[c]	*p*
Sex			
Women	1.00	--	
Men	1.31	0.78-2.20	.300
Age, years			
18-29	1.00	--	
30-39	1.10	0.35-3.46	.861
40-49	0.96	0.32-2.88	.945
50-64	1.38	0.57-3.35	.473
≥65	3.03	1.02-9.00	.046
Race/ethnicity			
Non-Hispanic White	1.00	--	
Non-Hispanic Black	1.17	0.57-2.40	.670
Hispanic	0.85	0.39-1.87	.687
Other	0.66	0.29-1.51	.320
Income, compared to Federal Poverty Level (%)			
<100	1.00	--	
100-199	0.93	0.50-1.75	.820
≥200	1.12	0.61-2.06	.714
Education			
Less than high school	1.00	--	
High school/GED	1.62	0.80-3.29	.174
Some college or more	3.07	1.53-6.13	.002
Medical conditions[d]			
Arthritis	0.68	0.40-1.14	.141
Lung disease	0.76	0.49-1.17	.205
Diabetes mellitus	0.61	0.33-1.12	.110
Hypertension	0.83	0.50-1.38	.454
Heart disease	0.40	0.19-0.87	.021
Number of healthcare visits in the past year			
0-3	1.00	--	
4-9	0.45	0.27-0.77	.004
≥10	0.39	0.22-0.72	.003
Any mental health provider contacts in the past year			
No	1.00	--	
Yes	0.27	0.16-0.44	<.001
Health insurance[e]			
Private insurance	1.78	1.08-2.94	.025
Medicaid	1.78	0.94-3.36	.075
Medicare	0.66	0.39-1.12	.122
Other insurance	1.25	0.77-2.02	.361
Type of antidepressant			
SSRI	1.00	--	
Non-SSRI	0.77	0.49-1.21	.251
Length of antidepressant medication treatment			
>3 months-1 year	1.00	--	

>1 year-2 years	1.03	0.49-2.15	.940
>2 years	0.85	0.53-1.38	.512

[a.] Data from 2013-2018 National Health and Nutrition Examination Survey. Model adjusted for all variables in the table.
[b.] AOR stands for the adjusted odds ratio.
[c.] CI stands for the confidence interval.
[d.] Respondents with each condition were compared to all other respondents.
[e.] Respondents with each type of health insurance were compared to all other respondents.

Appendix 3: Augmentation regimens in 144 respondents taking antidepressant medications for depression whose depression had not remitted at the time of the interview, 2013-2018.[a]

Augmentation treatment	N	%[b]
Antidepressants of different class	104	71.7
SSRI-Bupropion	47	31.8
SSRI-Tricyclic	17	13.2
SNRI-Bupropion	14	9.7
Tricyclic-Bupropion	14	9.7
SSRI-SNRI	11	6.4
SNRI-Tricyclic	10	5.7
SSRI-Tetracyclic	6	4.5
SNRI-Tetracyclic	5	2.1
Tetracyclic-Bupropion	3	1.1
Tricyclic-Tetracyclic	2	2.7
SNRI-Other antidepressants	0	0.0
Tricyclic-Other antidepressants	0	0.0
Tetracyclic-Other antidepressants	0	0.0
Bupropion-Other antidepressants	0	0.0
SSRI-Other antidepressants	0	0.0
Atypical antipsychotic medications		
Any atypical antipsychotics	38	25.7
Aripiprazole	14	8.6
Quetiapine	6	4.0
Risperidone	4	1.0
Lamotrigine	11	10.7
Thyroid hormone	4	0.9
Modafinil	2	0.9
Lisdexamfetamine	2	2.4
Pramipexole	0	0.0
Lithium	0	0.0

a. Data from 2013-2018 National Health and Nutrition Examination Survey.
b. Percentages are weighted and add up to more than 100% because some respondents used more than 1 augmentation treatment.

Appendix 4: Adjusted analyses for augmentation treatment among respondents taking antidepressant medications for depression whose depression had not remitted based on the alternative definition of remission (PHQ-9 score<10) at the time of the interview, 2013-2018.[a]

	AOR[b]	95% CI[c]	*p*
Sex			
Women	1.00	--	
Men	0.74	0.28-1.98	.541
Age, years			
18-29	1.00	--	
30-39	7.88	1.36-45.83	.023
40-49	5.35	0.90-31.88	.065
50-64	3.15	0.73-13.57	.121
≥65	1.39	0.28-6.80	.678
Race/ethnicity			
Non-Hispanic White	1.00	--	
Non-Hispanic Black	0.44	0.12-1.63	.216
Hispanic	0.53	0.13-2.11	.358
Other	0.05	0.01-0.27	.001
Income, compared to Federal Poverty Level (%)			
<100	1.00	--	
100-199	0.79	0.19-3.30	.739
≥200	3.32	1.13-9.79	.030
Education			
Less than high school	1.00	1.00	
High school/GED	4.54	1.05-19.66	.044
Some college or more	1.20	0.27-5.32	.802
Medical conditions[d]			
Arthritis	2.16	0.72-6.41	.163
Lung disease	1.46	0.63-3.39	.367
Diabetes mellitus	1.13	0.47-2.74	.779
Hypertension	1.59	0.67-3.78	.288
Heart disease	2.27	1.03-5.01	.043
Number of health care visits in the past year			
0-3	1.00	--	
4-9	1.18	0.25-5.56	.830
≥10	0.67	0.14-3.22	.610
Any mental health provider contacts in the past year			
No	1.00	--	
Yes	8.91	4.08-19.47	<.001
Health insurance[e]			
Private insurance	2.51	0.88-7.19	.085
Medicaid	1.78	0.61-5.21	.285
Medicare	0.78	0.24-2.54	.673
Other insurance	1.06	0.38-2.94	.913
Type of antidepressant			
SSRI	1.00	--	
Non-SSRI	0.48	0.20-1.16	.101
Length of antidepressant medication treatment			
>3 months-1 year	1.00	--	

>1 year-2 years	0.71	0.20-2.58	.597
>2 years	0.72	0.27-1.94	.507

[a.] Data from 2013-2018 National Health and Nutrition Examination Survey. Model adjusted for all variables in the table.
[b.] AOR stands for the adjusted odds ratio.
[c.] CI stands for the confidence interval.
[d.] Respondents with each condition were compared to all other respondents.
[e.] Respondents with each type of health insurance were compared to all other respondents.