Use of Non-Psychiatric Medications With Potential Depressive Symptom Side Effects and Level of Depressive Symptoms in Major Depressive Disorder

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ABSTRACT

Objective: To determine whether use of medications with potential depressive symptom side effects is associated with a higher level of depressive symptoms in adults with antidepressant-treated major depressive disorder (MDD).

Methods: The study was based on the 2013–2014, 2015–2016, and 2017–2018 National Health and Nutrition Examination Survey (NHANES)—a nationally representative cross-sectional survey of the US general population. In 885 adult participants from these NHANES cycles who reported receiving antidepressants for treatment of *International Classification of Diseases, Tenth Revision, Clinical Modification* MDD, the association between the number of medications with potential depressive symptom side effects and the level of depressive symptoms was assessed.

Results: A majority (66.7%, n = 618) of the participants with antidepressant-treated MDD used at least 1 non-psychiatric medication with potential depressive symptom side effects, and 37.3% (n = 370) used more than 1 such medication. The number of medications with depressive symptom side effects was significantly associated with lower odds of no to minimal depressive symptoms, defined as a Patient Health Questionnaire-9 (PHQ-9) score < 5 (adjusted odds ratio [AOR] = 0.75, 95% confidence interval [CI] = 0.64–0.87, $P < .001$), and higher odds of moderate to severe symptoms, defined as a PHQ-9 score ≥ 10 (AOR = 1.14, 95% CI = 1.004–1.29, $P = .044$). No such associations were found for medications without potential depressive symptom side effects.

Conclusions: Individuals treated for MDD frequently use non-psychiatric medications for comorbid medical conditions that are associated with an increased risk of depressive symptoms. In evaluating the response to antidepressant medication treatment, side effects of concomitantly used medications should be considered.

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Many individuals treated for major depressive disorder (MDD) continue to experience depressive symptoms after weeks of antidepressant treatment.[1–4] In the National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression trial, only 28% of participants achieved full symptom remission after up to 14 weeks of treatment with citalopram.[4] Because not achieving remission is associated with an increased risk of recurrence and worse outcomes,[5] full symptom remission is a widely accepted treatment goal in MDD treatment,[3,6] although in some cases it is difficult to achieve.[7]

Past research has identified several risk factors for persistent depressive symptoms in MDD, including social adversity, psychiatric comorbidities, substance use, and medical comorbidities.[1,8–10] Medical comorbidities are common in MDD,[11] and while some research suggests a comparable response to antidepressants in patients with and without medical comorbidities,[12] other research has found a less favorable treatment response in patients with medical comorbidities.[13,14]

The mechanisms linking poorer treatment response in MDD with comorbid medical conditions are not known. However, inflammation and childhood adversity, which are associated with several medical conditions and linked to worse treatment outcomes in depression, are thought to play a role.[15–17]

Patients with comorbid MDD and medical conditions often also use multiple non-psychiatric medications, many of which are associated with an increased risk of depressive symptoms.[18] An analysis of National Health and Nutrition Examination Survey (NHANES) data reported that the use of these medications increased from 35.0% in 2005–2006 to 38.4% in 2013–2014.[19] During this period, the use of ≥ 3 medications with potential depressive symptom side effects increased from 6.9% to 9.5%. This increase was associated with an increased prevalence of concurrent depression.[19] However, that study did not examine the association of the use of these medications with depressive symptoms in MDD.

Some studies have documented worsening of depressive symptoms in patients with MDD after exposure to medications with potential depressive symptom side effects (PDSS).[20,21] However, these studies were limited to clinical samples and focused on specific medications. The population-level association of a broad range of medications with PDSS and actual depressive symptoms in MDD has not been systematically examined.

In the present study, we use NHANES data to examine the association of taking medications with PDSS with the level of depressive symptoms among individuals treated with

Clinical Points

- Many patients with major depressive disorder treated in usual care settings concomitantly use non-psychiatric medications with potential depressive symptom side effects. The effect of using these medications on symptomatic recovery of depression is not well understood.
- In evaluating the reasons for inadequate symptomatic response to treatment of major depressive disorder, concomitantly used non-psychiatric medications with potential depressive symptom side effects should be considered.

antidepressants for MDD. This paper extends our earlier report, which found that only 43.5% of currently treated adults with MDD had minimal or no depressive symptoms when assessed.[9] Better understanding of the association of prescription medications with PDSS and depressive symptoms in MDD may inform treatment planning, management, and possibly prevention of treatment-resistant depression in clinical practice.

METHODS

Sample

Data were drawn from the NHANES 2013–2014, 2015–2016, and 2017–2018. NHANES uses a stratified complex multistage probability design to survey biennially the US general population.[22] Completed interviews were obtained from 17,961 adults aged 18+ years in the 3 survey waves. NHANES investigators obtained informed consent from participants before the interviews. Response rates, defined as the proportion of 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 were deidentified, are publicly available, and were exempted from institutional ethical review. Further details on the study design and sample description are provided elsewhere.[23] The sample for this report was limited to 885 adults who reported using antidepressant medications for at least 6 weeks for depression and whose depressive symptoms could be ascertained, representing 7.0% of the adult US population.

Assessments

Medications were assessed using a computer-based medication log and coded using Lexicon Plus, Cerner Multum. Interviewers inspected medication packages to confirm self-reports for 87.7%–89.4% of medications across the survey cycles.

Following past research,[19] prescription medications with PDSS were identified as medications with "depression" or "depressive symptoms" listed as common or serious adverse effects using Micromedex (Truven Health Analytics). All other prescription medications were defined as without PDSS. The accuracy of Micromedex, which is primarily based on the US Food and Drug Administration labeled side effects, has been previously established.[24] Psychiatric medications (eg, antipsychotic medications, lithium, selected anticonvulsants, stimulants, sedative-hypnotics, and anxiolytic medications), medications for treatment of Alzheimer's disease, medications for treatment of opioid use disorders, and medications for treatment of alcohol use disorder (eg, naltrexone) were not included in the analyses because the target disorders are associated with depressive symptoms or symptoms that may be indistinguishable from depressive symptoms (eg, primary insomnia, cognitive difficulties). Moreover, some psychiatric medications, such as lithium or antipsychotic medications, are commonly used as an augmentation treatment for MDD.[9] These exclusions are admittedly overinclusive and conservative because some of the excluded medications are also prescribed for medical indications (eg, mood stabilizer anticonvulsants for treatment of seizure disorders or buprenorphine for pain). As such, our estimate of the prevalence of medications with PDSS is likely an underestimate.

Respondents were asked about the "main reason" for taking each medication. These reasons were translated into the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10*-CM) categories (https://www.icd10data.com/ICD10CM/Codes) by the National Center for Health Statistics. Analyses were restricted to respondents who reported taking antidepressants for MDD coded as "major depressive disorder, single episode, unspecified" (F32.9) or "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).

Antidepressant-treated MDD was defined as taking an antidepressant for MDD for at least 6 weeks to ensure that participants had received medication treatment for a sufficient duration to potentially achieve symptom response.[6] Antidepressants included serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other antidepressants.[9]

Depressive symptoms were ascertained by the Patient Health Questionnaire-9 (PHQ-9) which assesses the 9 *DSM-5* symptom criteria of MDD in the past 2 weeks.[25] Frequency of each symptom ranges from "not at all" (=0) to "nearly every day" (=3). Total scores can range from 0 to 27. PHQ-9 scores of <5 indicate no to minimal depressive symptoms (henceforth the "no/minimal" symptom group).[25] In addition, moderate to severe depressive symptoms were defined as a PHQ-9 score ≥10 ("moderate/severe" symptom group).[25] The validity of PHQ-9 has been established in past research.[25,26]

Other variables included self-reported sex, age, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), income compared to Federal Poverty Level (FPL), education, health insurance, and common chronic medical conditions ascertained by asking if "…a doctor or other health professional" had ever told the participants that they had the condition. Chronic conditions included

hypertension, arthritis, lung disease (asthma, chronic obstructive pulmonary disease, and bronchitis), diabetes mellitus, thyroid disease, cancer, heart disease (angina, coronary heart disease, or history of heart attacks), liver disease, stroke, and congestive heart failure.

There were minimal missing data on most variables. However, family income data were missing for 8% (n = 71 of 885) and were imputed using hot deck imputation.[27] In addition, questions about chronic medical conditions except for diabetes mellitus, hypertension, and asthma were only asked of participants aged ≥ 20 years. For this study, participants aged 18–19 years were rated as not having these chronic conditions.

Statistical Analyses

The associations of the number of medications with PDSS with no/minimal depressive symptoms and, separately, with moderate/severe symptoms were assessed using binary logistic regression models. The number of medications *without* PDSS was also included in both models as a "placebo test."[28] Assuming that the effect of medications on depressive symptoms is specific to medications with PDSS and is not the result of a greater number of comorbid conditions,[29] only the number of medications with PDSS is expected to be significantly associated with these symptoms after adjusting for chronic health conditions.

Following each regression model, marginal probabilities were computed for participants taking between 0 to 5 medications (> 5 medications were reported by few participants).

To further limit the potential confounding effects of medical comorbidities, the logistic regression models were repeated in more homogeneous groups of participants with MDD and arthritis and in those with MDD and hypertension, the 2 most common comorbid medical comorbidities.

Also in further analyses, bivariate associations of individual medications with PDSS and depressive symptoms were assessed. Next, the analyses of the association of the number of medications with PDSS and depressive symptoms were repeated after limiting medications to those found to be associated ($P < .05$) with depressive symptoms in bivariate analyses.

Svy routines of Stata 17 software (StataCorp, 2021, College Station, TX) were used for analyses to account for the complex NHANES survey design and non-response. All percentages reported are weighted and therefore may not correspond with the reported raw numbers. A $P < .05$ (2-tailed) significance level was used.

RESULTS

Antidepressant-Treated MDD and Depressive Symptoms

A majority of the 885 participants with antidepressant-treated MDD were female (70.7%, n = 603), aged 50 years or older (62.0%, n = 567), and non-Hispanic White (81.7%, n = 544), with a college education (69.4%, n = 544).

The characteristics of depression treatment in these participants have been previously reported.[9] Briefly, Selective serotonin reuptake inhibitors were the most common class of antidepressant medications used for treatment of MDD (67.9%, n = 614). Consistent with past research,[30] a majority had been on the same antidepressant medication for a long time (96.8%, n = 861, for > 3 months; 79.2%, n = 684, for > 1 year; and 67.8%, n = 556, for > 2 years). Nevertheless, only 43.0% (n = 334) scored in the no/minimal symptom range on PHQ-9, and 28.4% (n = 300) scored in the moderate/severe range.

A majority (85%, n = 769) used ≥ 1 medication for medical conditions; 618 (66.7%) used ≥ 1 medication with PDSS. Many used multiple medications with PDSS: 37.3% (n = 370) used ≥ 2, 21.6% (n = 216) used ≥ 3, 10.7% (n = 106) used ≥ 4, and 4.9% (n = 47) used ≥ 5. In turn, 687 (74.6%) used at least 1 medication without PDSS, and 52.0% (n = 520) used > 1.

Sociodemographic and Health Correlates of Depressive Symptoms

Table 1 presents characteristics of participants based on level of depressive symptoms. There were no significant sex and age differences among the groups of antidepressant-treated participants with MDD based on depressive symptom severity. There were, however, significant differences across groups on race/ethnicity, socio-economic status, health insurance, and chronic health conditions. Hispanic and non-Hispanic Black participants had lower odds than their non-Hispanic White counterparts of having no/minimal symptoms (odds ratio [OR] = 0.47, 95% confidence interval [CI] = 0.31–0.73, and OR = 0.55, 95% CI = 0.34–0.90, respectively). Both Hispanics and non-Hispanic Blacks also had higher odds than non-Hispanic Whites of having moderate/severe symptoms (OR = 2.05, 95% CI = 1.33–3.14, and OR = 1.85, 95% CI = 1.11–3.08, respectively).

Compared to participants without a high school diploma, those with any college education had higher odds of having no/minimal symptoms (OR = 1.96, 95% CI = 1.19–3.24) and lower odds of moderate/severe symptoms (OR = 0.38, 95% CI = 0.22–0.65). Those with high school diplomas or GEDs also had lower odds than those without such education to have moderate/severe symptoms (OR = 0.57, 95% CI = 0.35–0.95) (Table 1).

Family income was also associated with depressive symptoms. Compared to participants with income < 100% FPL, those with income ≥ 200% FPL had higher odds of no/minimal symptoms (OR = 3.68, 95% CI = 2.34–5.78) and lower odds of moderate/severe symptoms (OR = 0.38, 95% CI = 0.25–0.57). Participants with income in the 100% to < 200% FPL range also had higher odds of no/minimal symptoms (OR = 2.31, 95% CI = 1.32–4.04) (Table 1).

Differences in depression symptom levels were also noted among different health insurance groups (Table 1). Compared to all other participants, those with private health insurance had higher odds of no/minimal symptoms (OR = 2.22, 95% CI = 1.53–3.21) and lower odds of

Table 1. Characteristics of 885 Adult NHANES Participants With Major Depressive Disorder According to Patient Health Questionnaire-9 (PHQ-9) Symptom Levels

	No/minimal symptoms vs more severe symptoms (PHQ-9 < 5 vs ≥ 5)							Moderate/severe symptoms vs less severe symptoms (PHQ-9 ≥ 10 vs < 10)						
	PHQ-9 < 5		PHQ-9 ≥ 5		Comparison of groups			PHQ-9 ≥ 10		PHQ < 10		Comparison of groups		
Characteristic	n	%[a]	n	%[a]	OR	95% CI	*P*	n	%[a]	n	%[a]	OR	95% CI	*P*
Sex														
Female	227	71.3	376	70.2	1.00	Ref	…	206	69.3	397	71.2	1.00	Ref	…
Male	107	28.7	175	29.8	0.95	0.66–1.37	.764	94	30.7	188	28.8	1.09	0.73–1.64	.662
Age, y														
18–29	29	7.6	43	8.0	1.00	Ref	…	22	8.7	50	7.5	1.00	Ref	…
30–39	32	10.4	70	15.7	0.69	0.26–1.84	.452	34	14.4	68	13.1	0.95	0.36–2.50	.911
40–49	50	17.5	94	16.2	1.13	0.55–2.34	.736	52	18.4	92	16.0	0.99	0.42–2.34	.984
50–64	110	33.6	211	37.5	0.94	0.43–2.02	.863	125	36.8	196	35.4	0.90	0.44–1.83	.760
≥ 65	113	30.9	133	22.6	1.43	0.65–3.14	.360	67	21.7	179	28.0	0.67	0.31–1.43	.293
Race/ethnicity														
Non-Hispanic White	223	85.7	321	78.6	1.00	Ref	…	163	74.7	381	84.4	1.00	Ref	…
Non-Hispanic Black	41	4.2	80	7.0	0.55	0.34–0.90	.018	48	8.0	73	4.9	1.85	1.11–3.08	.019
Hispanic	40	4.4	102	8.5	0.47	0.31–0.73	.001	61	9.9	81	5.4	2.05	1.33–3.14	.002
Other	30	5.8	48	5.9	0.89	0.45–1.76	.730	28	7.4	50	5.3	1.59	0.74–3.42	.224
Education														
No high school diploma	44	7.0	100	12.6	1.00	Ref	…	66	16.6	78	7.7	1.00	Ref	…
High school diploma/GED	74	20.4	122	20.5	1.80	0.92–3.54	.087	69	23.6	127	19.2	0.57	0.35–0.95	.031
Any college	216	72.6	328	66.9	1.96	1.19–3.24	.010	164	59.8	380	73.1	0.38	0.22–0.65	.001
Family income compared to FPL														
< 100%	42	7.2	143	20.2	1.00	Ref	…	84	22.0	101	11.7	1.00	Ref	…
100% to < 200%	92	20.1	164	24.4	2.31	1.32–4.04	.004	93	29.0	163	20.0	0.77	0.44–1.35	.354
≥ 200%	174	72.7	199	55.4	3.68	2.34–5.78	< .001	96	48.9	277	68.3	0.38	0.25–0.57	< .001
Health insurance[b]														
Private	187	69.2	219	50.4	2.22	1.53–3.21	< .001	107	42.9	299	64.6	0.41	0.30–0.57	< .001
Public[c]	213	55.1	383	63.8	0.70	0.47–1.04	.078	214	67.6	382	57.1	1.57	1.05–2.33	.027
No insurance	20	4.0	42	8.0	0.48	0.24–0.98	.045	17	6.3	45	6.2	1.01	0.60–1.72	.961
Chronic health conditions														
Hypertension	176	46.4	315	51.2	0.83	0.56–1.21	.321	183	53.8	308	47.3	1.30	0.86–1.95	.205
Arthritis	163	44.7	324	58.2	0.58	0.42–0.81	.002	183	63.5	304	48.1	1.88	1.35–2.62	< .001
Lung disease[d]	101	31.4	218	36.4	0.80	0.48–1.34	.388	132	43.7	187	30.6	1.76	1.24–2.50	.002
Diabetes mellitus	63	14.8	148	21.2	0.65	0.42–1.01	.056	94	23.5	117	16.4	1.56	0.98–2.49	.060
Thyroid disease	65	19.5	126	21.9	0.86	0.55–1.36	.522	67	21.3	124	20.7	1.04	0.72–1.51	.823
Cancer	60	21.3	73	15.0	1.53	0.98–2.39	.060	38	13.0	95	19.6	0.62	0.33–1.16	.132
Heart disease[e]	25	5.4	78	12.1	0.42	0.23–0.74	.004	54	16.4	49	6.3	2.90	1.70–4.97	< .001
Liver disease	14	3.6	60	9.8	0.34	0.12–1.00	.051	37	12.2	37	5.1	2.57	1.23–5.38	.014
Stroke	21	3.8	49	7.5	0.49	0.25–0.94	.032	29	7.7	41	5.2	1.52	0.89–2.60	.124
Congestive heart failure	16	2.9	37	3.9	0.74	0.37–1.49	.396	23	4.8	30	3.0	1.65	0.89–3.06	.110

[a]Percentages are weighted by survey weights and may not correspond with the n's.
[b]The public and private insurance categories are not mutually exclusive; some people have both. As a result, the total percentage adds up to more than 100%. ORs are based on comparing individuals with each category of insurance to all other individuals combined.
[c]Includes Medicare, Medicaid, military health plan (Tricare/Veterans Health Administration), state sponsored, and other governmental plans.
[d]Includes asthma, chronic obstructive pulmonary disease, and bronchitis.
[e]Includes angina, coronary heart disease, or history of heart attacks.
Abbreviations: FPL = Federal Poverty Level, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio from unadjusted analyses, ref = reference group.

moderate/severe symptoms (OR = 0.41, 95% CI = 0.30–0.57). Participants with public insurance also had higher odds of moderate/severe symptoms (OR = 1.57, 95% CI = 1.05–2.33). Participants with no insurance had lower odds of no/minimal symptoms (OR = 0.48, 95% CI = 0.24–0.98).

Notable associations were found between chronic health conditions and depressive symptoms. Compared to other participants, those with arthritis had lower odds of no/minimal symptoms (OR = 0.58, 95% CI = 0.42–0.81) and higher odds of moderate/severe symptoms (OR = 1.88, 95% CI = 1.35–2.62). Similarly, those with as compared to without heart disease had lower odds of no/minimal symptoms (OR = 0.42, 95% CI = 0.23–0.74) and higher odds of moderate/severe symptoms (OR = 2.90, 95% CI = 1.70–4.97). In addition, participants with stroke had lower odds of no/minimal symptoms (OR = 0.49, 95% CI = 0.25–0.94), and those with liver disease (OR = 2.57, 95% CI = 1.23–5.38) and lung disease (OR = 1.76, 95% CI = 1.24–2.50) had higher odds of moderate/severe symptoms (Table 1).

Association of Medications With Potential Depressive Symptom Side Effects With Depressive Symptoms

In unadjusted analyses in which only the number of medications was entered into the models, a larger number of medications with PDSS was significantly associated with lower odds of no/minimal symptoms (OR = 0.75, 95% CI = 0.67–0.85) and higher odds of moderate/severe symptoms (OR = 1.22, 95% CI = 1.08–1.27). No corresponding associations were observed for medications without PDSS (OR = 0.98, 95% CI = 0.90–1.07, and OR = 1.05, 95% CI = 0.98–1.12, respectively).

Table 2. Multivariable Logistic Regression Analyses for the Association of Number of Medications With and Without Potential Depressive Symptom Side Effects With Level of Depressive Symptoms in 885 Adult NHANES Participants With Major Depressive Disorder

	No/minimal symptoms vs more severe symptoms (PHQ-9 < 5 vs ≥ 5)			Moderate/severe symptoms vs less severe symptoms (PHQ-9 ≥ 10 vs < 10)		
Variables	AOR[a]	95% CI	*P*	AOR[a]	95% CI	*P*
Number of prescription medications with potential depressive symptom side effects	0.75	0.64–0.87	< .001	1.14	1.004–1.29	.044
Number of prescription medications without potential depressive symptom side effects	0.97	0.85–1.11	.674	1.02	0.92–1.13	.717
Sex						
Female	1.00	Ref	…	1.00	Ref	…
Male	1.06	0.71–1.60	.758	1.01	0.62–1.64	.979
Age, y	1.03	1.01–1.05	.001	0.98	0.96–0.99	.002
Race/ethnicity						
Non-Hispanic White	1.00	Ref	…	1.00	Ref	…
Non-Hispanic Black	0.77	0.45–1.31	.327	1.39	0.74–2.63	.298
Hispanic	0.69	0.37–1.30	.245	1.42	0.79–2.55	.239
Other	1.30	0.59–2.85	.509	1.29	0.56–2.97	.540
Education						
No high school diploma	1.00	Ref	…	1.00	Ref	…
High school diploma/GED	1.42	0.66–3.05	.364	0.66	0.35–1.26	.204
Any college	1.26	0.69–2.30	.451	0.49	0.26–0.91	.025
Family income compared to FPL	1.17	1.06–1.30	.003	0.89	0.77–1.02	.098
Health insurance						
Private	1.00	Ref	…	1.00	Ref	…
Public[b]	0.70	0.41–1.22	.204	1.25	0.75–2.06	.381
No insurance	0.45	0.20–1.03	.060	1.12	0.60–2.09	.724
Chronic health conditions						
Hypertension	1.11	0.71–1.72	.641	1.04	0.63–1.73	.872
Arthritis	0.52	0.33–0.83	.007	2.08	1.22–3.54	.008
Lung disease[c]	1.17	0.67–2.06	.571	1.30	0.81–2.11	.274
Diabetes mellitus	0.89	0.45–1.74	.720	1.14	0.61–2.13	.679
Thyroid disease	0.86	0.53–1.40	.544	0.88	0.60–1.30	.513
Cancer	1.61	1.05–2.47	.029	0.54	0.29–1.03	.060
Heart disease[d]	0.44	0.22–0.89	.023	2.28	1.11–4.69	.026
Liver disease	0.37	0.14–0.99	.048	2.02	0.89–4.57	.091
Stroke	0.85	0.39–1.89	.690	0.84	0.42–1.68	.613
Congestive heart failure	2.09	0.74–5.93	.162	0.68	0.30–1.52	.338

[a]AORs are adjusted for all other variables in the models.
[b]Includes Medicare, Medicaid, military health plan (Tricare/Veterans Health Administration), state sponsored and other governmental plans.
[c]Includes asthma, chronic obstructive pulmonary disease, and bronchitis.
[d]Includes angina, coronary heart disease or history of heart attacks.
Abbreviations: AOR = adjusted odds ratio from adjusted analyses, FPL = Federal Poverty Level, NHANES = National Health and Nutrition Examination Survey, PHQ-9 = Patient Health Questionnaire-9, ref = reference group.

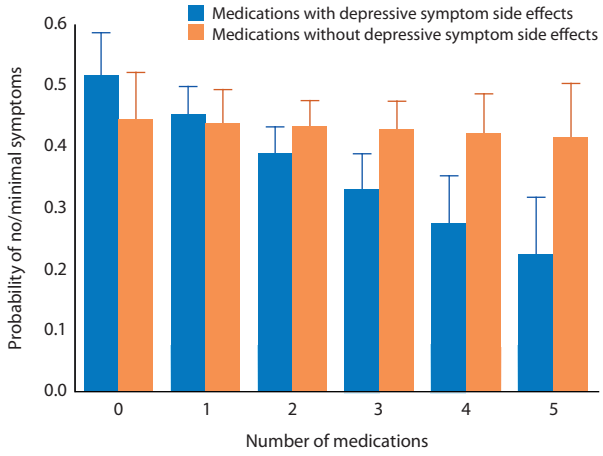
Significant associations of medications with PDSS with depressive symptoms persisted in multivariable models (AOR = 0.75, 95% CI = 0.64–0.87, and AOR = 1.14, 95% CI = 1.004–1.29, respectively) (Table 2). Analyses of predicted probabilities based on margins from these regression models highlight these associations (Figures 1 and 2). The predicted probability of no/minimal symptoms in those taking 5 medications with PDSS was less than half the predicted probability in those taking no medications with PDSS (0.23 vs 0.52). Similarly, the predicted probability of moderate/severe symptoms was about 50% higher in those taking 5 as compared to 0 medications with PDSS (0.36 vs 0.24). No corresponding associations were noted for medications without PDSS (Figures 1 and 2).

Further Analyses

In analyses limited to participants with arthritis, results were similar to the main analyses (data not shown). In adjusted models, the number of medications with PDSS was associated with lower odds of no/minimal symptoms (AOR = 0.64, 95% CI = 0.52–0.78) and higher odds of moderate/severe symptoms (AOR = 1.16, 95% CI = 1.001–1.33). Similar results were obtained in analyses limited to participants with hypertension (AOR = 0.71, 95% CI = 0.59–0.87 and AOR = 1.23, 95% CI = 1.04–1.46, respectively, data not shown).

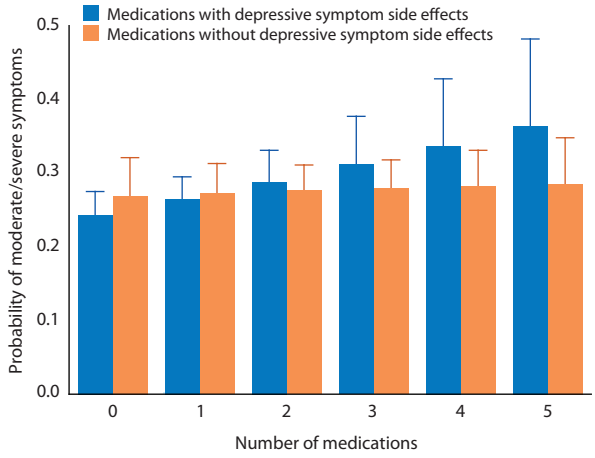
In analyses of individual medications (Table 3), omeprazole, gabapentin, meloxicam, tramadol, ranitidine, baclofen, oxycodone, tizanidine, propranolol, and morphine were significantly associated with severity of depressive symptoms. When adjusted logistic regression analyses for the number of medications with PDSS were repeated limiting medications to these 10, the results were even stronger than the main analyses reported in Table 2 (AOR = 0.42, 95% CI = 0.30–0.60 for no/minimal symptoms and AOR = 1.68, 95% CI = 1.24–2.27 for moderate/severe symptoms).

Figure 1. Predicted Probability of No/Minimal Depressive Symptoms (PHQ-9 Score < 5) Among 885 Adult NHANES Participants With Antidepressant-Treated Major Depressive Disorder According to the Number of Medications Used[a]



[a]Probabilities are based on computed margins from multivariable logistic regression models.
Abbreviations: NHANES = National Health and Nutrition Examination Survey, PHQ-9 = Patient Health Questionnaire-9.

Figure 2. Predicted Probability of Moderate/Severe Depressive Symptoms (PHQ-9 Score ≥ 10) Among 885 Adult NHANES Participants With Antidepressant-Treated Major Depressive Disorder According to the Number of Medications Used[a]



[a]Probabilities are based on computed margins from multivariable logistic regression models.
Abbreviations: NHANES = National Health and Nutrition Examination Survey, PHQ-9 = Patient Health Questionnaire-9.

Table 3. Bivariate Logistic Regression Analyses for the Association of Individual Medications With Potential Depressive Symptom Side Effects With Level of Depressive Symptoms in 885 Adult NHANES Participants With Major Depressive Disorder

			No/minimal symptoms vs more severe symptoms (PHQ-9 < 5 vs ≥ 5)							Moderate/severe symptoms vs less severe symptoms (PHQ-9 ≥ 10 vs < 10)						
	Total		PHQ-9 < 5		PHQ-9 ≥ 5					PHQ ≥ 10		PHQ < 10				
Medication	n	%	n	%	n	%	OR	95% CI	*P*	n	%	n	%	OR	95% CI	*P*
Omeprazole	132	13.6	32	8.4	100	17.6	0.43	0.26–0.70	.001	58	18.5	74	11.7	1.72	1.02–2.90	.041
Gabapentin	126	10.3	24	3.9	102	15.0	0.23	0.12–0.45	<.001	70	19.6	56	6.5	3.49	1.99–6.13	<.001
Meloxicam	44	4.6	12	2.1	32	6.5	0.31	0.11–0.85	.024	22	9.1	22	2.8	3.48	1.77–6.83	.001
Tramadol	39	3.6	10	2.3	29	4.5	0.50	0.20–1.26	.135	20	6.2	19	2.5	2.53	1.11–5.79	.028
Ranitidine	27	3.2	8	2.3	19	4.0	0.57	0.21–1.57	.269	13	5.9	14	2.2	2.76	1.11–6.89	.030
Baclofen	22	2.4	3	0.5	19	3.9	0.13	0.04–0.48	.003	12	4.7	10	1.5	3.20	1.46–7.05	.005
Oxycodone	20	2.0	3	0.4	17	3.2	0.14	0.03–0.63	.012	11	3.2	9	1.5	2.16	0.67–6.91	.190
Tizanidine	14	2.2	3	0.3	11	3.5	0.09	0.02–0.46	.005	5	3.4	9	1.7	2.09	0.49–8.91	.312
Propranolol	14	1.5	4	0.5	10	2.2	0.23	0.06–0.83	.027	5	1.9	9	1.3	1.48	0.33–6.63	.604
Morphine	13	1.4	4	0.3	9	2.1	0.15	0.03–0.81	.028	4	1.4	9	1.3	1.04	0.20–5.34	.964

Abbreviations: NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, PHQ-9 = Patient Health Questionnaire-9.

Furthermore, a clear trend was observed between number of these medications and depression levels. The proportion of participants with no/minimal symptoms ranged from 51.1% in those not using any of these medications to 33.0% in those using 1, 9.8% in those using 2, and 5.0% in those using 3 or more of these medications. Similarly, the proportion of participants with moderate/severe symptoms ranged from 21.9% in those not using any of these medications to 35.8% in those using 1, 54.7% in those using 2, and 63.4% in those using 3 or more.

DISCUSSION

Many individuals treated for MDD continue to experience depressive symptoms, which are associated with an increased risk of adverse outcomes.[5,31,32] These individuals also often use other medications with PDSS for treatment of comorbid medical conditions. About two-thirds of antidepressant-treated adults with MDD in this study used ≥ 1 medication with these potential side effects, and more than one-third used ≥ 2 such medications. Participants using medications with PDSS, especially those using multiple such medications, were less likely to have no/minimal depressive symptoms and more likely to have moderate/severe symptoms. No such associations were observed for medications without PDSS. These findings collectively indicate that the associations of medications with PDSS and depressive symptoms cannot be simply attributed to chronic medical comorbidities that are associated with both medication use and worse depression treatment outcomes.[13,14,33–36]

The findings are consistent with results from an NHANES 2005–2014 study that reported a national increase in use of medications with PDSS alongside an increase in the prevalence of depression.[19] Among the total sample

and those taking antidepressants in that study, taking ≥ 3 medications with PDSS was associated with an increased prevalence of depression.[19] However, that study did not specifically examine participants with MDD because MDD could not be defined in NHANES before 2013.

The mechanisms linking the use of medications with PDSS to higher levels of depressive symptoms in MDD may be the same as or similar to the mechanisms proposed for the depressive symptom side effects of these medications in general. These include modulation of CNS bioamines or receptors, increase in proinflammatory factors, and modulation of hormone production.[18]

Notably, 7 of the 10 medications found to be associated with higher depressive symptoms in bivariate analyses are used for treatment of pain or muscle spasms. The role of pain as a barrier to antidepressant effect and symptom remission from MDD is increasingly recognized.[33,37] However, the mechanisms of this interaction are not well understood.[38–41] These mechanisms and the role of pain medication in remission from MDD need further research.

With growing trends in polypharmacy,[19] the use of medications with PDSS in MDD will likely increase. If corroborated in future research, the results of this study suggest that these medications might intensify depressive symptoms or delay symptom remission of MDD. A review of the patient's medication list may provide clues to reasons for higher levels of depressive symptoms and facilitate selection of safer alternative medications if possible.

Several limitations of this study should be noted. First, although analyses were adjusted for multiple medical conditions and medications without PDSS, residual confounding by medical comorbidities or pain cannot be fully excluded. Second, no information was available on the initial severity of MDD, course of illness, future episodes, and timing of MDD onset in relation to medical comorbidities. The cross-sectional design of NHANES limits causal inference regarding the association of medications with PDSS with depressive symptoms. Third, all health information was based on self-report, and medications were verified through examination of packaging rather than prescription records. However, self-reports for most health conditions correspond closely to administrative records.[42,43] Fourth, due to sample size constraints, analyses could not be conducted within specific groups of medications. Future research with larger samples may examine associations based on single classes of medication. Fifth, the impact of duration of medication use could not be assessed because of the multiplicity of medications and lack of information on previously used medications. Lastly, the depression diagnoses were based on self-reported symptoms and may not correspond to research diagnoses.

In the context of these limitations, this study presents a broad overview of the prevalence of use of medications with PDSS in US adults treated for MDD and higher levels of depressive symptoms in those receiving these medications. Among patients with MDD, higher levels of depressive symptoms persisting after treatment pose increased risks of relapse and other adverse outcomes.[5,31,32] Improved management of medical comorbidities, including a judicious selection of medications with lower risk of depressive symptom side effects, could enhance the likelihood of achieving full remission and potentially improving patient outcomes.

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