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Prevalence of Prescription Medications With Depression as a Potential Adverse Effect Among Adults in the United States

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IMPORTANCE Prescription medications are increasingly used among adults in the United States and many have a potential for causing depression.

OBJECTIVES To characterize use of prescription medications with depression as a potential adverse effect and to assess associations between their use and concurrent depression.

DESIGN, SETTING, AND PARTICIPANTS Five 2-year cycles (2005-2006 through 2013-2014) of the National Health and Nutrition Examination Survey, representative cross-sectional surveys of US adults aged 18 years or older, were analyzed for use of medications with depression as a potential adverse effect. Multivariable logistic regression examined associations between use of these medications and concurrent depression. Analyses were performed among adults overall, excluding antidepressant users, and among adults treated with antidepressants and with hypertension.

EXPOSURES Prescription medications with depression as a potential adverse effect (listed in Micromedex).

MAIN OUTCOMES AND MEASURES Prevalence of any use and concurrent use of medications with a potential to cause depression and prevalence of depression (PHQ-9 score ≥10).

RESULTS The study included 26 192 adults (mean age, 46.2 years [95% CI, 45.6-46.7]; women, 51.1%) and 7.6% (95% CI, 7.1%-8.2%) reported depression. The overall estimated prevalence of use of medications with depression as an adverse effect was 37.2%, increasing from 35.0% (95% CI, 32.2%-37.9%) in the cycle years 2005 and 2006 to 38.4% (95% CI, 36.5%-40.3%) in 2013 and 2014 (*P* for trend = .03). An estimated 6.9% (95% CI, 6.2%-7.6%) reported use of 3 or more concurrent medications with a potential for depression as an adverse effect in 2005 and 2006 and 9.5% (95% CI, 8.4%-10.7%) reported such use in 2013 and 2014 (*P* for trend = .001). In adjusted analyses excluding users of antidepressants, the number of medications used with depression as possible adverse effects was associated with increased prevalence of concurrent depression. The estimated prevalence of depression was 15% for those reporting use of 3 or more medications with depression as an adverse effect vs 4.7% for those not using such medications (difference, 10.7% [95% CI, 7.2%-14.1%]). These patterns persisted in analyses restricted to adults treated with antidepressants, among hypertensive adults, and after excluding users of any psychotropic medication.

CONCLUSIONS AND RELEVANCE In this cross-sectional survey study, use of prescription medications that have depression as a potential adverse effect was common. Use of multiple medications was associated with greater likelihood of concurrent depression.

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Prescription medications are widely and increasingly used in the United States, with approximately 15% of adults estimated to have been using 5 or more concurrent prescription medications in 2011 and 2012.[1] Alongside evidence that adverse drug events from prescription medications are often implicated in emergency department visits and hospitalizations,[2] there is gaining recognition that many commonly used prescription medications, including hormonal contraceptives and β-blockers, are associated with an increased risk of depression.[3-5]

In the years 2009 through 2012, depression was estimated to affect more than 5% of US adults[6] and in 2011 and 2012, an estimated 28.7% of adults with depressive symptoms were undiagnosed or untreated.[7] Despite progress in understanding risk factors for depression, including among adults with comorbid medical disorders,[8] there is only limited information about the use of medications that have the potential for depression as an adverse effect. Several studies have investigated associations between medication classes and depression.[9-15] The strength of evidence for depression as an adverse effect varies across medication classes. For example, depression has been consistently associated with interferon α treatment of hepatitis C with mild to moderate depression developing in 45% to 60% of treated patients and moderate to severe depression developing in 15% to 40%.[10-12] By contrast, evidence linking β-blockers to depression[13,14] and suicide[15] is less consistent.

The current study extends prior research by using nationally representative survey data to consider a broad spectrum of medications that have a potential for depression as an adverse effect and examine their associations with concurrent depression.

Key Points

Question How frequently do US adults use prescription medications with depression as a potential adverse effect and is use of these medications associated with concurrent depression?

Findings In this cross-sectional US population-based survey study conducted between 2005 and 2014, the estimated overall prevalence of US adults using medications with depression as a potential adverse effect was 37.2%. The adjusted percentage of adults with concurrent depression was higher among those using more concurrent medications (eg, estimated 15% for ≥3 medications).

Meaning Use of prescription medications that have depression as a potential adverse effect was common and associated with greater likelihood of concurrent depression.

Methods

This study was considered exempt from human subjects approval by the institutional review board at the University of Illinois at Chicago. All National Health and Nutrition Examination Survey (NHANES) participants provided written informed consent and these data are publicly available.

Participants

NHANES is a nationally representative cross-sectional survey of the community-dwelling US population.[16] Our analyses were based on data collected from participants aged 18 years or older during the 5 most recent NHANES 2-year cycles (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014). NHANES uses a stratified complex multistage probability survey design. Participants were assigned weights to account for differential probability of selection and nonresponse. After excluding 3026 participants without prescription drug-use data or depression assessments, the final analytic sample was 26 192.

Depression Assessment

The Patient Health Questionnaire 9 (PHQ-9) consists of 9 questions about depression, as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition), experienced in the previous 2 weeks. Depression was defined as a PHQ-9 score of 10 or higher, which had a sensitivity of 88% and a specificity of 88% for major depression in an adult primary care sample.[17]

Prescription Medication Data

Information on prescription medication use was collected during the household interview using a computer-based medication log. In brief, participants were asked to show interviewers containers for all prescription medications taken in the prior 30 days. Medication names were then coded and linked by generic drug name to a proprietary drug database (Lexicon Plus; Cerner Multum) that includes information on all prescription drugs. Use of prescription medications with a potential adverse effect of depression was defined as a categorical variable (0, 1, 2, or ≥3 prescription medications that have a potential for an adverse effect of depression). Concurrent use was defined as the use of 2 or 3 or more medications that have a potential for depression as an adverse effect.

Antidepressant use was defined as use of at least 1 prescription medication classified as antidepressants. Psychotropic medications included antidepressants, central nervous system stimulants, anxiolytics, hypnotics and sedatives, anticonvulsants, and antipsychotics. To assess the specificity of the cross-sectional association between use of prescription medications that have depression as a potential adverse effect and depression, use of prescriptions that do not have depression as an adverse effect were also measured.

Depression as an Adverse Effect

Prescription medications that have a potential for depression as an adverse effect, including suicidal symptoms, were identified using Micromedex (Truven Health Analytics). Medications with *depression*, *depressive disorder*, *suicide*, *suicidal thoughts*, *suicidal ideation*, or *suicidal behavior* listed as common or serious adverse effects were defined as having a potential for depression as an adverse effect. *Suicide* and *suicidal thoughts* and *suicidal ideation* and *suicidal behavior* were further subclassified as having suicidal symptoms as adverse effects.

The accuracy, including sensitivity and specificity, comprehensiveness, and utility of Micromedex, which is primarily based on the US Food and Drug Administration–labeled adverse effects, has been previously established.[18,19] Specifically, in a study evaluating software for drug-drug interactions, Micromedex was found to have a sensitivity of 95%, a specificity of 100%, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 95% and was ranked the highest in accuracy.[19] Micromedex was also found to have a sensitivity of 93% and PPV of 99% in detecting black box warnings.[18]

Other Variables

Other variables included sex; age group (18-39, 40-64, ≥65 years); educational achievement (<high school, high school, some college, ≥college); family income to federal poverty level ratio (<1 [lowest income], 1 to <2, 2 to <3, 3 to <4, and ≥4 [highest income]); marital status (married or living with partner, never married, divorced or separated, and widowed); current employment status (yes, no); and number of chronic conditions based on self-reported diagnoses of hypertension, arthritis, cancer, cardiovascular disease (congestive heart failure, coronary heart disease, or angina), kidney disease, diabetes, pulmonary disease (emphysema, chronic bronchitis, or asthma), and stroke. Self-reported race/ethnicity by categories defined in NHANES (non-Hispanic white, non-Hispanic black, Hispanic, other) were included because race/ethnicity has been previously associated with depression.[20]

Statistical Analyses

Descriptive statistics were used to estimate the weighted prevalence of use and concurrent use of prescription medications that have depression as a potential adverse effect. Prevalence estimates and standard errors were determined using Taylor linearization methods to incorporate sampling weights that adjust for the NHANES complex sampling and survey design. Confidence intervals were constructed by inverting the corresponding Wald test. Significance of trends across all 5 survey cycles was tested using logistic regression. Multivariable logistic regression was used to model associations between use of medications that have depression as an adverse effect and depression. All variables listed in **Table 1** were included in the fully adjusted models because these variables have been previously associated with depression.[20] Fully adjusted models were used to compute predictive margins to estimate the weighted adjusted prevalence and difference in prevalence. Separate analyses were performed among adults treated and not treated with antidepressants. All CIs and tests use design-based estimates of variance. Model fit was assessed using a design-based *F*-adjusted mean residual test. All reported *P* values were 2 sided (.05 level). In this large, exploratory study, no adjustments were made for the multiple comparisons. The *P* values should therefore be interpreted with caution.

The Stata module for multiple imputation with chained equations was used to impute values for all covariates (listed in Table 1) with missing data.[21,22] Twenty imputed data sets were generated and used in all logistic regression analyses. All analyses were carried out using Stata Statistical Software: Release 14 (StataCorp LP).

Sensitivity Analyses

A series of sensitivity analyses were conducted to control for potential confounding by indication and reverse causality. First, primary analyses among nonusers and users of antidepressants were conducted after excluding adults who used any psychotropic medication including anticonvulsants. Among antidepressant users, these analyses excluded antidepressant users who also reported use of other psychotropic medications. Second, we restricted the sample (for both nonusers and users of antidepressants) to adults who reported having hypertension, which is itself associated with depression.[23] In addition, many commonly used antihypertensives (eg, β-blockers) have also been associated with having depression as an adverse effect.[9] Third, among adults ages 20 through 59 years (age range for which information on illicit drug use was captured in NHANES), illicit drug use was included as a control variable. Fourth, to test whether the use of medications with suicidal symptoms as adverse effects influence the association between use of medications that have depression as an adverse effect and depression, we additionally adjusted for the use of medications with suicidal symptoms as adverse effects and included an interaction term between the number of medications used that have depression as a potential adverse effect and the number used that have potential suicidal symptoms as potential adverse effects in the fully adjusted model for our primary analyses excluding antidepressant users. Fifth, analyses were conducted with suicidal ideation from the PHQ-9 as the outcome.

Results

An estimated 62.8% (95% CI, 61.7%-64.0%) of adults reported they did not use any prescription medication that had depression as a potential adverse effect in the prior 30 days, whereas an estimated 37.2% (95% CI, 36.0%-38.3%) used at least 1 (Table 1). Use of prescription medications that have depression as a potential adverse effect was significantly associated with several sociodemographic and health characteristics including older age (≥65 years), female sex, widowed marital status, and a higher number of chronic conditions. Overall, it was estimated that 7.6% (95% CI, 7.1%-8.2%) of adults reported depression during the study period.

The reported use of any prescription medication that had depression as a potential adverse effect increased from 35.0% (95% CI, 32.2%-37.9%) in cycle years 2005 and 2006 to 38.4% (95% CI, 36.5%-40.3%) in 2013 and 2014 year (**Figure**). Concurrent use of 3 or more of these prescription medications increased from 6.9% (95% CI, 6.2%-7.6%) to 9.5% (95% CI, 8.4%-10.7%). Any use of prescription medications that have suicidal symptoms as potential adverse effects increased from 17.3% (95% CI, 15.9%-18.8%) in 2005 and 2006 to 23.5% (95% CI, 21.8%- 25.2%) in 2013 and 2014.

Table 1. Prevalence in Use of Prescription Medications With Depression as a Potential Adverse Effect in Prior 30 Days Among US Adults, 2005-2014

	No. of Participants (%)[a]	No. (%) [95% CI] Taking Medication With Depression as an Adverse Effect[a]		*P* Value[b]
		None	Any	
Overall	26 192 (100)	17 042 (62.8) [61.7-64.0]	9150 (37.2) [36.0-38.3]	<.001
No. of medications with depression adverse effects				
1	5089 (21.0)		5089 (56.4) [55.2-57.7]	
2	2175 (8.7)		2175 (23.5) [22.3-24.7]	
≥3	1886 (7.5)		1886 (20.1) [19.1-21.2]	
Age group, y				
18-39	10 026 (38.8)	8118 (47.2) [45.5-48.9]	1908 (24.5) [23.0-26.0]	<.001
40-64	10 340 (44.1)	6466 (41.8) [40.3-43.4]	3874 (47.9) [46.5-49.2]	
≥65	5826 (17.2)	2458 (11.0) [10.3-11.6]	3368 (27.7) [26.1-29.3]	
Sex				
Men	12 900 (48.9)	9121 (54.9) [54.1-55.7]	3779 (38.9) [37.6-40.1]	<.001
Women	13 292 (51.1)	7921 (45.1) [44.3-45.9]	5371 (61.1) [59.9-62.4]	
Race/ethnicity				
Non-Hispanic white	11 736 (69.1)	6444 (62.8) [59.5-66.0]	5292 (79.6) [77.2-81.9]	<.001
Non-Hispanic black	5686 (11.2)	3964 (12.7) [11.1-14.6]	1722 (8.5) [7.2-10.0]	
Hispanic, any race	6583 (13.4)	4976 (16.9) [14.7-19.4]	1607 (7.5) [6.2-9.0]	
Other	2187 (6.4)	1658 (7.6) [6.7-8.5]	529 (4.4) [3.8-5.0]	
Marital status[c]				
Married/living with partner	14 639 (61.4)	9514 (61.2) [59.6-62.8]	5125 (61.6) [59.8-63.4]	<.001
Never married	6030 (20.6)	4700 (24.2) [22.6-25.8]	1330 (14.5) [13.3-15.9]	
Divorced or separated	3492 (12.4)	1999 (11.1) [10.5-11.8]	1493 (14.6) [13.5-15.6]	
Widowed	2017 (5.6)	821 (3.5) [3.2-3.8]	1196 (9.3) [8.6-10.0]	
Education[d]				
<High school	6947 (17.7)	4587 (18.3) [17.0-19.6]	2360 (16.7) [15.0-18.6]	.21
High school	6215 (23.4)	4030 (23.2) [22.2-24.3]	2185 (23.8) [22.1-25.5]	
Some college	7571 (31.5)	4890 (31.2) [30.1-32.4]	2681 (31.8) [30.4-33.3]	
College	5440 (27.4)	3521 (27.3) [25.5-29.2]	1919 (27.7) [25.4-30.1]	
Employed[e]				
No	11 841 (36.9)	6231 (29.3) [28.0-30.5]	5610 (49.8) [47.9-51.8]	<.001
Yes	14 345 (63.1)	10 808 (70.7) [69.5-72.0]	3537 (50.2) [48.2-52.1]	
Ratio of family income to federal poverty level[f]				
<1 (lowest income)	5406 (14.7)	3611 (15.6) [14.3-17.0]	1795 (13.3) [11.8-14.9]	.004
1 to <2	6371 (20.5)	4080 (20.6) [19.4-21.8]	2291 (20.4) [18.9-22.0]	
2 to <4	6354 (28.9)	4140 (29.0) [27.5-30.6]	2214 (28.8) [27.0-30.6]	
≥4 (highest income)	6118 (35.9)	3868 (34.9) [32.8-36.9]	2250 (37.6) [35.1-40.2]	
PHQ-9 Depression Symptom score (range 0-27)				
Minimal, 0-4	19 803 (77.4)	13 747 (82.7) [81.6-83.7]	6056 (68.5) [67.0-69.8]	<.001
Mild depression, 5-9	4071 (15.0)	2311 (12.6) [11.8-13.5]	1760 (19.0) [18.1-19.9]	
Moderate or severe depression, ≥10	2318 (7.6)	984 (4.7) [4.2-5.2]	1334 (12.6) [11.5-13.7]	
No. of chronic conditions[g]				
None	12 005 (47.8)	10 005 (59.7) [58.5-61.0]	2000 (27.6) [25.7-29.6]	<.001
1 or 2	10 100 (40.1)	5886 (35.7) [34.5-36.8]	4214 (47.6) [46.2-49.0]	
≥3	3723 (12.1)	961 (4.6) [4.2-5.1]	2762 (24.8) [23.4-26.3]	
Body mass index[h]				
Underweight, <18.5	470 (1.7)	344 (1.9) [1.6-2.2]	126 (1.4) [1.1-1.7]	<.001
Normal, 18.5 to <25	755 (30)	5340 (31.8) [30.5,33.1]	2215 (26.8) [25.4,28.3]	
Overweight, 25 to <30	8525 (33.2)	5693 (34.1) [33.0-35.2]	2832 (31.7) [30.1-33.3]	
Obese, ≥30	9360 (35.2)	5534 (32.2) [31.1-33.4]	3826 (40.1) [38.6-41.7]	

(continued)

Table 1. Prevalence in Use of Prescription Medications With Depression as a Potential Adverse Effect in Prior 30 Days Among US Adults, 2005-2014 (continued)

	No. of Participants (%)[a]	No. (%) [95% CI] Taking Medication With Depression as an Adverse Effect[a]		P Value[b]
		None	Any	
No. of medications without depression adverse effects				
None	13 835 (53.0)	11 696 (67.9) [66.8-69.0]	2139 (27.9) [26.4-29.5]	<.001
1	4075 (17.5)	2422 (15.7) [14.8-16.6]	1653 (20.5) [19.3-21.6]	
2	2613 (10.4)	1203 (7.5) [6.9-8.1]	1410 (15.2) [14.1-16.4]	
≥3	5669 (19.2)	1721 (8.9) [8.4-9.5]	3948 (36.4) [34.8-38.0]	

Abbreviation: Patient Health Questionnaire 9 (PHQ-9)

[a] Data, from the National Health and Nutrition Examination Survey (NHANES), are expressed as unweighted number of participants and weighted percentages and 95% CIs, weighted to be nationally representative.

[b] *P* value for difference in prevalence between none and any use of medications with depression as an adverse effect is based on a Pearson χ^2 test using Rao and Scott second-order correction.

[c] Excludes 14 participants for whom data on marital status was not collected.

[d] Excludes 19 participants for whom data on education was not collected.

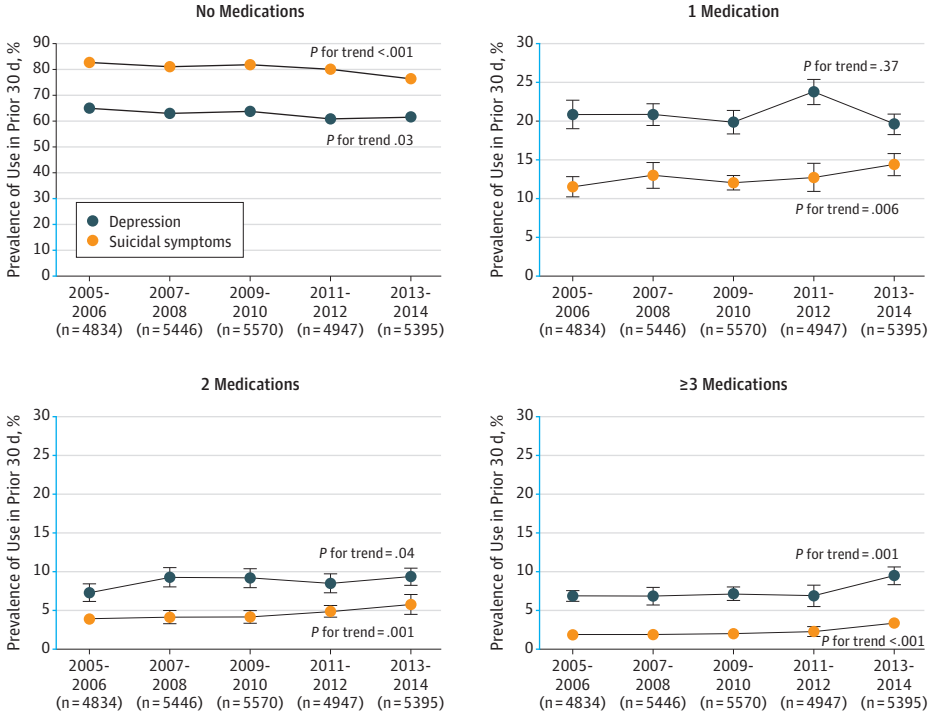
[e] Excludes 6 participants for whom data on employment was not collected.

[f] Excludes 1943 participants for whom data on family income was not collected. Data on ratio of family income to the US federal poverty level was calculated by Centers for Disease Control and Prevention based on household size and household income, and provided in NHANES data set.

[g] Excludes 364 participants for whom data on chronic conditions was not collected. Chronic conditions include arthritis, cancer, kidney failure, diabetes, cardiovascular disease (myocardial infarction, congestive heart failure, coronary heart disease, or angina), stroke, hypertension, and pulmonary disease (emphysema, chronic bronchitis, or current asthma).

[h] Excludes 284 participants for whom data on body mass index was not collected. Body mass index is calculated as weight in kilograms divided by height in meters.

Figure. Trends in Use and Concurrent Use of Prescription Medications With Depression and Suicidal Symptoms as a Potential Adverse Effect Among US Adults, 2005-2014



Data are from National Health and Nutrition Examination Study. Data are expressed as unweighted number of participants and weighted percentages and 95% CIs, which are indicated by error bars, weighted to be nationally representative. The y-axis scale shown in blue indicates a range from 0% to 30%.

Concurrent use of 3 or more prescription medications that had suicidal symptoms as adverse effects also significantly increased from 1.9% (95% CI, 1.5%-2.2%) in 2005 and 2006 to 3.3% (95% CI, 2.8%-4.0%) in 2013 and 2014.

It was estimated that 7.9% (95% CI, 7.0%-8.9%) of adults used antihypertensive agents associated with depression as a potential adverse effect (metoprolol and atenolol) (**Table 2**). Use of proton pump inhibitors and histamine H2 antagonists that are associated with depression as a potential adverse effect increased from 5.4% (95% CI, 4.6%-6.4%) in 2005 and 2006 to 9.5% (95% CI, 8.3%-10.9%) in 2013 and 2014 (difference, 4.1% [95% CI, 2.5%-5.7%]). Use of several analgesics and muscle relaxants (ibuprofen, hydrocodone, and cyclobenzaprine); anxiolytics; sedatives and hypnotics

Table 2. Changes in the Use of the Most Commonly Used Prescription Medications With Depression as a Potential Adverse Effect by Therapeutic Class Among US Adults, Cycle Years 2005 and 2006 vs 2013 and 2014[a]

	Estimated Prevalence of Use, No. (%) [95% CI]		Difference in Prevalence, % (95% CI)	*P* Value[b]
	2005-2006	2013-2014		
Antihypertensives[c]	463 (9.2) [7.5 to 11.4]	472 (7.9) [7.0 to 8.9]	−1.3 (−3.5 to 0.9)	.22
Metoprolol	247 (5.2) [3.8 to 7.0]	288 (4.9) [4.1 to 5.7]	−0.3 (−2.1 to 1.5)	.73
Atenolol	148 (3.1) [2.5 to 3.7]	142 (2.4) [1.9 to 3.0]	−0.7 (−1.4 to 0.1)	.09
Enalapril	38 (0.6) [0.4 to 1.0]	45 (0.6) [0.4 to 1.1]	0.03 (−0.4 to 0.4)	.99
Quinapril	31 (0.5) [0.3 to 0.9]	15 (0.4) [0.2 to 0.8]	−0.2 (−0.6 to 0.2)	.38
Antidepressants[d]	411 (11.2) [10.1 to 12.5]	643 (15.1) [13.5 to 16.9]	3.9 (1.9 to 6.0)	.001
Sertraline	64 (1.7) [1.3 to 2.4]	118 (2.8) [2.1 to 3.8]	1.1 (0.1 to 2.1)	.03
Citalopram	32 (0.9) [0.6 to 1.4]	102 (2.4) [1.9 to 3.0]	1.4 (0.8 to 2.1)	<.001
Bupropion	53 (1.7) [1.3 to 2.4]	93 (2.2) [1.7 to 2.9]	0.5 (−0.3 to 1.3)	.25
Fluoxetine	55 (1.4) [1.0 to 2.0]	74 (1.8) [1.3 to 2.5]	0.4 (−0.4 to 1.1)	.31
Trazodone	39 (0.9) [0.6 to 1.4]	73 (1.7) [1.3 to 2.1]	0.8 (0.2 to 1.3)	.006
Venlafaxine	43 (1.5) [1.2 to 1.8]	50 (1.3) [1.0 to 1.8]	−0.1 (−0.7 to 0.4)	.66
Escitalopram	63 (1.9) [1.5 to 2.3]	49 (1.2) [0.8 to 1.6]	−0.7 (−1.3 to −0.1)	.02
Duloxetine	19 (0.6) [0.3 to 1.0]	47 (1.1) [0.8 to 1.6]	0.5 (0.03 to 1.1)	.04
Paroxetine	41 (1.1) [0.8 to 1.5]	41 (0.9) [0.6 to 1.4]	−0.2 (−0.8 to 0.3)	.43
Amitriptyline	35 (1.0) [0.7 to 1.3]	40 (0.9) [0.7 to 1.2]	−0.1 (−0.5 to 0.3)	.63
Hormones/hormone modifiers	311 (8.4) [7.5 to 9.5]	355 (7.8) [6.7 to 9.0]	−0.6 (−2.2 to 0.9)	.40
Ethinyl estradiol	85 (5.0) [3.5 to 7.0]	97 (4.6) [3.7 to 5.7]	−0.2 (−1.2 to 0.8)	.65
Estradiol	36 (2.2) [1.4 to 3.5]	39 (2.3) [1.7 to 3.1]	0.04 (−0.6 to 0.6)	.90
Finasteride[d]	18 (0.8) [0.5 to 1.3]	41 (1.5) [0.9 to 2.6]	0.7 (−0.1 to 1.6)	.12
Anxiolytics, hypnotics and sedatives[d]	174 (4.5) [3.7 to 5.3]	312 (6.9) [5.3 to 8.7]	2.4 (0.5 to 4.3)	.01
Alprazolam	43 (1.1) [0.7 to 1.6]	105 (2.4) [1.5 to 3.8]	1.3 (0.1 to 2.5)	.03
Zolpidem	39 (1.2) [0.8 to 1.9]	84 (2.0) [1.7 to 2.4]	0.8 (0.2 to 1.4)	.01
Clonazepam	29 (0.7) [0.5 to 1.0]	53 (1.1) [0.8 to 1.5]	0.4 (−0.04 to 0.8)	.07
Lorazepam	33 (0.9) [0.5 to 1.5]	39 (1.0) [0.7 to 1.5]	0.1 (−0.5 to 0.7)	.72
Analgesics	286 (6.2) [5.4 to 7.1]	404 (7.4) [6.3 to 8.6]	1.1 (−0.3 to 2.6)	.12
Hydrocodone	124 (2.8) [2.3 to 3.3]	191 (3.7) [2.9 to 4.6]	0.9 (−0.05 to 1.8)	.06
Tramadol[d]	38 (0.8) [0.5 to 1.2]	89 (1.7) [1.3 to 2.2]	0.9 (0.3 to 1.5)	.003
Ibuprofen	83 (1.6) [1.3 to 2.1]	96 (1.4) [1.0 to 2.0]	−0.2 (−0.9 to 0.4)	.52
Cyclobenzaprine	35 (0.8) [0.6 to 1.2]	71 (1.3) [1.0 to 1.8]	0.5 (0.05 to 1.0)	.03
Gastrointestinal agents[e]	267 (5.4) [4.6 to 6.4]	500 (9.5) [8.3 to 10.9]	4.1 (2.5 to 5.7)	<.001
Omeprazole	87 (1.7) [1.2 to 2.4]	305 (5.5) [4.6 to 6.7]	3.8 (2.7 to 5.0)	<.001
Ranitidine	64 (1.3) [0.9 to 1.8]	82 (1.7) [1.3 to 2.2]	0.4 (−0.2 to 1.1)	.21
Esomeprazole	102 (2.2) [1.6 to 3.0]	72 (1.5) [1.1 to 2.0]	−0.7 (−1.5 to 0.1)	.10
Famotidine	17 (0.4) [0.2 to 0.7]	37 (0.7) [0.5 to 1.0]	0.3 (−0.02 to 0.7)	.07
Respiratory agents[f]	90 (2.8) [2.3 to 3.5]	101 (2.3) [1.8 to 2.9]	−0.5 (−1.3 to 0.3)	.19
Montelukast[d]	41 (1.2) [0.9 to 1.8]	70 (1.6) [1.2 to 2.1]	0.4 (−0.3 to 1.0)	.26
Cetirizine	52 (1.7) [1.4 to 2.2]	31 (0.7) [0.4 to 1.3]	−1.0 (−1.6 to −0.4)	.001
Anticonvulsants[g]	198 (4.7) [3.9 to 5.6]	397 (7.7) [6.8 to 8.7]	3.0 (1.7 to 4.3)	<.001
Gabapentin[d]	45 (1.0) [0.7 to 1.5]	144 (2.4) [1.8 to 3.0]	1.3 (0.6 to 2.0)	.001
Diazepam[d]	12 (0.2) [0.01 to 0.5]	26 (0.7) [0.3 to 1.2]	0.4 (0.002 to 0.9)	.05
Lamotrigine[d]	9 (0.3) [0.2 to 0.5]	27 (0.7) [0.4 to 1.0]	0.3 (0.01 to 0.6)	.04
Topiramate	19 (0.6) [0.3 to 1.0]	28 (0.6) [0.4 to 1.1]	0.06 (−0.4 to 0.5)	.78
Corticosteroids	77 (1.6) [1.1 to 2.3]	92 (1.5) [1.2 to 2.0]	−0.1 (−0.8 to 0.6)	.80

[a] Data from the National Health and Nutrition Examination Survey, expressed as unweighted number of participants and weighted percentages and 95% CIs, weighted to be nationally representative, and based on most commonly used medications with depression as an adverse effect in 2013 and 2014.

[b] *P* value for difference in prevalence between cycle years 2005 and 2006 and 2013 and 2014 are based on a Wald test using design-based estimates of variance.

[c] Antihypertensives include: antihypertensive combinations, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, calcium channel blockers, and diuretics.

[d] Medication with a suicidal symptom adverse effect.

[e] Gastrointestinal agents include: proton pump inhibitors and H2 antagonists.

[f] Respiratory agents include: antihistamines and leukotriene modifiers.

[g] Clonazepam and lorazepam also listed under most commonly used anticonvulsants.

Table 3. Association Between Use of Prescription Medications With Depression as a Potential Adverse Effect and Depression Among US Adults, 2005-2014[a]

		Estimated Prevalence of Depression (PHQ-9 Score ≥10)			
			% (95% CI)[c]		
	No. of Participants[b]	Unadjusted, No. (%) [95% CI][b]	Adjusted	Adjusted Difference	*P* Value[d]
Overall	23 561	1658 (5.8) [5.3 to 6.3]	5.7 (5.2 to 6.2)	NA	
No. of Medications With Depression Adverse Effect					
0	17 039	984 (4.7) [4.2 to 5.2]	4.7 (4.1 to 5.2)	[Reference]	
1	4394	358 (6.4) [5.4 to 7.5]	6.9 (5.7 to 8.1)	2.2 (0.8 to 3.6)	.002
2	1418	176 (10.4) [8.6 to 12.4]	9.5 (7.6 to 11.5)	4.9 (2.8 to 6.9)	<.001
3 or more	710	140 (19.2) [15.7 to 23.2]	15.3 (12.0 to 18.6)	10.7 (7.2 to 14.1)	<.001
No. of Medications Without Depression Adverse Effect					
0	13 288	843 (5.2) [4.7 to 5.8]	5.5 (4.7 to 6.3)	[Reference]	
1	3613	255 (6.2) [5.3 to 7.3]	6.6 (5.5 to 7.7)	1.1 (−0.3 to 2.5)	.11
2	2171	143 (4.9) [3.8 to 6.1]	5.1 (3.8 to 6.5)	−0.3 (−1.9 to 1.3)	.67
3 or more	4489	417 (7.7) [6.8 to 8.7]	6.0 (4.8 to 7.3)	0.6 (−1.2 to 2.3)	.52

Abbreviations: NA, not applicable; PHQ-9, Patient Health Questionnaire 9.

[a] Analyses excludes antidepressant users. Data are from National Health and Nutrition Examination Survey.

[b] Data are expressed as unweighted number of participants and weighted percentage and 95% CI, weighted to be nationally representative.

[c] The adjusted model includes survey cycle, number of medications with depression as a potential adverse effect, number of medications without depression adverse effects, long-term (≥365 d) use of medications with depression as an adverse effects, long-term (≥365 d) use of medications without depression as an adverse effect, sex, age group, race/ethnicity, marital status, employment status, educational achievement, ratio of family income to the US federal poverty level, body mass index, and number of chronic conditions.

[d] *P* values are based on a Wald test of the predictive margin calculated by averaging differences in predicted prevalence (on the logit scale) using a design-based estimate of variance.

(zolpidem, clonazepam, lorazepam); and montelukast, a leukotriene modifier, did not significantly change. Among women, several ethinyl estradiol hormonal contraceptives and estradiol hormone replacement therapy (HRT) were commonly used but did not significantly change during the study period.

The estimated prevalence of depression increased from 6.9% for patients taking 1 to 15.3% for patients taking 3 or more medications that have depression and a potential adverse effect vs 4.7% for patients not using such medications (**Table 3**). Concurrent use of medications that do not have depression as a potential adverse effect was not associated with concurrent depression; the estimated prevalence of depression was similar among adults using 0 or 3 or more medications without depression as an adverse effect. Corresponding estimates for all sociodemographic and health variables included in the model are included in eTable 1 in the Supplement.

Similar associations were observed among adults concurrently using medications that have suicidal symptoms as potential adverse effects (eFigure in the Supplement). Compared with adults not using medications that have suicidal symptoms as potential adverse effects (5.3% [95% CI, 4.8%-5.7%]), those using 1 (8.3% [95% CI, 6.6%-10.1%]), 2 (12.2% [95% CI, 8.1%-16.4%]), or 3 or more (17.8% [95% CI, 6.9%-28.7%]) medications that have suicidal symptoms as potential adverse effects were significantly more likely to report concurrent depression (difference, 3.1% [95% CI, 1.3%-4.8%] for 1 medication, 7.0% [95% CI, 2.9%-11.1%] for 2 medications, and 12.5% [95% CI, 1.7%-23.4%] for ≥3 medications). The inclusion of suicidal symptoms as adverse effects in the fully adjusted model slightly attenuated the observed associations between concurrent use of medications that have depression as a potential adverse effect and depression. Therefore, the interaction between the use of medications that have depression as an adverse effect and the use of medications that have suicidal symptoms as an adverse effect was examined. The interaction term, however, was not significant ($P = .72$), which indicates that the concurrent use of medications that have depression as an adverse effect with or without suicidal symptoms was independently associated with a greater likelihood of concurrent depression.

Most of these combinations involved the β-blockers metoprolol or atenolol, the proton pump inhibitor omeprazole, the narcotic hydrocodone, or the anticonvulsant gabapentin (eTable 2 in the Supplement). The estimated prevalence of concurrent depression among adults who used these medication combinations ranged from 15.8% (95% CI, 2.7%-55.6%) for finasteride and omeprazole to 60.9% (95% CI, 35.8%-81.4%) for gabapentin and cyclobenzaprine.

The independent association between use of medications with depression as a potential adverse effect and concurrent depression persisted in sensitivity analyses. In restricted analyses excluding adults using psychotropic medications, adults who were concurrently using 3 or more medications that have the potential of depression as an adverse effect were more likely to report concurrent depression (8.5% [95% CI, 5.0%-12.0%]) compared with adults not using any of them (4.5% [95% CI, 4.0%-5.0%]) (eTable 3 in the Supplement). Adults with hypertension using 3 or more medications that have depression as a potential adverse effect were also significantly more likely to report depression than were adults with hypertension who were not using these medications (eTable 4 in the Supplement), even after excluding psychotropic users (eTable 5 in the Supplement). The results per-

Table 4. Association Between Use of Prescription Medications With Potential Depression Adverse Effects and Depression Among US Adults Treated With Antidepressants, 2005-2014

		Estimated Prevalence of Depression (PHQ-9 Score ≥10)[a]			
			% (95% CI)[b]		
	No. of Participants[a]	Unadjusted, No. (%) [95% CI][a]	Adjusted	Adjusted Difference	*P* Value[c]
Overall	2631	660 (20.7) [18.8 to 22.8]	20.7 (18.7 to 22.8)	NA	
No. of Medications With Depression Adverse Effects[d]					
0	772	115 (12.2) [10.0 to 14.9]	14.2 (11.6 to 16.8)	[Reference]	
1	782	156 (16.9) [13.8 to 34.3]	17.9 (14.5 to 21.4)	3.8 (−0.04 to 7.6)	.05
2	507	157 (29.0) [24.2 to 34.3]	27.5 (22.5 to 32.6)	13.3 (7.6 to 19.0)	<.001
≥3	570	232 (34.0) [29.4 to 38.9]	28.2 (23.5 to 32.9)	14.0 (8.5 to 19.6)	<.001
No. of Medications Without Depression Adverse Effects					
0	549	97 (14.1) [11.3 to 17.5]	20.2 (15.7 to 24.6)	[Reference]	
1	462	106 (21.5) [17.5 to 26.3]	25.5 (20.8 to 30.2)	5.4 (0.02 to 10.7)	.05
2	441	113 (20.1) [16.9 to 23.9]	20.0 (16.8 to 23.2)	−0.1 (−5.4 to 5.1)	.96
≥3	1179	344 (25.0) [21.9 to 28.3]	19.3 (16.2 to 22.3)	−0.9 (−6.6 to 4.8)	.76

Abbreviation: PHQ-9, Patient Health Questionnaire-9

[a] Data, from the National Health and Nutrition Examination Survey, are expressed as unweighted number of participants and weighted percentage and 95% CIs, weighted to be nationally representative.

[b] Adjusted model includes survey cycle, number of medications with depression as an adverse effect, number of medications without depression as an adverse effects, long-term (≥365days) use of medications with depression as an adverse effect, long-term (≥365days) use of medications without depression an adverse effect, sex, age group, race/ethnicity, marital status, employment status, educational achievement, ratio of family income to the US federal poverty level, body mass index, and number of chronic conditions.

[c] *P* values are based on a Wald test of the predictive margin calculated by averaging differences in predicted prevalence (on the logit scale) using a design-based estimate of variance.

[d] Excludes number of antidepressants.

sisted after controlling for illicit drug use (eTable 6 in the Supplement) and with suicidal ideation as the outcome (eTable 7 in the Supplement).

Compared with adults taking antidepressants but not taking additional medications that have depression as a potential adverse effect, those taking 1 or more medications with depression as an adverse effect were more likely to report depressive symptoms (**Table 4**). In contrast, use of multiple medications without depression as an adverse effect was not associated with a greater likelihood of concurrent depression. These associations were also observed among adults with hypertension (eFigure in the Supplement) and persisted after excluding users of other psychotropic medications (eTable 8 in Supplement), after controlling for illicit drug use (eTable 9 in the Supplement) and with suicidal ideation as the outcome (eTable 10 in the Supplement).

Discussion

In this cross-sectional survey study, reported use of prescription medications that have depression as adverse effects was common. Use of multiple prescription medications with these potential effects was associated with greater likelihood of concurrent depression. These findings persisted in analyses restricted to adults with hypertension and after excluding users of any psychotropic medications. The results suggest that physicians should consider discussing these associations with their patients who are prescribed medications that have depression as a potential adverse effect.

Adults in the United States reported use of more than 200 medications that have been associated with depression or suicidal symptoms as adverse effects. With the exception of antidepressants, the only drug class with a black-box warning for suicidal risk,[24] the most commonly used medications that have depression as a potential adverse effect were antihypertensives, proton pump inhibitors, analgesics, and hormonal contraceptives. A great majority of medication combinations with depression as a potential adverse effect involved β-blockers and proton pump inhibitors. Some of these medications, including proton pump inhibitors and the emergency contraceptive levonorgestrel, are also available over the counter,[25] and product labeling for over-the-counter medications does not include comprehensive information on adverse effects including depression. Many patients may therefore not be aware of the greater likelihood of concurrent depression associated with these commonly used medications.

The likelihood of concurrent depression was most pronounced among adults concurrently using 3 or more medications with depression as a potential adverse effect, including among adults treated with antidepressants. This association, which persisted after excluding users of psychotropic medications, is broadly consistent with evidence from some previous pharmacoepidemiological studies of specific medication classes. For example, a recent cross-sectional analysis of older adults reported that treatment with proton pump inhibitors was associated with an adjusted odds ratio of 2.38 for depression.[26] A large prospective cohort study found that as compared with women who had never used hormonal contraceptives, users of combined oral contraceptives had an incidence rate ratio of 1.7 of starting antidepressants.[4] Establishing any etiological role of these medications with depression as a potential adverse effect in the onset or maintenance of depression requires prospective research.

The link between polypharmacy and concurrent depression appears to be limited to medications with depression as a potential adverse effect. The lack of an association between the number of medications without depression as an adverse effect and depression underscores the specificity of the association between medications that have depression as a potential adverse effect and concurrent depression. Further support for this linkage is provided by an association between medications that have depression as a potential adverse effect and depression among people with hypertension who were not using psychotropic medications.

The US Preventive Services Task Force (USPSTF) recently recommended screening adults for depression and providing adequate services for follow-up treatment.[27] Commonly used depression screening instruments, however, do not incorporate evaluations of prescribed medications that have depression as a potential adverse effect.[17,28,29] Longitudinal studies are warranted that examine whether provision of information about medications that have been associated with depression as a potential adverse effect will decrease the subsequent incidence of depression.

Limitations

This study had several limitations. First, because NHANES is cross-sectional in design, medication use and depressive symptoms cannot be temporally ordered, therefore precluding causal inference. Second, Micromedex software was used to identify medications with adverse effects of depression. This software may exclude some medications with this risk. For example, Micromedex does not include all calcium channel blockers, although there is some evidence these drugs are associated with depression risks.[5,9,30] Third, NHANES data only capture information on prescription medications. However, many prescription medications are also available over the counter, including those identified as having potential adverse effects of depression. The results may therefore underestimate the true prevalence of the use of medications that have depression as a potential adverse effect. Fourth, the NHANES does not provide a means of adjusting for a history of depression, which might confound associations between use of medications with depression as a potential adverse effect and concurrent depression. Lifetime and 12-month estimates of major depressive disorder in the adult US population are 13.23% and 5.28%, respectively.[31] In addition, the analyses did not control for impaired hepatic or kidney function, substance use disorders, or several other potential confounders that may predispose some individuals to receive these medications and report concurrent depressive symptoms.

Conclusions

In this cross-sectional survey study, reported use of prescription medications that have depression as a potential adverse effect was common. Use of multiple medications was associated with greater likelihood of concurrent depression.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Qato, Olfson.
Statistical analysis: All authors.
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