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Use of Selective-Serotonin Reuptake Inhibitors and Platelet Aggregation Inhibitors Among Individuals with Co-Occurring Atherosclerotic Cardiovascular Disease and Depression or Anxiety

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Abstract

Objective: Medications commonly used to treat heart disease, anxiety, and depression can interact resulting in an increased risk of bleeding, warranting a cautious approach in medical decision making. This retrospective, descriptive study examined the prevalence and the factors associated with the use of both selective-serotonin reuptake inhibitor and platelet aggregation inhibitor among individuals with co-occurring atherosclerotic cardiovascular disease and anxiety or depression.

Methods: Respondents aged 22 years and older, alive throughout the study period, and diagnosed with co-occurring atherosclerotic cardiovascular disease and anxiety or depression (n = 1507) in years 2007 through 2013 of the Medical Expenditures Panel Survey were included. The use of treatment was grouped as follows: selective-serotonin reuptake inhibitor and platelet aggregation inhibitor, selective-serotonin reuptake inhibitor or platelet aggregation inhibitor, and neither selective-serotonin reuptake inhibitor nor platelet aggregation inhibitor.

Results: Overall, 16.5% used both selective-serotonin reuptake inhibitor and platelet aggregation inhibitor, 61.2% used selective-serotonin reuptake inhibitor or platelet aggregation inhibitor, and 22.3% used neither selective-serotonin reuptake inhibitor nor platelet aggregation inhibitor. Respondents aged over 65 years (adjusted odds ratio = 1.93 (95% confidence interval = 1.08–3.45)) and having a diagnosis of diabetes (adjusted odds ratio = 1.63 (95% confidence interval = 1.15–2.31)) and hypertension (adjusted odds ratio = 1.84 (95% confidence interval = 1.04–3.27)) were more likely to be prescribed the combination.

Conclusion: The drug interaction was prevalent in patients who are already at higher risk of health disparities and worse outcomes thus requiring vigilant evaluation.

Keywords

Pharmacoepidemiology/drug safety, survey research, drug interaction

Background

Anxiety and depression are highly prevalent in individuals with heart disease.[1–3] Anxiety disorders are the most common mental illnesses in the United States with 31% estimated lifetime prevalence.[4] An estimated 6.7% of adults experienced an episode of depression, a potentially debilitating mental illness, in a typical 12-month period.[5] Among individuals with coronary heart disease, 36% were found to have anxiety disorder.[2] The 12-month prevalence of major depression was estimated at 9.3% for patients with coronary heart disease.[6]

Platelet aggregation inhibitors (PAIs) are a cornerstone of treatment for atherosclerotic cardiovascular disease (ASCVD) including secondary prevention and risk reduction for coronary artery disease (CAD),[7] peripheral artery disease (PAD),[8]

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and acute coronary syndromes (ACS) with percutaneous coronary intervention (PCI)[9] or coronary artery bypass graft (CABG).[10] Adverse effects of PAIs can include major or minor bleeding, gastrointestinal bleeding, hematoma, and less frequently, hemorrhagic stroke.[11,12] PAI are also used for secondary prevention and risk reduction for CADs.[9,13]

Selective-serotonin reuptake inhibitors (SSRIs) are first-line therapy for anxiety disorders including generalized anxiety disorder, post-traumatic stress disorder,[14] obsessive-compulsive disorder,[15] and panic disorders.[16] SSRIs are also potential first-line therapies for mild, moderate, or severe major depressive disorder (MDD). The evidence for depression treatment affecting cardiovascular outcomes is the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study which had a post hoc finding that a subset of patients receiving an SSRI had better outcomes.[17]

Among patients with ASCVD and depression or anxiety, some patients may be treated with an SSRI and a PAI. When these medications are given in combination, platelet aggregation may be impaired and the risk of bleeding events can be increased.[18,19] These events include stomach bleeding, bruising, nose bleeding, and other serious internal or external bleeding. This interaction has been assessed in non-US populations to show that SSRIs increased the risk of lower gastrointestinal bleeds (distal to the ligament of Treitz),[20] and the combined use of a PAI with an SSRI is associated with an increased risk of bleeding.[21] Therefore, it is important to monitor individuals with this medication combination. However, the extent to which SSRI/PAI combination occurs in real-world practice settings is not known. Furthermore, no study has assessed subgroup differences in SSRI/PAI combination use among adults with co-occurring ASCVD and anxiety or depression in the United States. Therefore, the primary objective of this study was to estimate the prevalence of SSRI/PAI combination among adults with co-occurring ASCVD and anxiety or depression. The secondary objective was to analyze subgroup differences in individuals using SSRI/PAI combination compared to those who received either SSRI or PAI.

Conceptual framework

Factors associated with SSRI/PAI use categories were guided by the Andersen expanded behavioral model for use of health services.[22] This model states that healthcare treatments are affected by (1) an individual's predisposing factors, (2) the factors which enable individuals to receive services, (3) the individual's level of need for the healthcare services, (4) personal health practices, and (5) the external healthcare environment. In this study, predisposing factors consisted of gender, race, and age; enabling factors included education, poverty status as a percentage of the federal poverty line (FPL), health insurance coverage, and prescription drug coverage; and need factors were perceived physical and mental health of the individuals as well as presence of diabetes or hypertension. Personal health practices included obesity measured with body mass index (BMI), exercise frequency, and smoking status. The external healthcare environment was represented by geographic region.

Methods

Study design

This is a retrospective, cross-sectional study designed to analyze patterns of SSRI/PAI combination use among adults with co-occurring ASCVD and anxiety or depression. In this study, ASCVD included ACS, history of myocardial infarction, angina (stable or unstable), arterial revascularization, or peripheral arterial disease related to atherosclerosis.[23]

Data source

This study used the Medical Expenditures Panel Survey (MEPS), a publicly available, nationally representative (of the civilian, non-institutionalized population) set of surveys.[24] MEPS data are released in full-year consolidated household files, medical conditions, prescription drug events, and others. Full-year consolidated household files contain individual-level data on demographics, healthcare expenditures, healthcare use, sources of payments, and health insurance coverage. The Medical Conditions files contain information on conditions taken from respondents which were coded to International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) codes by professional coders then were converted by Agency for Healthcare Research and Quality (AHRQ) to clinical classification codes. The information in the Prescribed Medicines files are at the event-level, and each record is a unique prescribed medicine including national drug code (NDC), medicine name, and any conditions reported with the prescription processing. NDCs were mapped to a therapeutic class based on Multum Lexicon therapeutic classification system and were made available to the researchers in the MEPS.[25]

Analytical sample

Individuals aged 22 years or older, alive during the calendar year, had co-occurring ASCVD and anxiety or depression were included in the sample for the analysis. ASCVD was identified using three-digit ICD-9-CM codes from the medical conditions files of the MEPS. We restricted the analysis to those with ASCVD because PAIs are used in these conditions. ASCVD were identified using the following ICD-9-CM codes as has been done in the previous research:[26–29] 410.x, 411.x, 412.x, 413.x, 414.x, 429.x, 440.x, and 443.x. Anxiety was defined with clinical classification code 651 and mood disorders were determined with clinical classification code 657. The analytical sample consisted of 1,507 unique individuals (Figure 1).
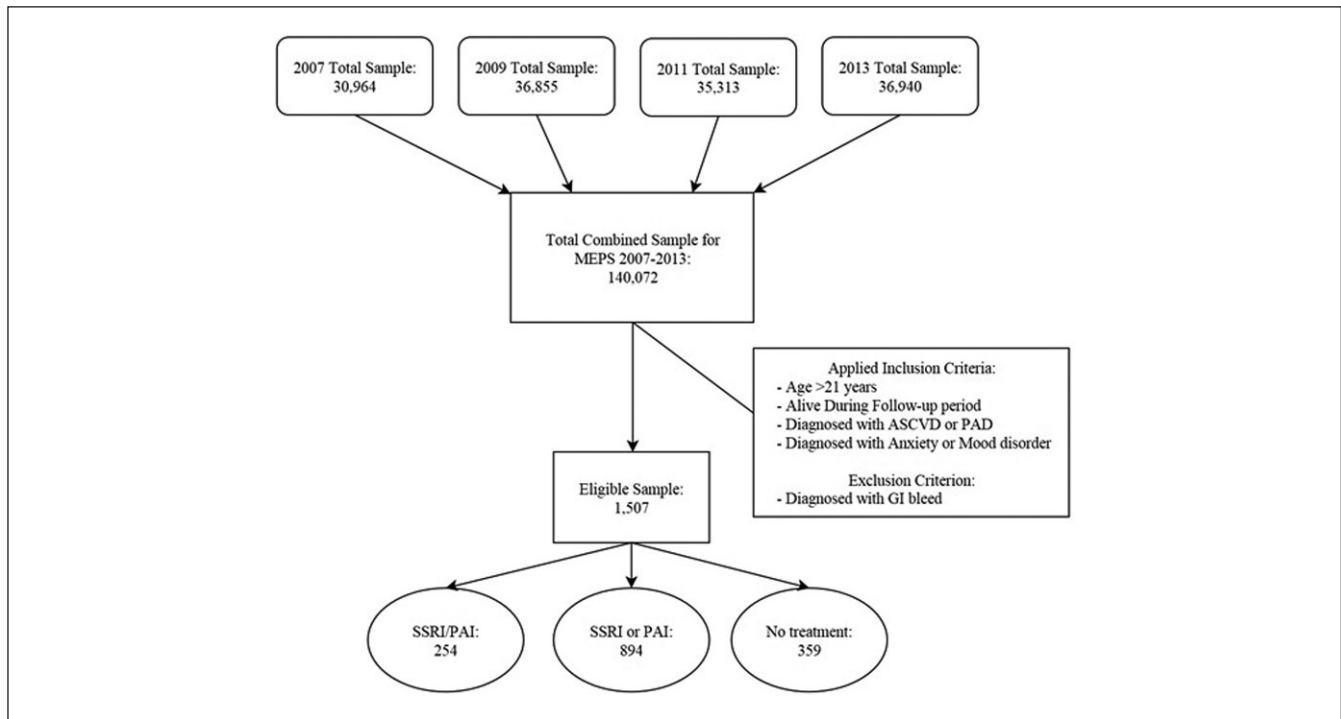
Figure 1. Final study sample: inclusion and exclusion criteria of the Medical Expenditures Panel Survey, 2007, 2009, 2011, and 2013.
MEPS: Medical Expenditures Panel Survey; ASCVD: atherosclerotic cardiovascular disease; PAD: peripheral arterial disease; GI: gastrointestinal; SSRI: selective-serotonin reuptake inhibitors; PAI: platelet aggregation inhibitors.

Measures

Dependent variable

SSRIs and PAIs were identified using the event-level data from the prescription drug files and were aggregated at the person-level. Multum-lexicon therapeutic class code of 208 represented SSRIs. Medications in this class included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. PAIs were identified with code 211. Medications in this category include prescription, oral agents: clopidogrel, cilostazol, prasugrel, ticagrelor, and ticlopidine. SSRI and PAI use was combined to yield the following three categories: (1) SSRI and PAI, (2) SSRI or PAI, and (3) no SSRI and no PAI.

Independent variables

The independent variables were as follows: gender (male and female); race (White, African American, and other minorities); age in years (22–49, 50–64, and ≥65); education (less than high school, high school, and more than high school); poverty status (poor, near poor, middle income, and high income); insurance coverage (private, public, and uninsured); prescription drug coverage (yes, and no); perceived physical health (excellent/very good, good, and fair/poor); perceived mental health (excellent/very good, good, and fair/poor); diagnosis of diabetes (diabetes and no diabetes); diagnosis of hypertension (hypertension and no hypertension); obesity (underweight/normal, overweight, and obese); exercise frequency (at least three times per week and less than three times per week); smoking status (current smoker, former and non-smoker); and region (northeast, mid-west, south, and west). There were 19 individuals who had missing data on obesity and 89 individuals had missing data on smoking status. For these individuals, we created missing indicators and these were included in the regression analyses.

Whites and African Americans were identified in the race variable and Hispanics were identified in the ethnicity variable. These were combined to Whites, African Americans, Hispanic, and other minorities. However, due to low cell counts in other minorities, Hispanic and other minorities were combined. Region categories were based on the census region at the beginning of the survey period.

Statistical analysis

Unadjusted group differences in SSRI and PAI use categories were tested with chi-square statistics. As the SSRI and PAI use consisted of three treatment categories, multinomial logistic regression was used to analyze patterns of SSRI and PAI use. The reference group for the dependent variable was "SSRI or PAI" use. The reference group was chosen because that is the condition where the SSRI and PAI interaction would not occur, and the group receiving neither therapy is being potentially undertreated. The independent variables with corresponding

Table 1. Characteristics of adults with co-occurring atherosclerotic cardiovascular disease and depression or anxiety: Medical Expenditures Panel Survey, 2007, 2009, 2011, and 2013.

All	N = 1507	Wt.%
Predisposing factors		
Gender		
Female	907	59.2
Male	600	40.8
Race/ethnicity		
White	957	80.3
African American	240	8.0
Others	310	11.7
Age (years)		
22–49	223	13.9
50–64	586	37.0
≥65	698	49.2
Enabling factors		
Education level		
Less than high school	473	24.4
High school graduate	521	36.9
Greater than high school	506	38.7
Poverty status		
Poor (<100% of FPL)	433	20.9
Near poor (100%–199% FPL)	427	27.3
Middle income (200%–399% FPL)	380	27.5
High income (400% or greater FPL)	267	24.2
Insurance coverage		
Private	639	51.7
Public	778	44.0
Uninsured	90	4.4
Prescription drug insurance		
Prescription coverage	795	57.9
No prescription coverage	712	42.1
Need factors		
Perceived physical health		
Excellent or very good	206	16.3
Good	404	29.8
Fair or poor	897	53.9
Perceived mental health		
Excellent or very good	384	29.7
Good	552	37.4
Fair poor	571	33.0
Diabetes		
Diabetes	623	37.6
No diabetes	883	62.4
Hypertension		
Hypertension	1262	82.6
No hypertension	245	17.4
Personal health practices		
Body mass index categories		
Under weight or normal	326	24.4
Overweight	474	30.8
Obese	688	43.8
Exercise frequency		
Three or more times per week	409	28.6
Less than three times per week	1090	71.0

Table 1. (Continued)

All	N = 1507	Wt.%
Smoking status+		
Current smoker	360	24.0
Former or non-smoker	1058	70.1
External healthcare environment		
Region		
Northeast	250	17.7
Midwest	341	24.1
South	627	39.7
West	289	18.4

FPL: Federal Poverty Line; Wt.: weighted.
Based on adults aged 22 years and older with atherosclerotic cardiovascular disease and either depression or anxiety and without gastrointestinal bleeding disorders during 2007, 2009, 2011, and 2013.

reference groups are shown in Table 3. For each of the independent variables, adjusted odds ratios (AORs), 95% confidence intervals (CIs), and significance levels from the multinomial regression are reported. All analyses were conducted considering the complex survey design of MEPS and using Statistical Analysis Software (SAS®) version 9.4.

We also conducted secondary analyses in which we included all patients on antidepressants that were not SSRIs and a PAI as a separate group. It was analyzed using a multinomial logistic regression, so that SSRI/PAI could be compared to non-SSRI antidepressants plus PAI. There were no significant differences between these groups; therefore, we do not present these results in this article.

Results

Sample description

Table 1 presents the weighted percent of the characteristics of the study sample that included individuals with co-occurring ASCVD and anxiety or depression. The majority of the sample included female (59.2%), Whites (80.3%), and high school graduates (75.6%). Nearly 50% were aged 65 years or older. Chronic conditions such as obesity (43.8%), diabetes (37.6%), and hypertension (82.6%) were also prevalent. Diabetes was diagnosed in our sample more frequently than the national average of 9.3%.[30] An overwhelming majority (82.6%) had hypertension, and the percentage of current smokers (24.0%) was higher than the national average of 19% in 2011[31] and 16.8% in 2014.[32]

Description of the sample by SSRI/PAI treatment categories

Overall, 16.5% used SSRI/PAI combination, 61.2% used either SSRI or PAI, and 22.3% used neither SSRI nor PAI. There were statistically significant differences in SSRI/PAI

treatment categories by race/ethnicity (p<0.001), age (p=0.009), insurance coverage (p=0.014), diabetes diagnosis (p<0.001), and hypertension diagnosis (p=0.001). Full group differences can be seen in Table 2. A higher percentage of adults with diabetes (21.6%) used SSRI/PAI combination compared to adults without diabetes (13.4%).

Multinomial logistic regression on SSRI/PAI treatment categories

AORs, 95% CIs, and significance levels from multinomial logistic regression on SSRI and PAI use categories for each of the independent variable are presented in Table 3. SSRI and PAI use was more likely among older adults (age>65 years) (AOR=1.93 (95% CI=1.08–3.45)), those with diabetes (AOR=1.63 (95% CI=1.15–2.31)), and those with hypertension (AOR=1.84 (95% CI=1.04–3.27)) than among younger adults, those without diabetes, and those without hypertension.

Discussion

This study sets out to examine the combined use of SSRI and PAI among adults with co-occurring ASCVD and anxiety or depression. According to the practice guidelines, SSRIs can be a reasonable first option for treating anxiety and depression. PAIs are considered a cornerstone of pharmacotherapy for many types of ASCVD. Although the mechanism is not clear, many studies have shown that combined use of SSRI and PAI is associated with an increased risk of bleeding events.[21,33] Therefore, we considered the combined SSRI and PAI use as treatment to be used with caution and one which requires closer monitoring and follow-up to reduce the risk of adverse consequences.

Our study found that one in six adults aged 22 years and older with co-occurring ASCVD and anxiety or depression used SSRI and PAI in combination. Given the bleeding risk reported by previous studies,[20,21] our findings suggest that alternatives to SSRIs need to be considered. However, all antidepressants are not equal in their potential impact on cardiovascular adverse events. Selective serotonin reuptake inhibitors are generally considered safer than tricyclic antidepressants.[34] Psychotherapy is another alternative that has been effectively used to treat depression after an acute myocardial infarction,[35] but psychotherapy is not widely used because of its limited availability and affordability. For example, only 2.8% of a sample from a previous MEPS study used psychotherapy in 2007 for treatment of depression.[36] Lack of available mental health services was identified as a barrier to psychotherapy use by 21.6% of a surveyed sample of patients.[37] In a 2009 survey of mental health services use, 46% indicated that cost was the reason for not receiving mental health services.[38] Therefore, the physicians may need to individualize the treatment based on the benefits and risks of SSRI/PAI combination use and the patient's financial situation.

The use of the SSRI/PAI combination was more likely among older adults (>65 years) in both the unadjusted and adjusted analyses. Increased age has a marked effect on platelet function and mental health conditions including depression and anxiety. Platelet function decreases with age thus leading to an increased risk of thrombotic diseases.[39] Additionally, elderly adults tend to be more reluctant to report symptoms of depression thus present with more severe disease requiring pharmacological intervention.[40] Choosing a treatment for ASCVD and depression or anxiety in elderly patients need to be done with caution and take into account their higher risk of thrombotic events.

In our study sample of adults with ASCVD and co-occurring anxiety of depression, there was a high prevalence of diabetes and/or hypertension and these individuals were more likely to use SSRI and PAI in combination. Patients with multiple chronic conditions or multimorbidity have complex medical needs[41] in which prescribed medications which could interact and this also affects quality of life, work productivity, employability, and mortality.[42] It is worth noting that in our study, a special type of multimorbidity, the presence of both chronic physical and mental health conditions, was also highly prevalent.[41] This combination is important because mental health conditions such as depression can produce the greatest burden compared to multimorbidity in chronic conditions without depression.[43] In the United States, the strategic framework for improving health outcomes and quality of life among those with multimorbidity calls for special attention to the presence of both chronic physical and mental health conditions.[44] Therefore, our findings highlight the need for a team-based approach with physicians, mental health specialists, pharmacists, and case managers who can provide support for prescription monitoring, patient awareness, and education.

The significant association with diabetes diagnosis and combined use of SSRI/PAI is important for two reasons: (1) patients with diabetes already have increased risk for bleeding relating to peptic ulceration[45] and (2) low potency PAI (e.g. aspirin and clopidogrel) may be less effective in these patients thus requiring more potent agents (e.g. prasugrel and ticagrelor).[46] Patients with multimorbidity (at minimum ASCVD, diabetes, and anxiety or depression) are now at a potentially greater risk for adverse effects associated with the medication combination and may not be able to identify which medications are the offending agents. The prescriber now needs to balance the harms and benefits of adding more potent PAIs to the regimen for patients with diabetes and ASCVD. Another chronic disease, hypertension, did have a significant association with treatment choice and was highly prevalent. This association could also result from heart disease having treatments that overlap with hypertension treatment (e.g. beta-blockers or angiotensin-converting-enzyme inhibitors).

Strengths of this study include that it is based on physiologic and conceptual frameworks that attempted to address an

Table 2. SSRI and PAI use among adults with co-occurring atherosclerotic cardiovascular disease and depression or anxiety: Medical Expenditures Panel Survey, 2007, 2009, 2011, and 2013.

	SSRI and PAI		SSRI or PAI		No SSRI and no PAI		
	N	Wt.%	N	Wt.%	N	Wt.%	Sig.
All	254	16.5	894	61.2	359	22.3	–
Predisposing factors							
Gender							
Female	150	16.1	539	61.8	218	22.2	
Men	104	17.0	355	60.4	141	22.6	
Race/ethnicity							***
White	154	15.7	596	63.1	207	21.3	
African American	32	13.8	136	53.3	72	32.9	
Others	68	23.8	162	53.8	80	22.4	
Age (years)							**
22–49	21	8.9	133	61.7	69	29.4	
50–64	99	16.6	365	64.5	122	18.9	
65	134	18.5	396	58.6	168	23.0	
Enabling factors							
Education level							
Less than high school	95	19.2	265	57.3	113	23.5	
High school graduate	90	16.8	308	61.7	123	21.5	
Greater than high school	67	14.3	317	63.1	122	22.6	
Poverty level							
Poor (<100% of FPL)	76	16.9	248	58.8	109	24.4	
Near poor (100%–199% FPL)	68	16.4	250	59.8	109	23.8	
Middle income (200%–399% FPL)	63	14.8	225	61.5	92	23.7	
High income (400% or greater FPL)	47	18.0	171	64.6	49	17.4	
Insurance coverage							*
Private	103	15.5	391	63.3	145	21.2	
Public	141	18.0	463	60.0	174	22.0	
Uninsured	10	12.0	40	48.6	40	39.4	
Prescription drug insurance							
Prescription coverage	134	15.8	495	63.7	166	20.5	
No prescription coverage	120	17.3	399	57.7	193	24.9	
Need factors							
Perceived physical health							
Excellent or very good	28	15.3	112	54.7	66	30.0	
Good	69	16.1	246	63.9	89	19.9	
Fair or poor	157	17.0	536	61.7	204	21.4	
Perceived mental health							
Excellent or very good	58	16.3	227	59.0	99	24.6	
Good	97	16.4	313	61.1	142	22.5	
Fair poor	99	16.6	354	63.3	118	20.1	
Diabetes							***
Diabetes	134	21.6	380	61.7	109	16.7	
No diabetes	120	13.4	514	61.0	249	25.6	
Hypertension							**
Hypertension	229	18.0	752	61.1	281	20.8	
No hypertension	25	8.9	142	61.6	78	29.5	
Personal health practices							
Body mass index categories							
Underweight or normal	53	15.4	185	60.0	88	24.6	
Overweight	87	18.8	269	57.7	118	23.5	
Obese	110	15.3	429	64.1	149	20.6	

Table 2. (Continued)

	SSRI and PAI		SSRI or PAI		No SSRI and no PAI		
	N	Wt.%	N	Wt.%	N	Wt.%	Sig.
Exercise frequency							
Three times per week or more	72	17.6	238	61.0	99	21.4	
Less than three times per week	179	15.8	652	61.4	259	22.8	
Smoking status+							
Current smoker	60	17.4	233	64.8	67	17.8	
Former or non-smoker	180	16.3	614	60.1	264	23.5	
External healthcare environment							
Region							
Northeast	56	20.0	144	62.2	50	17.9	
Midwest	53	16.8	214	62.4	74	20.8	
South	92	14.1	373	62.1	162	23.7	
West	53	17.7	163	56.7	73	25.6	

FPL: Federal Poverty Line; PAI: platelet aggregation inhibitor; Sig.: significance; SSRI: selective-serotonin reuptake inhibitor; Wt.: weighted.
Based on adults aged 22 years and older with atherosclerotic cardiovascular disease and either depression or anxiety and without gastrointestinal bleeding disorders during 2007, 2009, 2011, and 2013. The percentage columns represent the weight row percentages for each group. Asterisks represent significant group differences SSRI PAI use based on chi-square tests. Missing categories smoking and body mass index categories not presented.
***p < 0.001, **0.001 ≤ p < 0.01; *0.01 ≤ p < 0.05.

Table 3. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) from multinomial logistic on SSRI PAI use with co-occurring atherosclerotic cardiovascular disease and depression or anxiety: Medical Expenditures Panel Survey, 2007, 2009, 2011, and 2013.

	SSRI and PAI		Sig.	No SSRI and no PAI		Sig.
	AOR	95% CI		AOR	95% CI	
Predisposing factors						
Gender						
Male						
Female	0.97	(0.69–1.36)		0.83	(0.59–1.17)	
Race/ethnicity						
White						
African American	0.95	(0.62–1.44)		1.88	(1.27–2.79)	**
Others	1.57	(0.98–2.53)		1.17	(0.75–1.83)	
Age (years)						
22–49						
50–64	1.65	(0.90–3.04)		0.66	(0.42–1.05)	
≥65	1.93	(1.08–3.45)	*	0.82	(0.54–1.25)	
Enabling factors						
Education level						
Less than high school	1.38	(0.91–2.11)		1.11	(0.75–1.65)	
High school	1.21	(0.79–1.84)		0.91	(0.63–1.31)	
Greater than high school						
Poverty status						
Poor	0.97	(0.55–1.71)		1.54	(0.89–2.67)	
Near poor	0.84	(0.50–1.42)		1.51	(0.95–2.38)	
Middle income	0.81	(0.49–1.35)		1.50	(0.95–2.37)	
High income						
Insurance coverage						
Uninsured						
Private	1.00	(0.40–2.52)		0.37	(0.21–0.68)	**
Public	1.07	(0.43–2.68)		0.33	(0.19–0.56)	***

Table 3. (Continued)

	SSRI and PAI		Sig.	No SSRI and no PAI		Sig.
	AOR	95% CI		AOR	95% CI	
Prescription drug insurance						
No drug coverage						
Drug coverage	0.92	(0.62–1.36)		0.76	(0.53–1.07)	
Need factors						
Perceived physical health						
Excellent and very good						
Good	0.91	(0.54–1.54)		0.58	(0.35–0.95)	*
Fair/poor	0.97	(0.58–1.63)		0.69	(0.43–1.10)	
Perceived mental health						
Excellent and very good						
Good	0.89	(0.54–1.48)		0.97	(0.65–1.44)	
Fair/poor	0.85	(0.52–1.38)		0.75	(0.48–1.18)	
Diabetes						
No diabetes						
Diabetes	1.63	(1.15–2.31)	**	0.66	(0.47–0.92)	*
Hypertension						
No hypertension						
Hypertension	1.84	(1.04–3.27)	*	0.76	(0.54–1.08)	
Personal health practices						
Body mass index categories						
Underweight/normal						
Overweight	1.15	(0.77–1.72)		0.89	(0.59–1.34)	
Obese	0.81	(0.54–1.23)		0.80	(0.54–1.18)	
Exercise frequency						
Three or more times per week						
No exercise	0.83	(0.56–1.23)		1.22	(0.85–1.75)	
Smoking status+						
Former or non-smoker						
Current smoker	1.12	(0.73–1.72)		0.63	(0.44–0.92)	*
External healthcare environment						
Region						
Northeast						
Midwest	0.95	(0.60–1.50)		1.09	(0.63–1.86)	
South	0.73	(0.45–1.17)		1.23	(0.77–1.99)	
West	0.99	(0.58–1.67)		1.38	(0.81–2.35)	

FPL: Federal Poverty Line; PAI: platelet aggregation inhibitor; Sig.: significance; SSRI: selective-serotonin reuptake inhibitor; Wt.: weighted.
Based on adults aged 22 years and older with atherosclerotic cardiovascular disease and either depression or anxiety and without gastrointestinal bleeding disorders during 2007, 2009, 2011, and 2013. Asterisks represent significant group differences SSRI PAI compared to the reference group based on multinomial logistic regression. Missing categories smoking and body mass index categories not presented.
***$p < 0.001$, **$0.001 < p < 0.01$; *$0.01 \leqslant p < 0.05$.

issue which occurs frequently when treating co-occurring ASCVD and anxiety or depression and it was performed in a real-world, nationally representative sample of the US population. Potential limitations to this study include that the Multum Lexicon used to identify PAI does not include over-the-counter aspirin, a commonly used medication in this class, but would include prescription aspirin. Long-term aspirin can be used to inhibit platelet aggregation. Additionally, the Multum Lexicon used to identify SSRI is exclusive to that class and does not include selective-norepinephrine reuptake

inhibitor (SNRI) medications. Finally, due to the cross-sectional study design, the timing of the different medications and disease states could not be assessed. Future research needs to explore the reasons for the combined use of SSRI and PAI and its utility in a clinical setting.

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Declaration of conflicting interests

Ethical approval

Ethical approval was not sought for this study because this evaluation of the Medical Expenditure Panel Survey is considered non-human subjects research.

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Informed consent

Informed consent was not sought for this study because this evaluation of the Medical Expenditure Panel Survey is considered non-human subjects research. MEPS is a publicly available dataset.

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