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Article

Association of depression and suicidal ideation among adults with the use of H_2 antagonists

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SUMMARY

H_2 antagonists are a common class of medications used to treat gastroesophageal reflux disease. They can cross the blood-brain barrier and can affect the central nervous system. Studies have reported that the intake of H_2 antagonists may lead to mental confusion, delirium, hallucinations, sleep disturbances, and depression. Using a national database, we examined the cross-sectional association between suicidal ideation and H_2 antagonists. Data were obtained from the US National Health and Nutrition Examination Survey (NHANES) 2005-2018, in which Patient Health Questionnaire-9 (PHQ-9) scores were used to classify participants who had depression and suicidal ideation. The study population consisted of 13,533 adult Americans with PHQ-9 information, H_2 antagonist use, and all other covariates. The results showed significant associations between the use of H_2 antagonists and depression ($P < 0.001$) or suicidal ideation ($P < 0.001$). The covariates of education, race, marital status, poverty income rate, smoking, and a number of comorbidities were also statically significant with both depression and suicidal ideation. A multiple logistic regression model adjusted for these covariates showed that H_2 antagonist users had a 2.94 (95% CI: 2.01–4.32) higher risk of suicidal ideation than non-users. This association was strongest among participants aged 50–59 years. This study shows that suicidal ideation and depression may be caused by several factors, and H_2 antagonist use may be one of them. Further studies should be conducted to increase knowledge about the psychiatric effects of taking H_2 antagonists, especially in long-term treatment.

INTRODUCTION

H_2 antagonists are a class of drugs that have been widely used in recent decades to treat gastroesophageal reflux disease and peptic ulcers (1). Their pharmacological mechanism involves reducing the acid-triggering effect of histamine in the parietal cells of the stomach by blocking histamine H_2 receptors (2). We investigated four clinically-used H_2 antagonists in this study: Ranitidine, famotidine, nizatidine, and cimetidine. Famotidine is forty times and eight times more potent than cimetidine and ranitidine, respectively. It has a longer duration of action than both cimetidine and ranitidine, and it has less risk of causing drug-drug interactions because it does not metabolize through cytochrome P450 enzymes (3). Most patients generally tolerate H_2 antagonists well, with the most common side effects (1% to 10%) being diarrhea, dizziness, and headache (4). These H_2 antagonists can cross the blood-brain barrier with varying degrees of permeability, ranging from ranitidine, with the highest permeability, to famotidine, with the lowest, leading to potential adverse effects on the central nervous system (CNS) (5). Studies have reported that the intake of H_2 antagonists may lead to mental confusion, delirium, hallucinations, and sleep disturbances (6-7).

In recent years, scientists have gained a more comprehensive understanding of the histamine system, particularly histamine neurons. One example is the recently discovered ability of histamine neurons to release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which could potentially lead to the discovery of new drugs for CNS disorders, such as narcolepsy (8). In addition, histamine has been associated with aggressive behavior, and H_2 antagonists have shown a suppressive effect on this behavior, prompting us to investigate the neuropsychiatric effects of H_2 antagonists, such as depression and suicidal ideation (9).

H_2 antagonists can cross the blood-brain barrier and may potentially cause adverse effects on the CNS (6). The association between H_2 antagonist intake and depression has been recognized in recent decades, and several studies have been conducted to investigate this matter (10-12). However, the results of the various studies have been controversial: Patten *et al.* found that H_2 antagonists are a risk factor for depression, and clinical cases reported that the severity of depression improved significantly after discontinuation of ranitidine, a widely used H_2 antagonist (10-11). In contrast, a small double-blind, placebo-controlled study of 53 participants with duodenal ulcers showed no association between H_2antagonists and depression (12).

Our study examined the association between H_2 antagonist use and depression or suicidal ideation using the US National Health and Nutrition Examination Survey (NHANES). This survey was a continuous program with a two-year cycle developed in 1999 (13). The study aimed to collect and analyze health and nutritional data of adults and children in the United States. The survey was conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) (13). The participants were randomly selected in 15 counties across the US (13). Each participant approximately represents 65,000 others with similar characteristics in the country (13). The data collection process included both interviews and physical examinations, and the collected data were classified into six categories: demographics, dietary, examination, laboratory, questionnaire, and limited-access data (13). Apart from the

last category, the data are publicly available. Each data category has different subsections. This study employed the 'Prescription Medications' and the 'Mental Health - Depression Screener' subsections of the questionnaire to investigate the association between H_2 antagonists and depression or suicidal ideation (13).

According to the high permeability of H_2 antagonists on the blood-brain barrier and the studies on their effects on CNS, we hypothesized that H_2 antagonists are associated with psychiatric distress, such as depression and suicidal ideation (6, 10-11). This study shows that suicidal ideation and depression were associated with several factors, and H_2 antagonist use was one of them.

RESULTS

NHANES 2005-2018 contains demographic data for 70,190 participants (13). Of these, 42,432 have data on whether participants took H_2 antagonists in the past 30 days (13). The number of participants with Patient Health Questionnaire-9 (PHQ-9) data (i.e., depression and suicidal ideation) and those who took H_2 antagonists in the past 30 days were 36,259 and 1,143, respectively (13). The participants in this study were all over 20 years of age (13). After excluding all missing data, the final number of participants included in this study was 13,533, of which 717 of them were considered as H_2 antagonist users (**Figure 1**). The number of women and men were 6,151 and 7,382, respectively.

Weighting is a technique used in survey research to re-adjust the data, so the population can be reflected more accurately. NHANES assigned a specific weight to each sample of participants to represent the number of people in the US population who have similar characteristics. Here, the majority of participants had one comorbidity (97.8%), were nondiabetic (98.1%), and had no history of cancer (95.7%) (**Table 1**). Most participants were white (60.1%), married (52.1%), had never smoked (57.8%), and lived in a household with two to four people (68.2%) (**Table 1**).

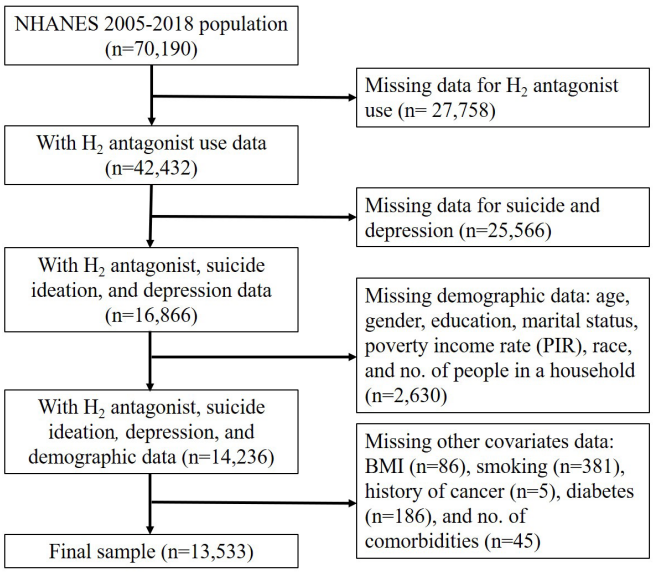

Figure 1: Flow chart of NHANES study population. The total number of participants in the dataset, NHANES 2005-2018 was 70,190. After excluding the participants without the H_2 antagonist data, suicide ideation and depression data, demographic data and other covariates, the final sample size in this study was 13,533.

The rates of suicidal ideation and depression among all weighted participants were 2.6% and 5.3%, respectively (**Table 1**). H_2 antagonist users had higher rates of suicidal ideation and depression than non-H_2 antagonist users (5.7% versus 2.4% and 13.4% versus 4.9%, respectively) **(Table 1**). The rate ratios of 2.37 ($P < 0.001$) for suicidal ideation and 2.73 ($P < 0.001$) for depression, meaning that H_2 antagonist users had a 2.37 times higher rate of suicidal ideation and a 2.73 times higher rate of depression than non-H_2 antagonist users.

The Rao-Scott bivariate χ^2 statistical test showed significant associations between suicidal ideation and most of the selected covariates, including education, race, marital status, poverty income rate (PIR), smoking, number of comorbidities, and diabetes **(Table 1)**. PIR is an index for the ratio of family income to poverty. The US Department of Health and Human Services (HHS) issues poverty guidelines for each state every year (13). NHANES calculated the PIR by dividing family income by the poverty guidelines. The value of PIR ranges from 0 to 5, where a higher value indicates higher family income (13). PIR equals 1 if the family income is the same as the poverty level. NHANES sets the maximum value of PIR to 5.00, to reduce the risk of disclosure.

Participants with lower education levels, lower PIR, a higher number of comorbidities, and those who were Hispanic, widowed, or current smokers had a higher prevalence of suicidal ideation. There was no association between age, sex, or body mass index (BMI) and suicidal ideation. Participants with a history of cancer were also more likely to have suicidal ideation (3.7% versus 2.5%), but this association was not statistically significant ($P > 0.05$). For depression, the associated covariates were similar to those for suicidal ideation, with the exception of gender and the number of people in the household **(Table 1)**. Female participants and those living alone or with more than five people in the household had a higher prevalence of depression.

The bivariate test also revealed significant associations between H_2 antagonists and depression or suicidal ideation in different age groups. The prevalence of both depression and suicidal ideation was higher among H_2 antagonist users in most age groups, and these differences occurred most markedly in the middle-aged groups, i.e., ages 30 to 59 years (**Figures 2,3**).

Forwarding stepwise logistic regression modeling was performed on all the variables and suicidal ideation to investigate the relationship between them. The models predicted whether the participants have suicidal ideation based on one or multiple predictor variables. Forwarding stepwise indicated that the model was generated by introducing the variables one at each time to the unadjusted model. If the variable improved the model by the means of statistical significance and odds ratio (OR), it stayed in the model. This method helped to fine-tune the model to select the best predictor variables. Logistic regression generally uses OR as a measure of association between the outcome and exposure. Here, the OR represents the odds between the H_2 antagonist users and the non-users who had suicidal ideation.

Each covariate had a reference category, meaning all other categories of that covariate were compared to the

Variable	Weighted Participants (%)	Suicidal Ideation		*p*-values[1]	Depression		*p*-values[1]
		Yes (%)	No (%)		Yes (%)	No (%)	
All	100	2.6	97.4		5.3	94.7	
H_2 antagonist				<0.001			<0.001
Yes	5.3	5.7	94.3		13.4	86.6	
No	94.7	2.4	97.6		4.9	95.1	
Education				<0.001			<0.001
Beyond high school	60.0	1.9	98.1		4.0	96.0	
High school or below	40.0	3.6	96.4		7.3	92.7	
Gender				0.2483			<0.001
Male	55.9	2.4	97.6		3.8	96.2	
Female	44.1	2.8	97.2		7.2	92.8	
Age				0.1780			0.6926
20–29	29.3	2.6	97.4		5.6	94.4	
30–39	25.1	2.5	97.5		5.3	94.7	
40–49	21.3	2.3	97.7		5.5	94.5	
50–59	14.6	3.5	96.5		5.3	94.7	
>=60	9.8	2.0	98.0		4.3	95.7	
Race				<0.001			<0.001
Hispanic	6.8	4.8	95.2		8.1	91.9	
Non-Hispanic white	60.1	2.0	98.0		4.6	95.4	
Non-Hispanic black	12.3	3.2	96.8		8.0	92.0	
Other	20.7	3.1	96.9		5.0	95.0	
Marital Status				<0.001			<0.001
Married	52.1	1.5	98.5		2.8	97.2	
Widowed or separated	13.0	4.6	95.4		10.3	89.7	
Never married	34.9	3.5	96.5		7.2	92.8	
Number of people in household				0.1125			<0.001
Living alone	9.4	3.6	96.4		9.3	90.7	
2–4	68.2	2.5	97.5		4.5	95.5	
>=5	22.4	2.6	97.4		6.3	93.7	
Poverty income ratio				<0.001			<0.001
<2	16.8	5.2	94.8		10.9	89.1	
2–4	37.4	3.1	96.9		6.3	93.7	
>4	45.9	1.2	98.8		2.5	97.5	
BMI				0.0614			0.0104
Underweight	1.8	0.9	99.1		5.9	94.1	
Normal or healthy weight	32.1	2.4	97.6		4.9	95.1	
Overweight	34.2	2.4	97.6		4.7	95.3	
Obese	31.8	3.1	96.9		6.4	93.6	
Smoking				<0.001			<0.001
Current smoker	23.3	4.2	95.8		10.4	89.6	
Previous smoker	18.8	1.8	98.2		3.7	96.3	
Never smoker	57.8	2.2	97.8		3.8	96.2	
History of cancer				0.1597			0.0206
Yes	4.3	3.7	96.3		8.1	91.9	
No	95.7	2.5	97.5		5.2	94.8	
Number of comorbidities[2]				<0.001			<0.001
0	97.8	2.5	97.5		5.1	94.9	
1	1.5	6.4	93.6		19.1	80.9	
2	0.5	1.5	98.5		11.6	88.4	
>3	0.2	5.7	94.3		11.8	88.2	
Diabetes				<0.001			<0.001
Yes	1.9	5.8	94.2		15.8	84.2	
No	98.1	2.5	97.5		5.1	94.9	

[1]Rao–Scott $\chi 2$ statistics
[2]Comorbidities included angina, coronary heart disease, heart failure, myocardial infarction, and stroke

Table 1: Weighted characteristics of 13533 participants by suicidal ideation and depression, NHANES 2005–2018.

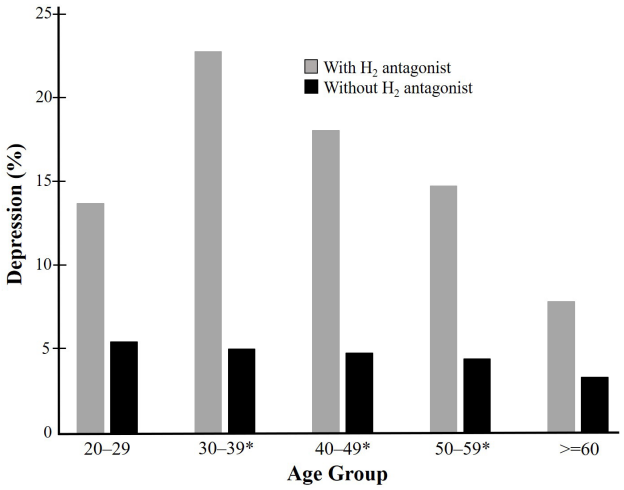

Figure 2: Weighted percentage of participants who had depression by age groups among those taking or not taking H_2 antagonist. The prevalence of depression was higher among the H_2 antagonist users than the non-users in all age groups. * indicates *p*-value of <0.001. The differences between H_2 antagonist users and non-users in the age groups between 30 and 59 years were statistically significant.

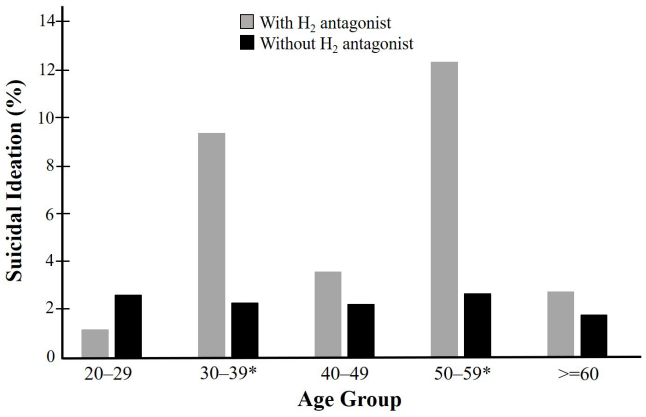

Figure 3: Weighted percentage of participants who had suicidal ideation by age groups among those taking or not taking H_2 antagonist. * indicates *p*-value of <0.001. Statistically significant differences were observed in the 30-39 years and 50-59 years age groups, while the differences in the 20-29, 40-49, and ≥ 60 years age groups were not significant.

reference in the model (**Table 2**). Here, we selected the reference category by the number of participants and/or those which led to statistical significance ($P < 0.05$). For instance, most participants were married, and we selected this category as the reference of the marital status covariate.

Another example is the smoking covariate. Most participants were never smokers; however, using this category as the reference caused statistical insignificance ($P > 0.05$) in other categories. Thus, we used the next numerous category (current smoker) as the reference.

We utilized an unadjusted model and two multiple models. An unadjusted model is also known as a null model, meaning the calculated OR only estimated the relative risk between suicidal ideation in the H_2 antagonist users and the non-users,

Variable	Odds ratios (95% confidence intervals) of suicidal ideation		
	Unadjusted	Adjusted model 1	Adjusted model 2
H_2 antagonist (yes vs. no)	2.44 (1.40–4.23)	2.79 (1.58–4.93)	2.94 (1.65–5.21)
Education			
Beyond high school		Reference	
High school or below		0.79 (0.60–1.05)	
Race			
Hispanic			Reference
Non-Hispanic white			0.51 (0.34–0.76)
Non-Hispanic black			0.54 (0.38–0.78)
Other			0.71 (0.48–1/05)
Marital Status			
Married		Reference	Reference
Widowed or separated		2.32 (1.60–3.38)	2.38 (1.63–3.48)
Never married		1.99 (1.44–2.786	1.98 (1.42–2.77)
BMI			
Underweight		Reference	Reference
Normal or healthy weight		4.30 (1.46–12.6)	4.23 (1.43–12.5)
Overweight		4.58 (1.56–13.4)	4.39 (1.49–12.9)
Obese		5.45 (1.83–16.2)	5.26 (1.76–15.7)
Poverty income ratio			
<2		3.11 (2.27–4.25)	3.02 (2.17–4.22)
2–4		2.08 (1.43–3.04)	2.07 (1.40–3.04)
>4		Reference	Reference
Smoking			
Current smoker		Reference	Reference
Previous smoker		0.52 (0.32–0.83)	0.48 (0.31–0.76)
Never smoker		0.71 (0.52–0.96)	0.63 (0.46–0.86)

[1]Comorbidities included angina, coronary heart disease, heart failure, myocardial infarction, and stroke

Table 2: Weighted and adjusted odds ratios of H_2 antagonist use and covariates with suicide ideation in 13533 participants, NHANES 2005–2018. The unadjusted model showed that H_2 antagonist users had a 2.44 higher risk of suicidal ideation than non-users. The education, marital status, BMI, PIR, and smoking adjusted model 1 revealed that the users had a 2.79 greater risk of having suicidal ideation than the non-users. The adjusted model 2 achieved higher ORs than both the unadjusted model and model 1.

whereas the adjusted OR considered the covariates in the model and estimated the associations between H_2 antagonist use and suicidal ideation by controlling for the covariates. The unadjusted model showed that H_2 antagonist users had a 2.44 higher risk of suicidal ideation than non-users (OR: 2.44; 95% CI: 1.40-4.23, **Table 2**). Adjusted models 1 and 2 achieved higher ORs than the unadjusted model, with ORs of 2.79 and 2.94, respectively (**Table 2**). Three models were also selected for the logistic regression of depression, and their OR values were higher than those of suicidal ideation (**Table 3**). The ORs of the unadjusted model, model 1 and model 2 were 3.01, 3.28, and 2.94, respectively, which may indicate that H_2 antagonists have a stronger association with depression than with suicidal ideation (**Table 3**).

DISCUSSION

This national survey study indicated an association between H_2 antagonist use and depression or suicidal ideation. Previous research on the effect of H_2 antagonists on depression has been controversial (10-12). The results of this study support the association between H_2 antagonists and depression, but further research should be conducted to reach a final conclusion and to help improve patient safety. This study also found that H_2 antagonists are more strongly associated with depression than with suicidal ideation, as evidenced from the bivariate analysis and multiple logistic analysis (**Tables 1–3**). We considered this result to be logical, because participants with major depression may lead to suicidal ideation. Previous studies suggest that approximately one-third of patients with depression have suicidal thoughts (14).

The psychological mechanisms of H_2 antagonists are not clear. One review article suggests that histamine receptors are associated with anxiety and depression and that increasing the amount of histamine in the CNS may produce antidepressant effects, while a bullfrog study showed that blockade of the H_2-receptor can suppress postsynaptic action potentials, which can lead to mental disorders such as depression (15-17). A clinical trial focusing on African Americans also indicated that H_2 antagonist use is more likely to lead to cognitive impairment (18).

Another clinical study also suggested that CNS intoxications, including delirium, mental status changes, confusion, and irritability, could be caused by H_2 antagonist use, with an incidence rate of about 0.2% in the general population and up to 80% in hospitalized patients (19). Therefore, dividing the participants of our study into two groups, outpatients and hospitalized patients, could increase

Variable	Odds ratios (95% confidence intervals) of depression		
	Unadjusted	Adjusted model 1	Adjusted model 2
H_2 antagonist (yes vs. no)	3.01 (2.21–4.10)	3.28 (2.36–4.55)	2.94 (2.01–4.32)
Education			
Beyond high school		Reference	Reference
High school or below		0.81 (0.69–0.97)	0.84 (0.71–0.99)
Gender			
Male		Reference	Reference
Female		2.01 (1.63–2.47)	2.04 (1.66–2.51)
Marital Status			
Married		Reference	Reference
Widowed or separated		2.48 (1.89–3.27)	2.41 (1.65–2.96)
Never married		2.18 (1.67–2.83)	2.04 (1.56–2.67)
Poverty income ratio			
<2		2.83 (2.16–3.71)	2.58 (2.00–3.33)
2–4		1.95 (1.48–2.60)	1.84 (1.40–2.42)
>4		Reference	Reference
Smoking			
Current smoker		Reference	Reference
Previous smoker		0.43 (0.31–0.60)	0.41 (0.29–0.58)
Never smoker		0.43 (0.34–0.54)	0.40 (0.32–0.50)
Diabetes			
Yes			Reference
No			1.64 (1.01–2.65)
Race			
Hispanic			Reference
Non-Hispanic white			0.61 (0.45–0.83)
Non-Hispanic black			0.76 (0.58–0.99)
Other			0.65 (0.48–0.88)
Number of people in household			
Living alone			1.43 (1.06–1.94)
2–4			Reference
>=5			1.23 (1.01–1.51)

Table 3: Weighted and adjusted odds ratios of H_2 antagonist use and covariates with depression in 13533 participants, NHANES 2005–2018. The unadjusted model showed that H_2 antagonist users had a 3.01 higher risk of depression than non-users. The education, gender, marital status, PIR, and smoking adjusted model 1 revealed that the users had a 3.28 greater risk of having depression than the non-users. The adjusted model 2 achieved higher ORs than the unadjusted model, but lower ORs than model 1.

the specificity of our results. However, the NHANES dataset did not include information on whether participants were hospitalized while taking H_2 antagonists. Nevertheless, the results of this study and those in the aforementioned publications suggest that patients at high risk of depression should be very cautious when taking H_2 antagonists.

The elderly are generally more susceptible to drug-related adverse effects, including those on the CNS, because many medicines, including H_2 antagonists, are metabolized in the liver by the cytochrome P450 system (20-21). In general, liver function deteriorates with age and elderly people tend to have a less efficient P450 system to metabolize the H_2 antagonists and are more sensitive to adverse effects (20). In our study, the differences between H_2 antagonist users and non-users were greatest in the age groups between 30 and 59 years, while the differences in the youngest (20-29 years) and the oldest (≥ 60 years) age groups were not statistically significant (**Figure 2**). This contrast could be due to the fact that these age groups are more prone to depression (22). The amount of suicidal ideation was significantly higher for the H_2 antagonist users than non-users in the two age groups: 30-39 years and 50-59 years (**Figure 3**). This result could indicate that H_2 antagonists have a stronger suicidal ideation effect on these two age groups.

Our study had several limitations that may affect the reliability of the results. The national database used in this study is a self-reported survey that may introduce personal bias and social desirability bias (23). The participants may have answered the questions exaggeratedly due to the potential likelihood of receiving more social services. The participants may also have understated their answers because of the potential discomfiture of admitting to having depression or suicidal ideation.

Our study is a cross-sectional study and has the usual limitations of lack of control variables and lack of follow-up, i.e., exposures and outcomes were measured simultaneously, potentially leading to recall bias and information bias (24). For example, our study showed that participants with a history of cancer were more likely to suffer from depression or suicidal ideation (**Table 1**). These differences are statistically significant only for depression, but not for suicidal ideation. However, studies from the literature suggest that suicidal ideation is significantly associated with cancer (25-26). This disparity may be due to the data collection procedure of the NHANES (13). The interview question used to consider participants having cancer was "*Have you ever been told that you have cancer or a malignant disease?*", while participants were asked if they had had suicidal thoughts in the past 2 weeks. This NHANES question indicates that some participants may have recovered from their cancer long before the time of data collection; thus, the impact of cancer on suicidal ideation may have been overestimated.

Due to the limited number of participants for each H_2 antagonist, this study analyzed the four H_2 antagonists (cimetidine, famotidine, nizatidine, and ranitidine) as a group, rather than analyzing them individually. A previous study concluded that different H_2 antagonists have different permeability to the brain; thus, the concentration at which they enter the CNS may vary, and so may their psychological effects (27). Consequently, the analysis of individual H_2 antagonists might yield more conclusive results. Another limitation of this study is the lack of dosing information of the H_2 antagonists, which meant that the dose-independent association could not be examined.

In this study, multiple logistic regression analysis included various covariates (**Table 1**). Some other factors, such as early abuse, trauma, and gambling addiction, have been associated with depression or suicidal ideation; however, these were excluded in this study because the NHANES 2005-2018 did not include this information (28-29). Including these factors in our study could potentially have led to logistic regression models with higher accuracy.

While the side effects of H_2 antagonists are known, the full extent of the relationship between the drug and depression/suicidal ideation is unclear. In this study, the association between H_2 antagonists and suicidal ideation was established using a national database. We recommend further research to determine the incidence of this possible side effect. If a causal relationship is found, both patients and health professionals should be made aware in order to raise public awareness and possibly prevent suicide attempts.

MATERIALS AND METHODS

Datasets

The NHANES, conducted by the NCHS of the CDC, served as the data source in this study. NHANES is a national continuous survey program, with two-year cycles developed in 1999 (13). The goal of the NHANES is to assess the well-being of non-institutionalized adults and children in the United States. The participant sampling procedures were complex, stratified, and multistage (30). NHANES selected the participants randomly through the statistical process using the US Census information (30). The process involved four stages: (1) categorized all the counties in the US into fifteen groups according to their characteristics, (2) selected 20 to 24 small groups (such as neighborhoods) from each of the fifteen groups, (3) selected about 30 households within each of the small groups, (4) each person of the household was contacted by NHANES for their basic information, such as age, race, and gender, through completing a brief online or telephone questionnaire (31). A computer program was then used to select some, all, or none of these people for further interviews and physical examinations.

The selected participants were contacted by NHANES to arrange for a telephone health interview which generally took 15 to 40 minutes (31). The participants were required to answer various types of questions, including close-ended, open-ended, and scored questions. NHANES arranged visits to the NHANES Mobile Exam Center, where the participants received health exams, such as height, weight, blood pressure measurement, body composition scan, and more (32).

Most of the data obtained in this study were obtained from the demographic sections of the NHANES program, while the data on H_2 antagonists were obtained from the 'Prescription Medications' category of the questionnaire **(Table 1)**. Data on depression and suicidal ideation were taken from the 'Mental Health - Depression Screener' category.

While the data of NHANES aimed to represent the US population, it was impractical to collect data from every person in the US. Thus, NHANES selected a proportion of civilians and assigned a weighted value to each of them based on their characteristics. This value indicated the estimated number of people in the US population represented by that sample participant. The sample weight was computed by three steps:

(1) calculated the base weight by accounting for the unequal probabilities, which were the product of the probability of selecting the primary sampling unit (PSU), probability of selecting the segment of the PSU, probability of selecting the household, and the probability of selecting the participant, (2) calculated the adjustment for nonresponse, and (3) calculated the post-stratification adjustment to match the total US population (33). Thus, each participant of the NHANES was accurately weighted to represent the US population and avoid oversampling. The weighting process is complicated, and details of the methods can be found on the NHANES official website (33).

The NCHS Ethics Review Board approved all data collection processes and data used in the NHANES program, and all participants provided informed consent to participate in the program.

Depression and suicidal ideation

This study has two outcome variables: depression and suicidal ideation. These outcomes were obtained using the PHQ-9 from the 'Mental Health - Depression Screener' category of the NHANES. The PHQ-9 is a validated self-report questionnaire that contains nine questions about depression-related symptoms and is commonly used for screening depression (34-35). Each of the nine questions can be scored from 0 to 3, where 3 means that the participant experienced the symptom almost every day in the past 2 weeks, 2 means that the symptom occurred on more than half of the days, and 1 and 0 refer to multiple and no symptomatic days in the past 2 weeks, respectively (35). The severity of depression was determined by summing the scores for each question; thus, the minimum and maximum scores were 0 and 27, respectively (35). The cut-off point between depression and non-depression in this study was 10, where a total score of ≥ 10 indicates moderate or severe depression, whereas < 10 indicates no depression or mild depression.

One of the PHQ-9 questions was used to assess suicidal ideation. The question asked, "*In the past 2 weeks, how often have you been plagued by the following: Thoughts that you would be better off if you were dead, or that you would hurt yourself in some way?*" and is considered a strong indicator of suicidal ideation (35). In this study, a participant with a score of 0 indicated that they had no suicidal ideation, while a score between 1 and 3 meant that the participant had some level of suicidal ideation.

H_2 antagonists

The 'Prescription Medication' category of the NHANES includes questionnaires on medication use (36). NHANES participants were asked to answer questions about whether they took medications and, if so, what they were called and how long they had been taking them. For this study, participants who had taken an H_2 antagonist for at least 30 days were selected to ensure that the H_2 antagonist had enough time to produce clinical effects on the participants. There were four H_2 antagonists listed in the data: Cimetidine, famotidine, nizatidine, and ranitidine (36).

Covariates

Covariates in this study included demographic data, as well as personal information that had been associated with depression or suicidal ideation in the literature (37-38). These data included education level, gender, age, race, marital status, number of people in the household, PIR, BMI, cancer, number of comorbidities, and diabetes. All participants were classified into different categories based on these variables **(Table 1)**. In terms of BMI, participants were divided into four different subcategories: Underweight (< 18.5 kg/m^2), normal or healthy weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (> 30.0 kg/m^2). These subcategories were assigned based on CDC reference values (39). For smoking status, participants who were current non-smokers but had smoked at least 100 cigarettes in their lifetime were considered former smokers. The number of comorbidities was the total number of specific cardiovascular diseases that the participants had. These diseases were angina, coronary artery disease, heart failure, myocardial infarction, and stroke. Cardiovascular disease, cancer, and diabetes were found to be associated with depression (40). Participants missing data on any of the covariates were excluded from this study.

Statistical analysis

R Studio (R version 4.1.2) was used to assess associations between the exposure variables (use of H_2 antagonists) and all other variables. Sampling weighting provided by NHANES was used to minimize potential oversampling bias and to justify non-response and post-stratification adjustment of the survey. Weighting was performed according to NHANES guidance (41). The Rao-Scott χ^2 test was used to assess bivariate associations between depression or suicidal ideation and other variables (42). The Rao-Scott χ^2 test was calculated using the 'svychisq' function of the R package 'survey' (43). Multiple regression analysis was performed using the 'svyglm' function of 'survey' (43). Odds ratio and 95% confidence intervals (CI) were calculated using the function 'odds.ratio' of the package 'questionr' (44). Logistic regression models of covariates were developed using forward stepwise modelling, starting with education, sex, age, race, marital status, number of persons in household, PIR, BMI, smoking, cancer, diabetes, and number of comorbidities.

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