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Antidepressants and Valvular Heart Disease

A Nested Case–Control Study in Taiwan

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Abstract: Empirical evidence regarding the association between antidepressants and valvular heart disease (VHD) is scarce.

Using Taiwan's National Health Insurance Research database, this nested case-control study assessed the association between antidepressants and VHD in a Chinese population.

Among a cohort of patients who used at least 3 prescription antidepressants, 874 cases with VHD and 3496 matched controls (1:4 ratio) were identified. Conditional logistic regression models were used to examine the timing, duration, dose and type of antidepressants use, and the risk of VHD.

Current use of antidepressants was associated with a 1.4-fold increase in the risk of VHD (adjusted odds ratio [aOR] 1.44; 95% confidence interval [CI] 1.17–1.77). Among current users, a dose–response association was observed in terms of the cumulative duration and the cumulative antidepressant dose. Significantly higher risks of VHD were observed among the current users of tricyclic antidepressants (aOR 1.40 [1.05–1.87]).

We found that the use of antidepressants was associated with a greater risk of VHD and that the risks varied according to different antidepressants.

(*Medicine* 95(14):e3172)

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, DDD = defined daily dose, ICD-9-CM = International Classification of Disease-Ninth edition-Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants, VHD = valvular heart disease.

KEY POINTS

- This study is the first to explore the association between the use of antidepressants and the risk of incident valvular heart disease (VHD) among an ethnic Chinese population.
- Current use of antidepressants was associated with a 1.4-fold increase in the risk of VHD.
- A dose–response association was observed in terms of the cumulative duration and the dose of antidepressants and the risk of VHD.

INTRODUCTION

Drug-induced valvular heart disease (VHD) primarily presents as cardiac-valvular regurgitation and has raised serious concerns as fenfluramine was withdrawn from the market.[1–3] One of the possible mechanisms of drug-induced VHD is that some drugs may directly activate the 5-HT_{2B} receptor located on the aortic and mitral valves, which would then lead to cardiac valve fibrosis.[4–6] For example, drugs with well-known risks of causing VHD, such as appetite suppressants (e.g., fenfluramine), migraine prophylactics (e.g., ergotamine and methysergide), and antiparkinson agents (e.g., pergolide and carbergoline), have been reported to have high affinities and agonist activities at the 5-HT_{2B} receptor.[4–6]

Nevertheless, several observational studies and animal studies have suggested other mechanisms of drug-induced VHD, such as elevations of 5-HT concentrations in the circulation and 5-HT transporter deficiencies.[7–10] In patients with carcinoid syndrome tumors, high 5-HT levels have been observed to be associated with valvulopathy,[9,11] and this association resembles the pattern of VHD developed in pergolide and cabergoline users.[5,12] Animal studies have also reported that daily injections of 5-HT in rats result in both elevated 5-HT levels and valve abnormalities.[8,10,13] Additionally, because 5-HT transporters are highly expressed in platelets and the pulmonary artery endothelium and are responsible for the removal of 5-HT from the plasma and the clearance of 5-HT,[14,15] 5-HT transporters are considered to play a critical protective role against the potentially harmful effects of 5-HT on the left side of the heart.[7,16] This hypothesis is consistent with an animal study that reported that the valvulopathy that

Editor: Leonardo Roever.
Received: September 7, 2015; revised: January 14, 2016; accepted: January 30, 2016.
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Funding: this research was funded by the Ministry of Science and Technology, Taiwan (grant no. MOST103-2320-B-002-015). HFY received a part-time assistantship sponsored by the Food and Drug Administration, Taiwan (MOHW103-FDA-41100).
Author contributions—conceived and designed the experiments: CHL, FYH, YBL, SSG, CCW, and LJS; performed the experiments: CHL; analyzed the data: CHL; contributed reagents/materials/analysis tools: FYH; wrote the manuscript: CHL, FYH, YBL, SSG, CCW and LJS.
The authors have no conflicts of interest to disclose.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003172

develops in 5-HT transporter-knockout mice may result from a reduction of in the clearance of 5-HT and a subsequent elevation of the 5-HT level.[7] Therefore, the development of drug-induced VHD probably results from a complex interaction between 5-HT, the 5-HT transporter, and the 5-HT_{2B} receptor.

Together, these hypotheses illustrate the urgent need for more information about the safety of antidepressants. Although the pharmacologic mechanisms of antidepressants are related to serotonin metabolism,[17] for example, inhibition of the 5-HT transporter and downregulation of the 5-HT transporter,[18–20] empirical evidence regarding the safety of antidepressant treatments is scarce.[21–23] Some studies have found that the use of antidepressants does not increase the risk of VHD. However, these studies are limited by small sample sizes,[21,23] confounded by indications[21,23] and suffer from unclearly defined populations.[22] Therefore, this study aimed to evaluate the association between the use of antidepressants and VHD using a population-based large-scale cohort with 10 years of follow-up data.

MATERIAL AND METHODS

Data Sources

The National Health Insurance Research Database (NHIRD) is a claims-based database of Taiwan's mandatory National Health Insurance (NHI) program. The NHI program was launched in 1995 and covers >99% of Taiwan's population (~23 million residents). This database provides comprehensive records of healthcare utilization, including ambulatory care, inpatient care, and prescription medications, and has been used for pharmacoepidemiological research that has been published in many studies.[24] Our study was based on a subset of the NHIRD, termed the Longitudinal Health Insurance Database (LHID), which contains the claim data of ~3 million individuals who were randomly sampled from the Registry for Beneficiaries of the NHIRD.

Ethical Statement

Because the identification numbers of all subjects in the NHIRD were encrypted to protect individual privacy, this study was exempted from full review by the Institution Review Board of the National Taiwan University Hospital, and the requirement for informed consent was waived. The Institution Review Board of the National Taiwan University Hospital approved this study (201312069W).

Study Cohort

We identified a cohort of patients aged 20 years and older who had received at least 3 prescriptions of antidepressants between January 1, 2002, and December 31, 2010. The date of the first antidepressants prescription was assigned as the cohort entry date. The patients who had used an antidepressant with 3 years prior the cohort entry date were excluded. Patients with diagnoses of VHD (*International Classification of Disease-Ninth edition-Clinical Modification* [ICD-9-CM] codes: 3961–9, 3970, 4240–3); who had undergone cardiac valve replacement (NHI codes: 68016A/B, 68017A/B, 68018A/B); had VHD-associated etiologies (rheumatic disease [ICD-9-CM codes: 391–5, 3971–9, 398], endocarditis [0932,421,4249], cardiomyopathy [425], carcinoid syndrome [2592], congenital heart disease [6485,746], pericarditis [420], myocarditis [422], or congestive heart failure [428]);[25–27] and those who had used drugs with potential risks of drug-induced VHD (ATC code for ergotamine N02CA02, N02CA52, N02CA72, A03CB31; pergolide N04BC02; cabergoline N04BC06, G02CB03; bromocriptine N04BC01, G02CB01) within 1 year before the cohort entry date were excluded.

Cases and Controls

Our cases and controls were selected from the identified cohort (i.e. patients aged 20 years and older who had received at least 3 prescriptions of antidepressants between January 1, 2002, and December 31, 2010). The cases were defined as patients who were first hospitalized with a diagnosis of VHD (ICD-9-CM codes 3961–9, 3970, 4240–3) or who were first hospitalized to receive a cardiac valve replacement (NHI code 68016A/B, 68017A/B, 68018A/B) between January 1, 2002, and December 31, 2010.). The admission date was defined as the index date. To further increase the validity of the identification of VHD cases, we required that all of the identified cases underwent echocardiography (NHI code 18005B, 18006B) 3 months before the index date.

As the disease progression of VHD from the asymptomatic to the symptomatic stage typically requires 3 years or longer,[26] only the cases who presented with VHD >3 years after the first use of antidepressants were retained to account for the latency period. Using incidence-density sampling, each case was matched with 4 controls according to age (±1 year), sex, and cohort entry date (±30 days).

Exposure Assessment

We retrieved all of the antidepressant prescriptions, including selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine), tricyclic antidepressants (TCAs; clomipramine, imipramine, maprotiline, amitriptyline, and dothiepin), serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine, and milnacipram), and other antidepressants (bupropion, mirtazapine, and trazodone; Appendix 1, http://links.lww.com/MD/A850), 3 years prior to the index dates of our study cohort. We created antidepressant exposure categories based on the timing and duration of the use of the identified prescriptions. Antidepressants users were categorized as current, recent, and past users based on the receipt of prescriptions for antidepressants within 180 days, between 181 and 365 days, and between 366 and 1095 days before the index date, respectively. Nonusers were defined as patients with no record of antidepressant use within 3 year before the index date.

We further examined the cumulative durations, cumulative doses and last daily doses of antidepressants to explore the dose-response relationship between the use of antidepressants and risk for VHD. The cumulative duration was calculated by summing all prescribed days of antidepressant use within the 3 years prior the index date. The cumulative dosage was computed according to the defined daily dose (DDD). The last daily dose was the daily dosage of the prescription nearest to the index date. If a patient received >1 antidepressant, we summed the daily doses of all of the antidepressants.

Exposure to antidepressants was categorized by the type of antidepressant, affinity for the 5-HT transporter and individual antidepressant. The antidepressants were classified into the following 3 categories according to their affinities for the 5-HT transporter: a high-affinity group (fluoxetine, paroxetine, sertraline, and clomipramine), a moderate-affinity group (citalopram, fluvoxamine, imipramine, venlafaxine, and amitriptyline), and a low-affinity group (trazodone, bupropion, maprotiline, mirtazapine, and dothiepin)[28,29] (Appendix 1, http://links.lww.com/MD/A850).

Statistical Analyses

We used McNemar's test to compare the demographic characteristics between the cases and controls. Univariate conditional logistic regressions were used to estimate the crude association between each covariate and the risk of VHD. Multivariate conditional logistic regressions were used to evaluate the associations between the exposure to antidepressants and the risk of VHD. All of the multivariate models were adjusted for the comorbidities and co-medications of the patients based on the claims data for 1 year before the index date. The comorbidities included hypertension [ICD-9-CM codes: 401.xx-405.xx], diabetes [250.xx], lipid disorders [272.xx], chronic obstructive pulmonary disease [493.2, 496.xx], chronic kidney disease [585.xx], congestive heart failure [428.xx], myocardial infarction [410.xx-412.xx, 414.xx], cerebrovascular disease [430.xx-438.xx], and depression [296.x, 300.0, 300.4].[28] The co-medications included drugs with potential risks of causing of VHD, including ergotamine, pergolide, cabergoline, and

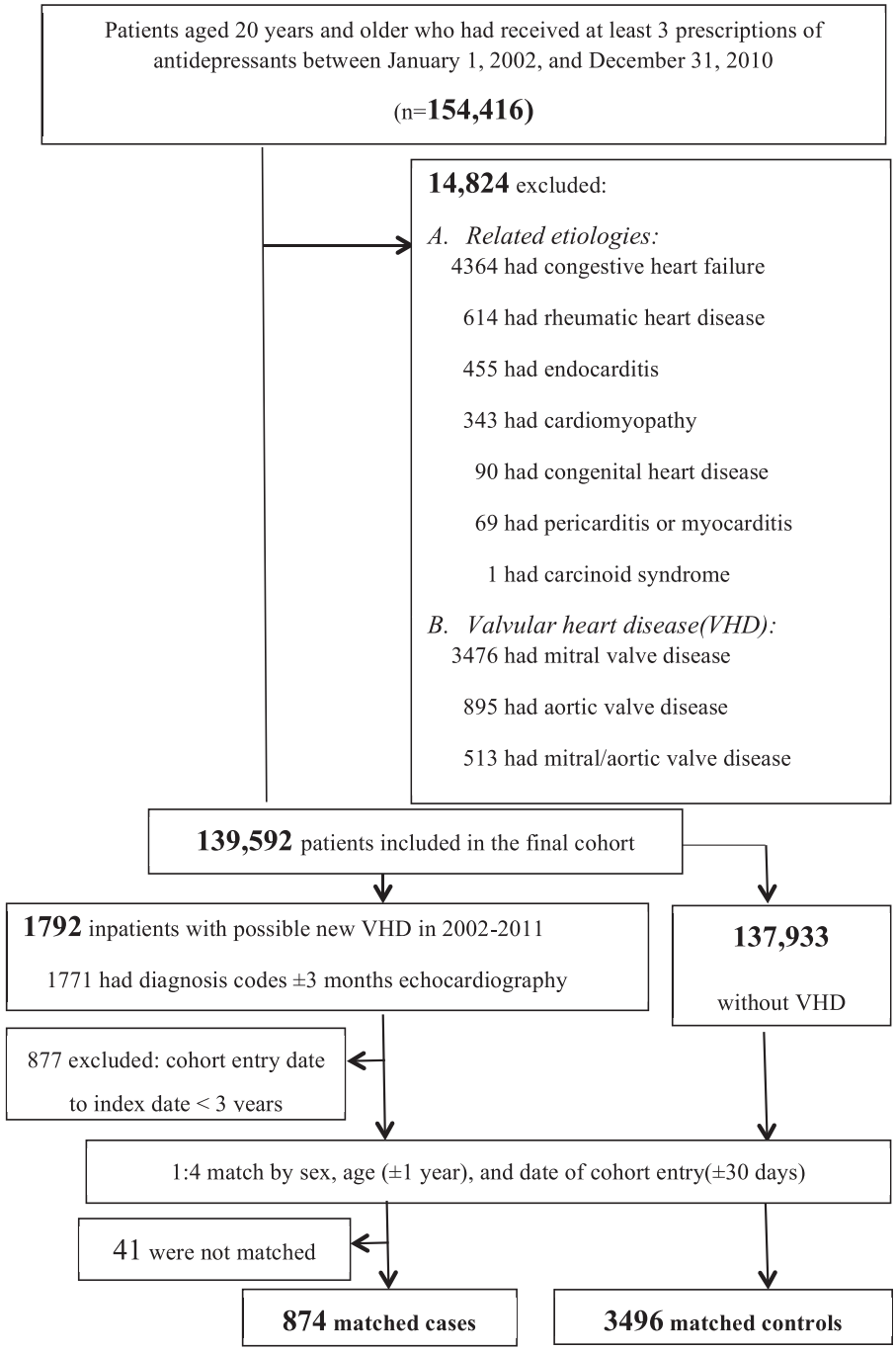

FIGURE 1. Flowchart of the patient screening.

bromocriptine.[1] The associations are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The statistical test results were considered significant with a 2-sided P value of < 0.05. All data management and analyses were performed using SAS 9.3 for Windows (SAS Institute, Cary, NC).

RESULTS

Among 139,592 new users of antidepressants, we identified 874 cases of VHD and 3496 matched controls (Figure 1). The distributions of age, sex, and cohort entry date of the cases and controls were well matched. The cases were more likely to have co-morbid conditions than the controls. A greater proportion of cases were current users of antidepressants (28.5% vs 20.7%, Table 1).

After adjusting for the comorbidities, the current users of antidepressants were associated with a 1.4-fold increase in the risk of VHD (adjusted OR [aOR] 1.44; 95% CI 1.17–1.77; $P < 0.01$) compared with the nonusers. Neither the recent users (aOR 1.09; 95% CI [0.80–1.50]; $P = 0.59$) nor the past users (aOR 1.01; 95% CI [0.81–1.25]; $P = 0.94$) of antidepressants were associated with an increased risk of VHD compared with the nonusers. Additionally, we found that the patients with underlying congestive heart failure (aOR 4.04; 95% CI [3.14–5.19]), myocardial infarction (aOR 2.10; 95% CI [1.73–2.55]), chronic kidney disease (aOR 2.14; 95% CI [1.58–2.89]), hypertension (aOR 1.77; 95% CI [1.46–2.14]), and chronic obstructive pulmonary disease (aOR 1.62; 95% CI [1.23–2.14]) had higher risks of VHD (Table 2).

Among the current users of antidepressants, the aOR for VHD was the highest among those who used antidepressants for 91 to 180 days (<90 days, aOR 1.50; 95% CI [1.06–2.13]), 91 to 180 days (aOR 2.70 [1.68–4.32]), 181 to 365 days (aOR 1.10 [0.68–1.80]), and >366 days (aOR 1.30 [1.00–1.69]). The aOR of VHD increased with the cumulative dose of antidepressants (≤90 DDDs, aOR 1.54 [1.16–2.04]; 91–180 DDDs, aOR 1.58 [1.07–2.35]; and 181–365 DDDs, aOR 1.73 [1.14–2.63]). The risk of VHD did not differ from that of nonusers when the cumulative antidepressant dosage was >366 DDDs among the current users (Table 3).

The risks of VHD were significantly greater for current users who used TCAs (aOR 1.40; 95% CI [1.05–1.87]) and antidepressants with moderate (aOR 1.41; 95% CI [1.08–1.83]) or low (aOR 1.49; 95% CI [1.12–1.97]) affinities for the 5-HT transporter. The recent users of SNRIs (aOR 3.36; 95% CI [1.17–9.63]) were associated with an increased risk of VHD; however, the CIs varied widely (Table 4). The separate ORs for VHD were estimated for the exposures to individual antidepressants. We found that current users of citalopram (aOR 2.30; 95% CI [1.14–4.62]), duloxetine (aOR 4.77; 95% CI [1.89–12.02]), imipramine (aOR 1.40; 95% CI [1.03–1.91]), and trazodone (aOR 1.54; 95% CI [1.14–2.08]), and recent users of venlafaxine (aOR 4.09; 95% CI [1.89–12.02]) were associated with increased risks of VHD (Appendix 2, http://links.lww.com/MD/A850).

DISCUSSION

Via the application of a nested case-control study design to a nationwide-based cohort, this study is the first to explore the association between the use of antidepressants and the risk of incident VHD among an ethnic Chinese population. We found a 1.4-fold increase in the risk of VHD among current users of antidepressants. Among current users, a dose–response effect was found in patients with cumulative DDDs. Moreover, the users who were currently taking TCAs and antidepressants with moderate and low affinities for the 5-HT transporter were at significant higher risks of VHD.

TABLE 1. Characteristics of the Cases and Matched Controls

	Case (N = 874) n (%)	Control (N = 3496) n (%)	*P*
Mean age (y ± SD)	65.2 ± 14.1	65.1 ± 14.0	
Male (%)	398 (45.5)	1592 (45.5)	
Mean duration of follow-up (days ± SD)	2007.3 ± 620.7	2006.7 ± 620.2	
Comorbidities			
Hypertension	604 (69.1)	1717 (49.1)	<0.01*
Diabetes	296 (33.9)	836 (23.9)	<0.01*
Lipid disorder	256 (29.3)	722 (20.7)	<0.01*
Chronic obstructive pulmonary disease	112 (12.8)	217 (6.2)	<0.01*
Chronic kidney disease	106 (12.1)	137 (3.9)	<0.01*
Congestive heart failure	207 (23.7)	164 (4.7)	<0.01*
Myocardial infarction	312 (35.7)	513 (14.7)	<0.01*
Cerebrovascular disease	237 (27.1)	626 (17.9)	<0.01*
Depression	41 (4.7)	121 (3.5)	<0.01*
Co-medications			
Ergotamine	40 (4.6)	138 (4.0)	0.19
Pergolide	3 (0.3)	6 (0.2)	0.16
Bromocriptine	5 (0.6)	18 (0.5)	0.74
Timing of exposure to antidepressants			
Non-user	352 (40.3)	1698 (48.6)	<0.01*
Current user	249 (28.5)	722 (20.7)	<0.01*
Recent user	78 (8.9)	230 (6.6)	<0.01*
Past user	195 (22.3)	846 (24.2)	0.06

* $P < 0.05$.

TABLE 2. Crude and Adjusted Odds Ratios for the Risk of VHD and Exposure to Antidepressants

	Crude OR		aOR[§]	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Current user[‡]	1.68 (1.39–2.02)	<0.01[*]	1.44 (1.17–1.77)	<0.01[*]
Recent user[‡]	1.65 (1.24–2.19)	<0.01[*]	1.09 (0.80–1.50)	0.59
Past user[‡] (reference: nonuser)	1.14 (0.93–1.39)	0.21	1.01 (0.81–1.25)	0.94
Comorbidities in the past year				
Hypertension	2.61 (2.20–3.10)	<0.01[*]	1.77 (1.46–2.14)	<0.01[*]
Diabetes	1.66 (1.41–1.95)	<0.01[*]	1.09 (0.90–1.31)	0.39
Lipid disorder	1.63 (1.38–1.94)	<0.01[*]	1.23 (1.01–1.49)	0.04[†]
Chronic obstructive pulmonary disease	2.30 (1.79–2.95)	<0.01[*]	1.62 (1.23–2.14)	<0.01[*]
Chronic kidney disease	2.88 (2.33–3.55)	<0.01[*]	2.14 (1.58–2.89)	<0.01[*]
Congestive heart failure	6.56 (5.19–8.29)	<0.01[*]	4.04 (3.14–5.19)	<0.01[*]
Myocardial infarction	3.36 (2.82–4.00)	<0.01[*]	2.10 (1.73–2.55)	<0.01[*]
Cerebrovascular disease	1.76 (1.47–2.10)	<0.01[*]	1.34 (1.10–1.64)	<0.01[*]
Depression	1.37 (0.95–1.96)	0.09	1.15 (0.77–1.72)	0.50

[*] $P < 0.01$.
[†] $P < 0.05$.
[‡] Users categorized according to the days between the last prescription and the index date: current user, ≦180 days; recent user, 181–365 days; past user, 366–1095 days.
[§] Adjusted for hypertension, diabetes, lipid disorder, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, myocardial infarction, cerebrovascular disease, and depression.

To our knowledge, empirical data regarding the association of the risk of VHD with antidepressants use are very limited. Our findings could thus add to the literature by exploring different definition of exposure to antidepressant and the risk for VHD. However, our findings are inconsistent with those from a matched case-control study conducted by Lapi et al[22] in which the authors reported that the risk of VHD was not associated with the use of antidepressants based on administrative claims data from the United Kingdom (aOR 1.16 [0.96–1.40] for current users compared with past users). Ours is the first study to show a positive association between the present use of antidepressants and the risk for VHD, and several factors may have contributed to the discrepancy between the findings of our study and that of Lapi et al.[22] The major strength of our study is that we defined patients who were hospitalized with VHD as cases, whereas Lapi et al identified their cases based on inpatient and outpatient claims. Our approach thus identified more homogeneous cases because the severities of VHD identified in inpatient and outpatient settings could be very different. Additionally, we adopted a latency period of 3 years to exclude the cases with VHD that occurred too quickly for the antidepressant use to have contributed, which enhanced the

TABLE 3. Cumulative Duration, Cumulative Dose, and Last Daily Dose of Antidepressants and Risk of VHD Among Current Users

			Crude OR		aOR	
	Case (N = 874) n (%)	Control (N = 3496) n (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Cumulative duration						
≦90 days	61 (7.0)	170 (4.9)	1.75 (1.28–2.40)	<0.01[*]	1.50 (1.06–2.13)	0.02[†]
91–180 days	37 (4.2)	54 (1.5)	3.29 (2.14–5.07)	<0.01[*]	2.70 (1.68–4.32)	<0.01[*]
181–365 days	26 (3.0)	96 (2.8)	1.34 (0.86–2.09)	0.20	1.10 (0.68–1.80)	0.69
≥ 366 days	125 (14.3)	402 (11.5)	1.52 (1.20–1.92)	<0.01[*]	1.30 (1.00–1.69)	<0.05[†]
Cumulative dose						
≦90 DDD	106 (12.1)	276 (7.9)	1.87 (1.45–2.42)	<0.01[*]	1.54 (1.16–2.04)	<0.01[*]
91–180 DDD	49 (5.6)	117 (3.4)	2.07 (1.44–2.95)	<0.01[*]	1.58 (1.07–2.35)	0.02[†]
181–365 DDD	40 (4.6)	106 (3.0)	1.81 (1.24–2.65)	0.01[†]	1.73 (1.14–2.63)	0.01[†]
≥366 DDD	54 (6.2)	223 (6.4)	1.18 (0.85–1.63)	0.02[†]	1.06 (0.75–1.51)	0.74
Last daily dose						
<1 DDD	164 (18.8)	459 (13.1)	1.74 (1.41–2.16)	<0.01[*]	1.46 (1.16–1.86)	<0.01[*]
≥1 DDD	85 (9.7)	263 (7.5)	1.59 (1.21–2.09)	<0.01[*]	1.39 (1.03–1.87)	0.03[†]

[*] $P < 0.01$.
[†] $P < 0.05$.
Adjusted with hypertension, diabetes, lipid disorder, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, myocardial infarction, cerebrovascular disease, and depression.

TABLE 4. Use[‡] of Antidepressants and Risk of VHD, Classified by Type of Antidepressants or Affinity for Serotonin Transporter

			Crude OR		aOR[§]	
	Case (N = 874) n (%)	Control (N = 3496) n (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Type of antidepressant						
SSRI						
Current user	75 (8.6)	242 (6.9)	1.52 (1.14–2.02)	<0.01*	1.36 (0.99–1.86)	0.06
Recent user	27 (3.1)	92 (2.6)	1.44 (0.92–2.25)	0.11	1.18 (0.72–1.95)	0.51
Past user	79 (9.0)	298 (8.5)	1.31 (1.00–1.73)	0.05†	1.19 (0.88–1.60)	0.26
SNRI						
Current user	20 (2.3)	60 (1.7)	1.67 (0.99–2.82)	0.06	1.67 (0.95–2.94)	0.08
Recent user	6 (0.7)	12 (0.3)	2.56 (0.95–6.87)	0.06	3.36 (1.17–9.63)	0.02†
Past user	20 (2.3)	60 (1.7)	1.67 (0.99–2.81)	0.05†	1.57 (0.88–2.78)	0.12
TCA						
Current user	95 (10.9)	261 (7.5)	1.77 (1.36–2.30)	<0.01*	1.40 (1.05–1.87)	0.02†
Recent user	51 (5.8)	131 (3.8)	1.89 (1.34–2.67)	<0.01*	1.12 (0.76–1.65)	0.57
Past user	138 (15.8)	509 (14.6)	1.33 (1.06–1.67)	0.01†	1.05 (0.82–1.35)	0.71
Affinity for serotonin transporter						
HA group						
Current user	48 (5.5)	178 (5.1)	1.32 (0.94–1.85)	0.11	1.15 (0.79–1.66)	0.47
Recent user	22 (2.5)	68 (2.0)	1.59 (0.97–2.60)	0.06	1.21 (0.70–2.10)	0.49
Past user	68 (7.8)	257 (7.4)	1.31 (0.97–1.76)	0.07	1.21 (0.88–1.66)	0.24
MA group						
Current user	117 (13.4)	328 (9.4)	1.74 (1.37–2.22)	<0.01*	1.41 (1.08–1.83)	0.01†
Recent user	54 (6.2)	149 (4.3)	1.77 (1.26–2.47)	<0.01*	1.12 (0.77–1.62)	0.56
Past user	153 (17.5)	558 (16.0)	1.35 (1.08–1.68)	<0.01*	1.09 (0.86–1.39)	0.46
LA group						
Current user	104 (11.9)	289 (8.3)	1.76 (1.36–2.27)	<0.01*	1.49 (1.12–1.97)	<0.01*
Recent user	30 (3.4)	86 (2.5)	1.73 (1.11–2.67)	0.01†	1.29 (0.80–2.10)	0.30
Past user	93 (10.6)	364 (10.4)	1.28 (0.98–1.65)	0.07	1.16 (0.88–1.54)	0.29

HA = high affinity, LA = low affinity, MA = moderate affinity.

* $P < 0.01$.

† $P < 0.05$.

‡ Users categorized by days between last prescription and index date: current user, ≦180 days; recent user, 181–365 days; past user, 366–1095 days; ever user,>1095 days.

§ Adjusted with hypertension, diabetes, lipid disorder, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, myocardial infarction, cerebrovascular disease, and depression.

association between antidepressant exposure and subsequent VHD, whereas Lapi et al[22] did not consider this issue. The criteria for the cohort selections in the 2 studies were also different. We chose patients who had at least 3 prescriptions of antidepressants, whereas Lapi et al examined those who had at least 1 prescription of antidepressants.[22] Furthermore, Lapi et al stratified their analyses by the timing of the exposure to antidepressants and utilized patients with the smallest cumulative durations or the worst adherences as the reference group, which may have masked the effect of timing and the dose-response relationship.[22] To address this limitation, we defined the reference group as those who had not used antidepressants within 3 years before the index date. Another possible explanation may be that our study cohort was composed of an ethnic Chinese population, which contrasts with the ethnicity of the population examined by Lapi et al.[22]

Our findings regarding potential risk factors for VHD, such as congestive heart failure (aOR 2.7; $P < 0.01$), coronary artery disease (aOR 1.4; $P < 0.01$), and hypertension (aOR 1.6[1.2–2.0]), were consistent with those of existing studies.[21,29] We further found that patients with chronic kidney disease and chronic obstructive pulmonary disease were associated with greater risks of VHD. Thus, we suggest that patients who use antidepressants should pay more attention to the risk of VHD, especially those with underlying risk factors.

Our study also adds to the current evidence via the investigation of the risks of VHD associated with different types of antidepressants. Our negative findings regarding SSRI users and the risks of VHD are in line with those of 2 previous cohort studies.[21,23] Using an inpatient sample with routine echocardiography in a medical centre as a study cohort, Mast et al[21] demonstrated that the prevalence of regurgitation does not significantly differ between those who are receiving SSRIs and those who are not (26.7% vs 30.4%; $P = 0.19$). Maréchaux et al also showed that the risk of VHD in SSRI users is similar to that of non-SSRI users (7.7% vs 8.9%; $P = 0.71$) among patients who have been exposed to benfluorex, which is an antidiabetic agent with a potential risk for causing VHD.[23] However, by exploring the nationwide claims database, our study accessed a more general population than these 2 existing studies.

As with all observational studies based on claim databases, some limitations related to this study should be recognized. First, the NHIRD lacks physical parameters and social histories, including body mass indices and smoking histories, which may be associated with the risk of VHD. However, we used chronic obstructive pulmonary disease as a surrogate for smoking

history. Moreover, we adjusted for a broad variety of covariates in our model and still demonstrated a greater risk of VHD among the current users of antidepressants. Second, information about adherence to the prescribed medication regimens is not contained in the NHIRD. Finally, a larger sample size is required to investigate the relationships between different antidepressants and the risk of VHD as there were many categories with a small sample size (Appendix 2, http://links.lww.com/MD/A850).

CONCLUSIONS

This population-based study demonstrated that the current use of antidepressants was associated with an increased risk of VHD in a Chinese population in Taiwan. Furthermore, the risk varied between the different types of antidepressants, and this effect cannot be explained by the potencies of their pharmacodynamics or their pharmacokinetics properties. When patients with specific underline diseases use antidepressants, they should be closely monitored for the risk of VHD.

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