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ORIGINAL RESEARCH

Comparative Cardiovascular Safety of Duloxetine and Gabapentin in Patients with Hip Osteoarthritis

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Objective: Duloxetine, an antidepressant commonly used as a nonopioid analgesic for chronic pain management, has been speculated to increase cardiovascular (CV) complications. This study aims to evaluate the CV and mortality risks associated with duloxetine compared to gabapentin in patients with hip osteoarthritis (OA).

Methods: In this population-based, retrospective cohort study using Korean health insurance data (2013–2022), we evaluated the cardiovascular risk of duloxetine versus gabapentin in patients with hip osteoarthritis, applying inverse probability of treatment weighting (IPTW) with adjustment methods, with outcomes included composite cardiovascular events, major cardiovascular events (MACE), stroke, heart failure, and acute myocardial infarction (AMI).

Results: A total of 3383 and 18,874 patients were included in the duloxetine and gabapentin groups, respectively, with a mean follow-up of 4.1 years. The composite outcomes risk was higher with duloxetine than with gabapentin (HR 1.10; 95% CI, 1.03–1.17). Duloxetine was associated with increased risk of MACE (HR 1.15; 95% CI, 1.06–1.27), hemorrhagic stroke (HR 1.52; 95% CI, 1.23–1.86), and heart failure (HR 1.19; 95% CI, 1.05–1.34), whereas a lower risk was observed for AMI (HR 0.65, 95% CI, 0.52–0.82). In our subgroup analysis of patients with no baseline cardiovascular diseases (CVDs), duloxetine users had a higher likelihood of experiencing composite outcomes (HR 1.29), MACE (1.41), hemorrhagic stroke (HR 1.79), ischemic stroke (HR 1.18), and heart failure (HR 1.44) compared to gabapentin users.

Conclusion: Duloxetine was generally associated with increased CV risks, while a lower risk of AMI and no significant increase in mortality were observed compared to gabapentin. Our subgroup analysis further suggests that when potential confounding from preexisting CVDs was minimized, duloxetine was associated with incident CV complications in patients without prior CVDs.

Keywords: duloxetine, cardiovascular risk, osteoarthritis pain management, nonopioid analgesic

Introduction

Degenerative osteoarthritis (OA) is the most common age-related joint disorder, characterized by cartilage degradation, bone shape changes, and inflammation[1] It primarily causes pain and stiffness, significantly impacting mobility, mood, and quality of life, particularly in older population and women.[2,3] Studies have demonstrated that OA patients are also at high risk for cardiovascular (CV) adverse outcomes, as the severity of disability and the duration of hip and knee OA are strongly associated with an increased risk of CV events and mortality.[4] Another significant challenge for OA patients is physical disability, primarily caused by chronic pain. OA-related pain is multifactorial, arising from both intra- and extra-articular factors, as well as sensitization of the central and peripheral nervous systems.[5] These mechanisms contribute to functional impairment and depressive mood, imposing a substantial burden on healthcare systems.[2,6,7] Current management strategies for OA pain primarily rely on nonsteroidal anti-inflammatory drugs (NSAIDs), while opioids are used in limited circumstances.[8] However, their use in OA patients, especially elderly patient populations, is often limited due to significant side effects. NSAIDs, for instance, are linked to CV risks as well as gastrointestinal and renal complications,[9]

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while opioids carry a high potential for addiction.[6,10] These concerns underscore the need for safer analgesic alternatives, particularly for elderly patients at high risk of CV complications.[11,12] Recent clinical guidelines recommend duloxetine as a potential pharmacologic option for OA pain, whereas gabapentin is not routinely recommended and is generally prescribed off-label.[8] Although duloxetine has been compared with NSAIDs and opioids for analgesic effectiveness in OA, its cardiovascular safety has not been well characterized, and evidence on gabapentin is even more limited.

Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is one of the most commonly prescribed nonopioid analgesics for managing chronic musculoskeletal pain, fibromyalgia, and diabetic peripheral neuropathy and has emerged as an off-label option for targeting stress urinary incontinence and chemotherapy-induced peripheral neuropathy.[13] Despite its therapeutic potential, the safety profile of duloxetine remains underexplored, particularly in OA patients with chronic pain. While its dual mechanism, targeting serotonergic and adrenergic pathways, may help address both peripheral and central sensitization in the pathophysiology of OA pain, it also introduces unique CV and bleeding risks.[12,14,15] On one hand, duloxetine's serotonergic activity enhances serotonin reuptake inhibition, potentially providing antiplatelet effects that may reduce the risk of ischemic events, such as stroke and acute myocardial infarction (AMI).[16,17] However, this same activity has also been linked to an increased risk of hemorrhagic events, including intracranial and gastrointestinal hemorrhage, possibly due to reduced platelet aggregation resulting from the inhibition of serotonin uptake in platelets.[18,19] Additionally, its adrenergic effects, stemming from norepinephrine reuptake inhibition, may increase sympathetic nervous system activity, leading to elevated blood pressure and heart rate, further exacerbating CV risks.[18,20,21] Given the current focus on nonopioid therapies for chronic pain management, it is essential to evaluate the CV risks of duloxetine in OA patients across all adult age groups, particularly those with multiple comorbid conditions who are more vulnerable to CV complications.[17,22,23] We therefore investigated the potential association between duloxetine use and major cardiovascular outcomes in patients with hip OA.

Gabapentin, an anticonvulsant, is another widely used nonopioid off-label medication for OA pain. Unlike duloxetine, which modulates central pain pathways, gabapentin primarily targets peripheral pain sensitization.[24–27] This distinction suggests that gabapentin may have a lower likelihood of contributing to CV or bleeding risks compared to duloxetine. However, the effects of gabapentin on CV outcomes in OA patients remain insufficiently studied.[25] Given the pharmacologic differences between duloxetine and gabapentin, their respective safety profiles may differ, especially in OA patients with multiple comorbid conditions who are at elevated risk for CV and bleeding complications.[17,22]

Although previous studies have reported potential bleeding risks and suggested that duloxetine may influence hemodynamic parameters and increase CV risks,[28] whether this translates into an increased risk of major CV events, such as AMI, stroke, or mortality, in OA patients with multiple comorbid conditions has not been fully elucidated. The contrasting pharmacologic profiles of duloxetine and gabapentin highlight the need for a comparative risk analysis to evaluate their CV safety in OA patients. Gabapentin's relatively mild CV safety profile makes it a relevant comparator for evaluating the CV risks of duloxetine.[29] In this study, we specifically included patients with hip OA, as their pain is often more intense than that of knee OA, leading to greater analgesic use. Additionally, nonopioid treatment options for hip OA are more limited, as topical NSAIDs and joint injections are used less frequently for hip OA.[30] This study aims to assess the major CV outcomes and mortality risks associated with duloxetine compared to gabapentin, providing evidence to support safe analgesic strategies that address the specific needs of hip OA patients with multiple comorbid conditions.

Methods

Data Source

Patient data were extracted from the Korean Health Insurance Review and Assessment Service (HIRA) database which contains claims data for the nearly entire South Korean population of approximately 50 million beneficiaries.[31,32] HIRA datasets cover all outpatient and inpatient visits, patients' demographic details, healthcare institution types, medical procedures and services, diagnoses, and medical utilization information, such as admission dates, length of hospitalization, medical specialty, and prescription records. Diagnoses are coded according to the Korean Standard Classification of Disease Sixth Revision, an adapted version of the International Classification of Disease Tenth Revision (ICD-10). The comprehensive datasets, generated under the national health insurance schemes, serves as a valuable resource for

healthcare research.[33] The protocol of this study was approved by the Institutional Review Board (IRB) of Kyung Hee University (KHSIRB-23-272-1(EA)) and Ajou University (202502-HB-EX-002). Due to the retrospective nature of the study, the IRB waived the requirement for informed consent. Additional ethics approval was not required, as HIRA granted authorization to analyze anonymized patient data for research purposes.

Study Design and Cohort

This nationwide population-based cohort study included adult patients with hip OA in Korea from January 2013 to December 2022. Patients were identified for the initial study cohort if they had been diagnosed with hip OA (ICD-10 code, M16) between January 2014 and December 2017 and had received duloxetine or gabapentin for OA pain management. The year 2013 served as the reference period for assessing baseline characteristics of patients recruited in 2014. Patients with psychiatric disorders at baseline were excluded to ensure that study medications were used primarily for analgesic purposes and to minimize potential confounding from individuals taking duloxetine for other indications, such as major depressive disorder and generalized anxiety disorder.[24] The index date for study entry was defined as the date of the first use of study medication in each patient, and patients were followed until an outcome event, death, or study end. To include only patients newly initiated on either duloxetine or gabapentin during the study period, those who had prior exposure to either medication during the baseline period or concurrent use of both during the study period were excluded. Additional exclusion criteria included: (1) individuals younger than 20 years or older than 85 years at the time of study entry; (2) those with end-stage renal disease or a history of renal transplantation before study entry or within 180 days post the index date; (3) a history of metastatic cancer before study entry or within 180 days after the index date. Comedication with other analgesics and treatments for comorbid conditions, such as diabetes and CV disease (CVD) at baseline, were permitted. An overview of the cohort selection process is presented in Figure S1 in the supplementary material.

Study Outcomes

The primary outcome was the incidence and risk of composite outcomes, which include all-cause death, cardiac death, new-onset AMI, stroke (both ischemic and hemorrhagic), arrhythmia, and heart failure. The secondary endpoints included the individual outcomes that comprised the composite primary outcomes. All-cause deaths were identified using ICD-10 codes I46.1, R96, R98, and R99, which encompass sudden cardiac arrest, instant death, and unspecified causes of mortality in claims data during the follow-up period. Major adverse cardiovascular events (MACE) were defined as a composite of cardiac death (I46.1), AMI (I21-22), and stroke (I60-64), including both ischemic stroke (I63) and hemorrhagic stroke (I60-62),[34,35] identified through hospital encounters with an outcome event diagnosis. For both AMI and stroke, only those events recorded as the primary diagnosis during hospitalization were included in the study analysis. Arrhythmia was identified using ICD-10 codes I48 and I49, while heart failure was identified using ICD-10 code I50[36] The outcome definitions and diagnostic codes used in this study were based on methodologies employed in previous research.[37,38] The outcome date was determined as the earliest date a patient experienced a given outcome event. All patients were followed up from the cohort entry date, defined as the date of the first prescription for duloxetine or gabapentin after a hip OA diagnosis, until the occurrence of a CV outcome event, death, or the end of the study period (December 31, 2022), whichever came first. This allowed for a maximum follow-up period of nine years.

Covariates

The baseline period was defined as the 12 months preceding the index date, during which patient demographics and baseline characteristics, including sex, age, and diagnosis data related to comorbidities, were identified. Patient cohorts were further categorized into four age groups: 20–44 years, 45–64 years, and 65–84 years. Preexisting comorbidities, such as diabetes mellitus (DM), DM with complications, cancer, renal disease, and CVDs, at study entry were identified using ICD-10 codes and incorporated into the analysis as baseline variables. CVDs include hypertension, ischemic heart disease, and other heart conditions, such as pericarditis, myocarditis, and related disorders. The Charlson Comorbidity Index (CCI) was calculated for the year prior to the index date.[39] Prescription data on treatments for comorbid conditions during the study period were also extracted and assessed as comedications if the respective therapy lasted for more than

30 days. The comedications considered included angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), nitrates, statins, anticoagulants, and antiplatelets.

Statistical Analysis

To assess the risk of CV outcomes and mortality associated with duloxetine compared to gabapentin, inverse probability of treatment weighting (IPTW) based on propensity scores was employed to balance baseline characteristics between treatment groups. Propensity scores, which represent the conditional probability of being assigned to either duloxetine or gabapentin based on observed baseline covariates, were calculated using a binary logistic regression model.[40] (Rosenbaum & Rubin, 1983) By applying IPTW, we created a pseudo-population in which the covariate distribution was balanced between the treatment groups, allowing for a more accurate estimation of the average treatment effect in the population.[41] Covariate balance was assessed using standardized mean differences (SMDs), with values below 0.1 indicating adequate balance after weighting.[42] A weighted Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for CV outcomes and mortality risks. The risk analysis based on the weighted model was further adjusted for relevant covariates, including age, sex, CCI, baseline DM and CVD, and the use of ACE inhibitors/ARBs, statins, and antiplatelets. These analyses were conducted over the entire follow-up period and within a predefined mid-term interval of up to 2 years to examine time-dependent variations in risk. The risk analysis for composite outcomes was then stratified by baseline covariates, including age, sex, CCI, comorbidities and comedication patterns with CV drugs, to account for the varying effects of study medications across different patient factors. We additionally examined the proportional hazards assumption using Schoenfeld residuals, visualized group differences with Kaplan–Meier curves for the composite outcome, and tested a negative control outcome (appendicitis; ICD-10 K35, K36, K37) with no plausible association with either duloxetine or gabapentin.[43] The *p*-values were two-sided, with statistical significance defined as $p < 0.05$. Statistical analyses were performed using R Statistical Software (version 4.1.0; R Core Team, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Subgroup analysis

A subgroup analysis of non-CVD patients was conducted by excluding those with baseline CV conditions, such as hypertension, ischemic heart disease, and other aforementioned heart conditions, using the IPTW with adjustment methods. This analysis was designed to further assess the effects of duloxetine versus gabapentin on CV and mortality outcomes while minimizing potential confounding from preexisting CV conditions.[44,45]

Sensitivity Analysis

To further validate our study findings, we conducted sensitivity analyses utilizing three approaches. First, risk analysis using the IPTW with adjustment methods was repeated, varying the follow-up periods: up to 1 year, up to 2 years, and the entire follow-up period. Second, we performed a lagged exposure analysis, excluding outcome events occurring within 30, 90, 150, or 180 days after treatment initiation to reduce potential protopathic bias. Lastly, a separate risk analysis was conducted after propensity score matching (PSM) with adjustment, using nearest-neighbor matching with a caliper of 0.2 and a 1:3 matching ratio between groups.

Results

Characteristics of Study Patients

Of the 487,994 patients diagnosed with hip OA who received either duloxetine or gabapentin between 2014 and 2017, 465,737 were excluded for reasons specified in Figure 1. Consequently, a total of 22,257 patients (3383 in the duloxetine group and 18,874 in the gabapentin group) were deemed eligible for study entry. Baseline characteristics of the study patients, both before and after IPTW, were summarized side by side in Table 1. In both treatment groups, female patients outnumbered male patients (61.2% vs 62.3% in the duloxetine and gabapentin groups, respectively). The age distribution was similar between groups, with patients aged 45–64 years accounting for approximately 57% of the study patients, followed by those aged 65–84 years, who made up about 38%. The mean CCI was 2.3±1.9 in the duloxetine group and

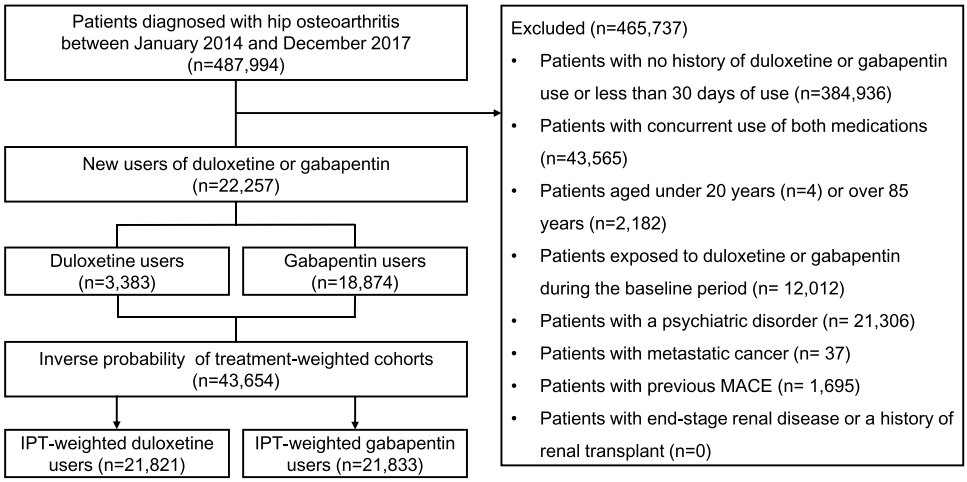

Figure 1 Flow chart of the process of selecting study patients.
Abbreviations: IPT, inverse probability of treatment; MACE, major adverse cardiovascular event.

2.4±2.1 in the gabapentin group, and the largest proportion of patients had a CCI score of ≥3 (36.9% vs 39.6%). Overall, the between-group distribution of comorbid conditions was comparable. CVD was the most prevalent preexisting condition (55.9% versus 57.2%), with hypertension being the most common CV condition (52.9% vs 54.2%). DM

Table 1 Baseline Characteristics of Study Patients (Duloxetine Vs Gabapentin)

	Overall Cohort			Weighted Cohort		
	Duloxetine (n=3383)	**Gabapentin (n=18874)**	**SMD**	**Duloxetine (n=21821)**	**Gabapentin (n=21833)**	**SMD**
Sex, n (%)						
Male	1313 (38.8)	7123 (37.7)	0.022	8203 (37.6)	8230 (37.7)	0.002
Female	2070 (61.2)	11751 (62.3)		13618 (62.4)	13603 (62.3)	
Age, mean±SD	63.2±11.5	63.7±11.2	0.047	63.2±11.5	63.6±11.3	0.037
20–44 years, n (%)	170 (5.0)	807 (4.3)	0.037	1051 (4.8)	958 (4.4)	0.026
49–64 years, n (%)	1910 (56.5)	10841 (57.4)		12218 (56.0)	12450 (57.0)	
65–84 years, n (%)	1303 (38.5)	7226 (38.3)		8552 (39.2)	8426 (38.6)	
CCI, mean±SD	2.3±1.9	2.4±2.1	0.065	2.3±1.9	2.4±2.1	0.037
≤ 1, n (%)	1405 (41.5)	7473 (39.6)	0.067	5443 (24.9)	5082 (23.3)	0.052
2, n (%)	728 (21.5)	3935 (20.8)		4745 (21.7)	4602 (21.1)	
≥3, n (%)	1250 (36.9)	7466 (39.6)		8207 (37.6)	8432 (38.6)	
Comorbidity, n (%)						
DM	1025 (30.3)	6282 (33.3)	0.064	7109 (32.6)	7102 (32.5)	0.001
DM with complications	311 (9.2)	2189 (11.6)	0.079	2128 (9.8)	2440 (11.2)	0.047
Cancer	303 (9.0)	1560 (8.3)	0.025	1715 (7.9)	1741 (8.0)	0.004
Renal disease	78 (2.3)	510 (2.7)	0.025	396 (1.8)	379 (1.7)	0.006
Cardiovascular disease	1891 (55.9)	10797 (57.2)	0.026	12315 (56.4)	12308 (56.4)	0.001
Hypertension	1790 (52.9)	10239 (54.2)	0.027	11654 (53.4)	11665 (53.4)	<0.001
Ischemic heart disease	446 (13.2)	2200 (11.7)	0.046	2784 (12.8)	2466 (11.3)	0.045
Other heart disease[†]	305 (9.0)	1742 (9.2)	0.007	1878 (8.6)	1948 (8.9)	0.011

(*Continued*)

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Table 1 (Continued).

	Overall Cohort			Weighted Cohort		
	Duloxetine (n=3383)	**Gabapentin (n=18874)**	**SMD**	**Duloxetine (n=21821)**	**Gabapentin (n=21833)**	**SMD**
Comedication, n (%)						
Beta-blocker	301 (8.9)	1544 (8.2)	0.026	1648 (7.6)	1657 (7.6)	0.001
ACEi/ARB	309 (9.1)	1770 (9.4)	0.008	2027 (9.3)	2001 (9.2)	0.004
CCB	264 (7.8)	1400 (7.4)	0.015	1530 (7.0)	1547 (7.1)	0.003
Nitrate	122 (3.6)	583 (3.1)	0.029	735 (3.4)	654 (3.0)	0.021
Statin	1064 (31.5)	5888 (31.2)	0.005	6636 (30.4)	6705 (30.7)	0.007
Antiplatelet	668 (19.7)	3499 (18.5)	0.031	4224 (19.4)	3945 (18.1)	0.033
Anticoagulant	73 (2.2)	382 (2.0)	0.009	462 (2.1)	422 (1.9)	0.013

Note: †Other heart disease includes pericarditis, myocarditis and related conditions.
Abbreviations: SMD, standardized mean difference; SD, standard deviation; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; ACEi, angiotensin-converting enzyme Inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

was the next most common comorbidity (30.3% vs 33.3%). Regarding comedication history, statins were the most commonly used treatment (31.5% vs 31.2%), followed by antiplatelets (19.7% vs 18.5%). After IPTW, all SMD values were below 0.1, confirming appropriate balance in terms of age, CCI, comorbidities, and comedication history between groups. Extreme propensity score values at the 1st and 99th percentiles were trimmed to improve comparability between groups. The propensity score distribution after trimming is shown in Figure S2 in the supplementary material. The overall mean duration of follow-up was 4.1±2.3 years, which was comparable between groups.

The Incidence and Risk of CV and Mortality Events

Over the entire follow-up period, the incidence rate (IR) per 100 person-years (PY) for composite outcomes was 2.16 (95% CI, 1.94–2.40) in the duloxetine group and 2.03 (95% CI, 1.93–2.13) in the gabapentin group (Table 2). The HR for composite outcomes comparing duloxetine to gabapentin was 1.10 (95% CI, 1.03–1.17) in the weighted model with adjustment. The incidence of MACE in IR/100 PY was 1.04 (95% CI, 0.89–1.21) in the duloxetine group and 0.93 (95% CI, 0.86–0.99) in the gabapentin group, with an HR of 1.15 (95% CI, 1.06–1.27) when comparing duloxetine to gabapentin. Among the individual MACE outcomes, the primary contributor to the increased risk with duloxetine was hemorrhagic stroke, with an HR of 1.52 (95% CI, 1.23–1.86), while the risk of AMI was lower with duloxetine, with an HR of 0.65 (95% CI, 0.52–0.82). Given the limited number of hemorrhagic stroke events (n=38), the study had 80% power at α=0.05 to detect HRs of approximately 3.5 or greater, and these results should therefore be interpreted with caution. The HR for heart failure was 1.19 (95% CI, 1.05–1.34). In a Fine–Gray competing-risk model treating death as a competing event, the subdistribution HR for MACE was 1.16 (95% CI, 0.98–1.37), directionally consistent with the cause-specific Cox estimate but attenuated. However, duloxetine was not associated with an increased risk of all-cause death, cardiac death, ischemic stroke, or arrhythmia compared to gabapentin. All statistically significant HRs in the weighted model remained significant after adjustment, with similar patterns observed in the mid-term follow-up analysis. When followed up for up to 2 years, the HR of duloxetine versus gabapentin was 1.23 (95% CI, 1.13–1.35) for composite outcomes and 1.32 (95% CI, 1.14–1.51) for MACE, with an HR of 1.69 (95% CI, 1.23–2.32) for hemorrhagic stroke. Increased heart failure risk was observed again in the mid-term follow-up analysis, with an HR 1.78 (95% CI, 1.45–2.19). Overall, these results suggest that duloxetine users were at an increased risk of composite outcomes, MACE (specifically hemorrhagic stroke), and heart failure compared to gabapentin users. Absolute risk differences further illustrated the higher risk of composite and individual cardiovascular outcomes in duloxetine users compared to gabapentin (Figure S3). To account for the differential effects of duloxetine based on patient risk factors, the composite outcomes analysis was repeated after stratification by age, sex, CCI, comorbidities, and comedication patterns with CV drugs, and the results are summarized in Figure 2. Overall, patients treated with duloxetine tended to have a higher risk of

Table 2 Cardiovascular Risks in Duloxetine vs Gabapentin Users: Unweighted and Weighted Analyses

Category	Duloxetine (n= 3383)			Gabapentin (n=18874)			HR (95% CI)			
	No. of Events	PY	IR/100PY (95% CI)	No. of Events	PY	IR/100PY (95% CI)	Unweighted Model	Weighted Model	Weighted Model with Adjustment[†]	*p*-value[‡]
Up to 2 years										
Composite outcomes[§]	165	6079.2	2.71 (2.32–3.16)	743	33950.2	2.18 (2.03–2.35)	**1.24 (1.05–1.47)**	**1.23 (1.13–1.35)**	**1.23 (1.13–1.35)**	**<0.01**
All-cause death	69	6197.2	1.11 (0.86–1.40)	480	34303.1	1.39 (1.27–1.53)	0.80 (0.62–1.04)	**0.80 (0.70–0.90)**	**0.80 (0.71–0.91)**	**<0.01**
MACE	72	6191.7	1.16 (0.90–1.46)	304	64474.6	0.88 (0.75–0.98)	**1.33 (1.02–1.73)**	**1.33 (1.15–1.53)**	**1.32 (1.14–1.51)**	**<0.01**
Cardiac death	9	6252.0	0.14 (0.06–0.27)	33	34758.2	0.09 (0.06–0.13)	1.44 (0.66–3.13)	1.47 (0.96–2.23)	1.46 (0.95–2.22)	0.08
AMI	5	6256.4	0.08 (0.03–0.19)	59	34733.1	0.17 (0.13–0.22)	0.47 (0.19–1.17)	**0.48 (0.32–0.73)**	**0.48 (0.31–0.72)**	**<0.01**
Stroke	58	6204.9	0.93 (0.70–1.21)	214	34570.5	0.62 (0.54–0.71)	**1.51 (1.13–2.02)**	**1.54 (1.31–1.81)**	**1.52 (1.29–1.79)**	**<0.01**
Hemorrhagic	16	6241.6	0.26 (0.15–0.42)	53	34741.0	0.16 (0.11–0.20)	1.68 (0.96–2.94)	**1.72 (1.25–2.35)**	**1.69 (1.23–2.32)**	**<0.01**
Ischemic	69	6197.1	1.11 (0.87–1.41)	362	34423.4	1.05 (0.94–1.17)	1.06 (0.82–1.37)	1.08 (0.94–1.23)	1.07 (0.93–1.22)	0.30
Arrhythmia	34	6222.9	0.54 (0.37–0.76)	190	34573.2	0.55 (0.47–0.63)	1.00 (0.69–1.43)	1.02 (0.84–1.23)	1.02 (0.85–1.23)	0.81
Heart failure	38	6174.4	0.62 (0.44–0.84)	124	34453.3	0.36 (0.29–0.43)	**1.71 (1.19–2.46)**	**1.79 (1.46–2.20)**	**1.78 (1.45–2.19)**	**<0.01**
Entire follow-up period										
Composite outcomes	340	15708.9	2.16 (1.94–2.40)	1601	78988.9	2.03 (1.93–2.13)	1.08 (0.96–1.22)	**1.09 (1.03–1.16)**	**1.10 (1.03–1.17)**	**0.03**
All-cause death	204	16336.3	1.25 (1.08–1.43)	1110	80492.9	1.38 (1.30–1.46)	0.93 (0.79–1.08)	0.93 (0.96–1.00)	0.93 (0.86–1.01)	0.07
MACE	171	16321.9	1.04 (0.89–1.21)	756	81596.6	0.93 (0.86–0.99)	1.13 (0.96–1.34)	**1.16 (1.06–1.26)**	**1.15 (1.06–1.27)**	**<0.01**
Cardiac death	19	16857.7	0.11 (0.07–0.18)	82	83561.8	0.09 (0.07–0.12)	1.17 (0.70–1.95)	1.18 (0.90–1.55)	1.18 (0.89–1.54)	0.23
AMI	19	16834.4	0.11 (0.07–0.18)	149	83145.8	0.18 (0.15–0.21)	0.63 (0.39–1.03)	**0.65 (0.51–0.81)**	**0.65 (0.52–0.82)**	**<0.01**
Stroke	139	16412.9	0.85 (0.71–1.0)	540	82016.5	0.66 (0.6–0.72)	**1.13 (1.18–1.45)**	**1.32 (1.18–1.46)**	**1.32 (1.19–1.46)**	**<0.01**
Hemorrhagic	38	16772.7	0.23 (0.16–0.32)	129	83203.2	0.16 (0.13–0.18)	**1.48 (1.02–2.13)**	**1.50 (1.22–1.84)**	**1.52 (1.23–1.86)**	**<0.01**
Ischemic	161	16340.2	0.98 (0.84–1.15)	827	81046.8	1.02 (0.95–1.09)	0.99 (0.91–1.08)	0.99 (0.91–1.08)	0.99 (0.91–1,09)	0.95
Arrhythmia	74	16649.4	0.44 (0.35–0.56)	365	82441.7	0.44 (0.4–0.49)	1.06 (0.82–1.36)	1.06 (0.93–1.21)	1.07 (0.94–1.22)	0.31
Heart failure	89	16422.5	0.54 (0.43–0.66)	381	81752.4	0.47 (0.42–0.52)	1.15 (0.91–1.45)	**1.17 (1.03–1.33)**	**1.19 (1.05–1.34)**	**0.01**

Notes: [†]Adjusted for age, sex, CCI, baseline DM and CVD, and the use of ACE inhibitors/ARBs, statins, and antiplatelets. [‡]*p*-values are derived from the weighted model with adjustment. [§]Composite outcomes were defined as the occurrence of any of the listed cardiovascular outcomes (all-cause death, cardiac death, AMI, stroke, arrhythmia, or heart failure).Statistically significant HR (95% CI) and *p* values were highlighted in bold.

Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-year; IR, incidence rate; MACE, major adverse cardiovascular event; AMI, acute myocardial infarction; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Subgroup	Duloxetine No of events/PY	IR/100PY	Gabapentin No of events/PY	IR/100PY	HR (95% CI)
Age (years)					
20–44	6/939.2	0.6	14/3803.7	0.4	1.78 (0.98–3.23)
45–64	257/8347.6	3.1	1260/43398.6	2.9	1.07 (1.01–1.16)
65–84	77/6403.1	1.2	326/31587	1.0	1.19 (1.03–1.35)
Sex					
Male	148/6060.1	2.4	603/30000.1	2.0	1.26 (1.14–1.39)
Female	192/9629.9	2.0	997/48789.3	2.0	1.00 (0.92–1.08)
CCI					
≤1	122/6852.1	1.8	432/32292.7	1.3	1.33 (1.19–1.49)
≥2	218/8837.9	2.5	1168/46496.6	2.5	1.02 (0.94–1.10)
Comorbidities					
Cancer	25/1115.6	2.2	135/6273.4	2.2	0.98 (0.77–1.24)
DM	116/4252.8	2.6	665/25279.9	2.6	1.00 (0.90–1.10)
DM with complications	42/1363.3	3.1	265/9008.5	2.9	1.39 (1.17–1.64)
CVD	235/8303.9	2.8	1196/43543.2	2.7	1.05 (0.97–1.13)
Renal disease	12/294.4	4.1	86/1911.9	4.5	0.84 (0.60–1.18)
Comedications					
ACEi/ARB	45/1284.9	3.5	201/7314.9	2.7	1.32 (1.11–1.57)
Beta-blocker	61/1278	4.8	285/5877.5	4.8	1.02 (0.87–1.19)
CCB	42/1226.9	3.4	185/5908.6	3.1	1.19 (1.00–1.43)
Statin	123/4593.8	2.7	555/23591.9	2.4	1.12 (1.01–1.25)
Antiplatelet	95/3005	3.2	466/14442.1	3.2	1.01 (0.90–1.13)

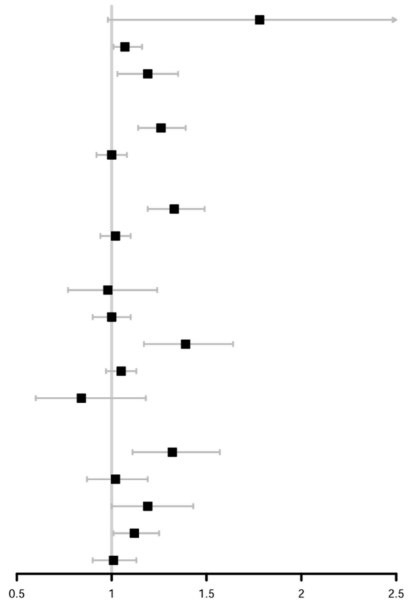

Figure 2 Stratified risk analyses of composite outcomes associated with duloxetine vs gabapentin in patients with Hip osteoarthritis.
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-year; IR, incidence rate; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; CVD, cardiovascular disease; ACEi, angiotensin-converting enzyme Inhibitor; ARB, angiotensin II receptor blocker.

developing CV complications than those using gabapentin, especially in older age groups: the HR was 1.07 and 1.19 for the 45–64-year and 65–84-year age groups, respectively. In terms of CCI, patients with a CCI of ≤1 had an elevated CV risk with duloxetine (HR 1.33; 95% CI, 1.19–1.49), whereas those with a CCI of ≥2 showed no significant difference (HR 1.02; 95% CI, 0.94–1.10). Other strata suggesting an elevated CV risk with duloxetine include males (HR 1.26; 95% CI, 1.14–1.39), comedication with ACE inhibitors or ARBs (HR 1.32; 95% CI, 1.11–1.57), and comedication with stains (HR 1.12; 95% CI, 1.01–1.25). The risk of CV complications was comparable between treatment groups, regardless of preexisting comorbid conditions, including DM, cancer, renal disease, and CVD.

Subgroup Analysis

The risk analysis for CV and mortality outcomes were repeated in non-CVD patients using the IPTW and adjustment methods, and the results are summarized in Figure 3. Interestingly, non-CVD patients exposed to duloxetine therapy were more likely to experience composite outcomes (HR 1.29; 95% CI, 1.14–1.45), MACE (HR 1.41; 95% CI, 1.19–1.66), and stroke (HR 1.63; 95% CI, 1.35–1.96), including hemorrhagic stroke (HR 1.79; 95% CI, 1.28–2.53) and ischemic stroke (HR 1.18; 95% CI, 1.01–1.39), relative to gabapentin-treated patients with no preexisting CVD. Additionally, duloxetine use was associated with an increased risk of heart failure in non-CVD patients.

Before sensitivity analyses, we additionally examined model assumptions and visualized survival differences. Schoenfeld residual tests did not indicate major violations of the proportional hazards assumption (Figure S4). Kaplan–Meier curves demonstrated consistently higher cumulative incidence of composite outcomes among duloxetine users compared to gabapentin (Figure S5).

Sensitivity Analysis

For sensitivity analysis, we repeated the risk analysis for CV and mortality outcomes with varying follow-up periods, and the results are summarized in Table S1 of the supplementary material. Our sensitivity analyses confirmed the robustness and consistency of our study findings. The HR for composite outcomes indicated a consistent trend of elevated CV risk with duloxetine use in hip OA patients, compared to gabapentin use. The HR (95% CI) was 1.19 (1.06–1.33) for a follow-up period

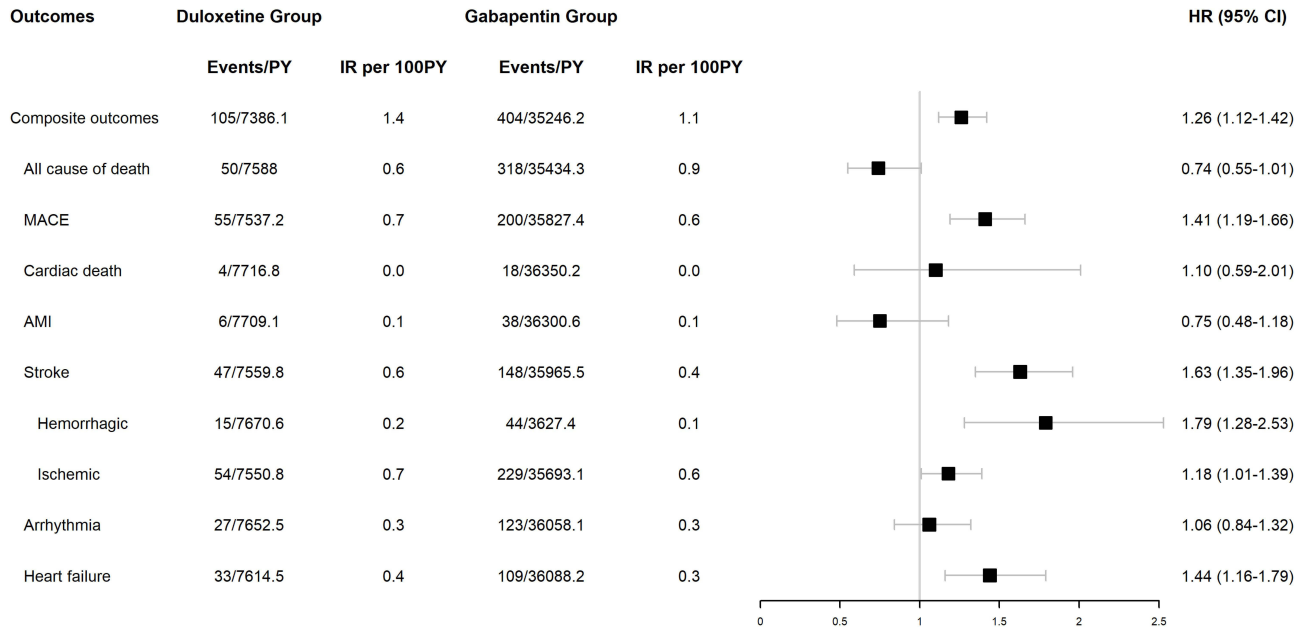

Figure 3 Subgroup analyses of cardiovascular events and mortality risk associated with duloxetine vs gabapentin in Hip osteoarthritis patients without baseline cardiovascular disease.
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-year; IR, incidence rate; MACE, major adverse cardiovascular event; AMI, acute myocardial infarction.

of up to 1 year, 1.23 (1.13–1.35) for up to 2 years, and 1.10 (1.03–1.17) for the entire follow-up period of 4.1±2.3 years. Similar trends were observed for other outcomes across all three follow-up periods. Additionally, we applied four different grace periods and repeated the risk analysis for composite outcomes and MACE. The results are summarized in Table S2.

In the lagged exposure analysis, the HR (95% CI) for composite outcomes was 1.12 (1.05–1.19) at 30 days, 1.11 (1.04–1.19) at 90 days, 1.09 (1.01–1.16) for 150 days, and 1.08 (1.01–1.16) for 180 days. Similar trends were observed in the risk analysis for MACE, indicating a consistent risk of CV complications with duloxetine compared to gabapentin, regardless of the grace period settings. Lastly, we conducted a separate analysis using PSM with adjustment methods for the entire follow-up period. As shown in Table S3, there were no significant between-group differences in baseline variables. Risk analysis in the propensity score-matched cohort yielded findings consistent with those of the main analysis, with detailed results summarized in Table S4. As a negative control outcome, appendicitis (ICD-10 K35, K36, K37) showed no significant association between duloxetine and gabapentin users (Table S5).

Discussion

In this population-based cohort study, we performed a risk analysis to investigate the effects of duloxetine on CV and mortality outcomes as compared to gabapentin in patients with hip OA, using IPTW with adjustment methods. Over the entire follow-up period, we found that the risk of composite outcomes was higher with duloxetine than with gabapentin (HR 1.10; 95% CI, 1.03–1.17). When broken down into secondary outcomes, duloxetine was associated with an increased risk of MACE (HR 1.15; 95% CI, 1.06–1.27), hemorrhagic stroke (HR 1.52; 95% CI, 1.23–1.86), and heart failure (HR 1.19; 95% CI, 1.05–1.34), whereas a lower risk was observed for AMI (HR 0.65, 95% CI, 0.52–0.82).

OA patients often require long-term analgesic therapy due to OA-associated chronic pain. Nonopioid analgesics are increasingly favored to reduce opioid use in this population. Given the advanced age of these patients and the chronic, progressive nature of OA, evaluating the CV safety of duloxetine, a nonopioid treatment option, is crucial. In line with our hypothesis, duloxetine was associated with an increased CV risk, likely attributable to its norepinephrine reuptake inhibition, which may lead to blood pressure dysregulation and heightened sympathetic activity.[46–48] In our stratified analyses by patient factors (age, sex, CCI, comorbidities, and comedications), duloxetine's elevated risk for composite outcomes remained significant after statistical adjustments in older patients aged 45–64 years (HR 1.07) and 65–84 years (HR 1.19), males (HR 1.26), CCI ≤1 (HR 1.33), those with advanced DM with complications at baseline (HR 1.39), and

those comedicated with ACE inhibitors/ARBs (HR 1.32) or statins (HR 1.12). Although these findings suggest that duloxetine may warrant careful monitoring in higher-risk subgroups, particularly older males and patients with lower comorbidity burden, with attention to blood pressure, heart rate, and bleeding complications, they should be regarded as exploratory given the multiple endpoints and subgroup analyses assessed.

Previous studies have suggested a potential link between SNRIs, including duloxetine, and CV risks, possibly due to increased cardiac sympathetic activity, which may result in tachycardia and elevated blood pressure.[15,17,49,50] Consistent with our findings, other studies have also reported an increased CV events in elderly patients and those with preexisting DM.[48,51] Additionally, a study reported an increased incidence of intracranial hemorrhage in SNRI users compared to selective serotonin reuptake inhibitor (SSRI) users among patients without depression as a comorbid condition (HR 1.63; 95% CI, 1.14–2.32).[52] Similarly, Leong et al reported an elevated risk of stroke (HR 1.20; 95% CI, 1.08–1.33) in SNRI users compared to SSRI users.[18] Notably, they also observed increased all-cause mortality in SNRI users without mood or anxiety disorders, suggesting a high CV and mortality risk in non-psychiatric populations exposed to duloxetine. These results align with our findings, as we also excluded patients with a history of psychiatric disorders from risk analysis. Although our study did not find a notable increase in all-cause mortality risk, we observed an elevated risk of stroke, particularly hemorrhagic stroke, associated with duloxetine use in hip OA patients without psychiatric comorbidities.

Interestingly, in our subgroup analysis of patients with no baseline CVDs, those exposed to duloxetine had a higher likelihood of experiencing composite outcomes (HR 1.29), MACE (1.41), both hemorrhagic stroke (HR 1.79) and ischemic stroke (HR 1.18), and heart failure (HR 1.44) compared to those receiving gabapentin. These results further confirm that when potential confounding effects from preexisting CVDs were minimized, duloxetine was associated with higher risk of incident CV complications in patients without prior CVDs. Given that this study focused on a non-psychiatric patient population, these risks should be carefully considered when prescribing duloxetine for pain management. Patients with CV risk factors may require cautious use and close monitoring of CV complications. Clinicians should evaluate individual CV risk profiles and implement appropriate monitoring strategies to minimize potential adverse effects, ensuring its safer use as a nonopioid analgesic option for chronic pain management.

This study has several limitations. First, its focus on hip OA patients receiving duloxetine for analgesic purposes may limit the generalizability of the findings to other patient populations and indications for duloxetine. Second, despite the use of IPTW, adjusted multiple logistic regression methods, and rigorous sensitivity analyses, residual confounding may still exist due to unidentified covariates. Lastly, endpoint events and patient comorbidities were identified using ICD-10 diagnosis codes. Consequently, missing or inaccurate documentation in the HIRA database may have led to over- or under-estimation of outcome event frequencies and comorbid condition distributions between treatment groups. Finally, because our study population consisted of hip OA patients without psychiatric comorbidities, the generalizability of these findings to other OA populations (eg, knee OA) or international cohorts may be limited. Further studies with larger sample sizes and extended follow-up periods are needed to validate these findings and evaluate the long-term safety of duloxetine in relation to CV events and mortality across diverse patient populations with conditions beyond OA.

Conclusion

In this study, we investigated the potential risk of CV events and mortality associated with duloxetine compared to gabapentin in patients with hip OA. Our study results demonstrated that overall CV risks tended to be higher with duloxetine treatment than with gabapentin, including composite outcomes and MACE, particularly hemorrhagic stroke, as well as heart failure, with the exception of AMI. Given the growing need for nonopioid analgesics that can be used long-term in OA-related pain management, a risk-based, personalized therapeutic approach should be considered. Long-term exposure to duloxetine may lead to CV events in older OA patients, who are already vulnerable to CV complications, and may also increase the risk of incident CV events in patients without preexisting CVD. Accordingly, careful monitoring of cardiovascular and bleeding risk is advisable when duloxetine is prescribed.

Data Sharing Statement

The data used in this study were obtained with permission from the HIRA in Korea. According to HIRA regulations, the database cannot be shared, leased, or sold to any third party other than the approved researchers with authorized access.

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Disclosure

There are no competing interests to declare.

References

1. Loeser RF. The role of aging in the development of osteoarthritis. *Trans Am Clin Climatol Assoc*. 2017;128:44.
2. Quintana JM, Arostegui I, Escobar A, Azkarate J, Goenaga JI, Lafuente I. Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population. *Arch Intern Med*. 2008;168(14):1576–1584. doi:10.1001/archinte.168.14.1576
3. Hawker GA. Osteoarthritis is a serious disease. *Clin Exp Rheumatol*. 2019;37(Suppl 120):3–6.
4. Hawker GA, Croxford R, Bierman AS, et al. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. *PLoS One*. 2014;9(3):e91286. doi:10.1371/journal.pone.0091286
5. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(9):1145–1153. doi:10.1016/j.joca.2013.03.018
6. Murphy NJ, Eyles JP, Hunter DJ. Hip osteoarthritis: etiopathogenesis and implications for management. *Adv Ther*. 2016;33:1921–1946. doi:10.1007/s12325-016-0409-3
7. Lespasio MJ, Sultan AA, Piuzzi NS, et al. Hip osteoarthritis: a primer. *Perm J*. 2018;22:17–084.
8. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220–233. doi:10.1002/art.41142
9. Shin S. Safety of celecoxib versus traditional nonsteroidal anti-inflammatory drugs in older patients with arthritis. *J Pain Res*. 2018; Volume 11:3211–3219. doi:10.2147/JPR.S186000
10. Sarzi-Puttini P, Cimmino MA, Scarpa R, et al. Osteoarthritis: an overview of the disease and its treatment strategies. *Semin Arthritis Rheum*. 2005;35(1):1–10. doi:10.1016/j.semarthrit.2005.01.013
11. Corriere MA, Dickson AL, Daniel LL, et al. Duloxetine, gabapentin, and the risk for acute myocardial infarction, stroke, and out-of-hospital death in medicare beneficiaries with non-cancer pain. *Clin J Pain*. 2024;39(5). doi:10.1097/ajp.0000000000001105
12. Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. *Pain Med*. 2015;16(7):1373–1385. doi:10.1111/pme.12800
13. Cipriani A, Koesters M, Furukawa TA, et al. Duloxetine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev*. 2012;2012(10). doi:10.1002/14651858.CD006534.pub2
14. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract*. 2011;11(1):33–41. doi:10.1111/j.1533-2500.2010.00401.x
15. Piña IL, Di Palo KE, Ventura HO. Psychopharmacology and cardiovascular disease. *J Am Coll Cardiol*. 2018;71(20):2346–2359. doi:10.1016/j.jacc.2018.03.458
16. Woroń J, Siwek M, Gorostowicz A. Adverse effects of interactions between antidepressants and medications used in treatment of cardiovascular disorders. *Psychiatr Pol*. 2019;53(5):977–995. doi:10.12740/PP/OnlineFirst/96286
17. Sofat N, Harrison A, Russell MD, et al. The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. *JPR*. 2017;Volume10. doi:10.2147/jpr.s147640
18. Leong C, Alessi-Severini S, Enns MW, et al. Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: a propensity score-matched population-based study. *J Clin Psychopharmacol*. 2017;37(3):332–340. doi:10.1097/JCP.0000000000000701
19. Douros A, Ades M, Renoux C. Risk of intracranial hemorrhage associated with the use of antidepressants inhibiting serotonin reuptake: a systematic review. *CNS Drugs*. 2018;32:321–334. doi:10.1007/s40263-018-0507-7
20. Mago R, Tripathi N, Andrade C. Cardiovascular adverse effects of newer antidepressants. *Expert Rev Neurother*. 2014;14(5):539–551. doi:10.1586/14737175.2014.908709
21. Micca JL, Ruff D, Ahl J, Wohlreich MM. Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials. *BMC Musculoskelet Disord*. 2013;14:1–7. doi:10.1186/1471-2474-14-137
22. Kukkar A, Bali A, Singh N, Jaggi AS. Implications and mechanism of action of gabapentin in neuropathic pain. *Arch Pharm Res*. 2013;36:237–251. doi:10.1007/s12272-013-0057-y
23. Nicholson B. Gabapentin use in neuropathic pain syndromes. *J Peripheral Nerv Syst*. 2000;5(4):245. doi:10.1111/j.1529-8027.2000.22-35.x
24. Brannan SK, Mallinckrodt CH, Brown EB, Wohlreich MM, Watkin JG, Schatzberg AF. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. *J Psychiatr Res*. 2005;39(1):43–53. doi:10.1016/j.jpsychires.2004.04.011
25. Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: mechanistic insights. *Neuroscience*. 2016;338:183–206. doi:10.1016/j.neuroscience.2016.06.057
26. Shelton RC. Serotonin and norepinephrine reuptake inhibitors. In: *Antidepressants: From Biogenic Amines to New Mechanisms of Action*. 2019:145–180.
27. Cheng J, Chiou L. Mechanisms of the antinociceptive action of gabapentin. *J Pharmacol Sci*. 2006;100(5):471–486. doi:10.1254/jphs.CR0050020
28. Park K, Kim S, Ko Y, Park B. Duloxetine and cardiovascular adverse events: a systematic review and meta-analysis. *J Psychiatr Res*. 2020;124:109–114. doi:10.1016/j.jpsychires.2020.02.022

29. Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. *JAMA Intern Med*. 2019;179(5):695–701. doi:10.1001/jamainternmed.2019.0086
30. van Laar M, Pergolizzi JV Jr, Mellinghoff H, et al. Pain treatment in arthritis-related pain: beyond NSAIDs. *Open Rheumatol J*. 2012;6:320. doi:10.2174/1874312901206010320
31. Kwon S. Thirty years of national health insurance in South Korea: lessons for achieving universal health care coverage. *Health Policy Plan*. 2009;24(1):63–71. doi:10.1093/heapol/czn037
32. Kim J, Yoon S, Kim L, Kim D. Towards actualizing the value potential of korea health insurance review and assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci*. 2017;32(5):718. doi:10.3346/jkms.2017.32.5.718
33. Kim HK, Song SO, Noh J, Jeong I, Lee B. Data configuration and publication trends for the Korean national health insurance and health insurance review & assessment database. *Diabet Metabol J*. 2020;44(5):671–678. doi:10.4093/dmj.2020.0207
34. Kimm H, Yun JE, Lee S, Jang Y, Jee SH. Validity of the diagnosis of acute myocardial infarction in Korean national medical health insurance claims data: the korean heart study (1). *Korean Circ J*. 2012;42(1):10–15. doi:10.4070/kcj.2012.42.1.10
35. Park J, Kwon S, Choi E, et al. Validation of diagnostic codes of major clinical outcomes in a national health insurance database. *Int J Arrhythmia*. 2019;20(1):1–7. doi:10.1186/s42444-019-0005-0
36. Kim YA, Cho H, Lee N, et al. Doxorubicin-induced heart failure in cancer patients: a cohort study based on the Korean national health insurance database. *Cancer Med*. 2018;7(12):6084–6092. doi:10.1002/cam4.1886
37. Haukkala A, Konttinen H, Uutela A, Kawachi I, Laatikainen T. Gender differences in the associations between depressive symptoms, cardiovascular diseases, and all-cause mortality. *Ann Epidemiol*. 2009;19(9):623–629. doi:10.1016/j.annepidem.2009.01.010
38. Lenzi J, Noto G, Corazza I, Lepiksone J, Fantini MP. Measuring the quality of care in small countries: the empirical analysis of 30-day mortality following acute myocardial infarction and ischaemic stroke in Latvia. *Health Policy*. 2020;124(7):695–700. doi:10.1016/j.healthpol.2020.05.017
39. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004;57(12):1288–1294. doi:10.1016/j.jclinepi.2004.03.012
40. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41–55. doi:10.1093/biomet/70.1.41
41. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661–3679. doi:10.1002/sim.6607
42. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107. doi:10.1002/sim.3697
43. Schuemie MJ, Ryan PB, DuMouchel W, Suchard MA, Madigan D. Interpreting observational studies: why empirical calibration is needed to correct p-values. *Stat Med*. 2014;33(2):209–218. doi:10.1002/sim.5925
44. Wiemken TL, McGrath LJ, Andersen KM, et al. Coronavirus disease 2019 severity and risk of subsequent cardiovascular events. *Clinl Infect Dis*. 2023;76(3):e42–e50. doi:10.1093/cid/ciac661
45. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424. doi:10.1080/00273171.2011.568786
46. Calvi A, Fischetti I, Verzicco I, et al. Antidepressant drugs effects on blood pressure. *Front Cardiovasc Med*. 2021;8:704281. doi:10.3389/fcvm.2021.704281
47. Cui Y, Abdi SAH, Wei J, Azhar G. The long-term cardiovascular risks of duloxetine use in older adults: a retrospective medical record-based adverse drug reaction assessment. *J Clin Med*. 2024;13(24):7595. doi:10.3390/jcm13247595
48. Behlke LM, Lenze EJ, Carney RM. The cardiovascular effects of newer antidepressants in older adults and those with or at high risk for cardiovascular diseases. *CNS Drugs*. 2020;34:1133–1147. doi:10.1007/s40263-020-00763-z
49. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C, Detke MJ. Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. *J Clin Psychopharmacol*. 2005;25(2):132–140. doi:10.1097/01.jcp.0000155815.44338.95
50. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. *Drug Safety*. 2007;30:437–455. doi:10.2165/00002018-200730050-00007
51. Yekehtaz H, Farokhnia M, Akhondzadeh S. Cardiovascular considerations in antidepressant therapy: an evidence-based review. *J Tehran Univ Heart Cent*. 2013;8(4):169.
52. Lee YC, Lin CH, Lin MS, Lu Y, Chang CH, Lin JW. Comparison of the effects of serotonin-norepinephrine reuptake inhibitors versus selective serotonin reuptake inhibitors on cerebrovascular events. *J Clin Psychiatry*. 2016;77(1):3473.