Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study

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ABSTRACT

OBJECTIVE

To define the risk of intracranial haemorrhage among patients treated with antidepressants and non-steroid anti-inflammatory drugs (NSAIDs), compared with the risk among those treated with antidepressants without NSAIDs.

DESIGN

Retrospective nationwide propensity score matched cohort study.

SETTING

Korean nationwide health insurance database between 1 January 2009 and 31 December 2013.

PARTICIPANTS

Patients who began receiving antidepressants for the first time (index date) without a history of having received a prescription for antidepressants during the preceding year. Patients who had been diagnosed as having cerebrovascular diseases within a year before the index date were excluded.

MAIN OUTCOME MEASURE

Time to first hospital admission with intracranial haemorrhage within 30 days after drug use. Matched Cox regression models were used to compare the risk of intracranial haemorrhage among patients who were treated with antidepressants with and without NSAIDs, after propensity score matching with a 1:1 ratio.

RESULTS

After propensity score estimation and matching in a 1:1 ratio, the cohort used in the analysis included 4 145 226 people. The 30 day risk of intracranial haemorrhage during the entire study period was higher for combined use of antidepressants and NSAIDs than for use of antidepressants without NSAIDs (hazard ratio 1.6, 95% confidence interval 1.32 to 1.85). No statistically meaningful differences were found in risk of intracranial haemorrhage between the antidepressant drug classes.

CONCLUSIONS

Combined use of antidepressants and NSAIDs was associated with an increased risk of intracranial haemorrhage within 30 days of initial combination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) are generally believed to each increase the risk of abnormal bleeding

However, very little is known about the risk of intracranial haemorrhage associated with the combined use of antidepressants and NSAIDs

WHAT THIS STUDY ADDS

Combined use of antidepressants and NSAIDs was associated with an increased risk of intracranial haemorrhage within 30 days of initial combination

Introduction

Depression produces the greatest decrement in health of all common chronic conditions,[1] and depression in older people is an important public health problem.[2] Antidepressants can help depressive patients effectively, but concern exists that antidepressants may interact unfavourably with non-steroidal anti-inflammatory drugs (NSAIDs).[3 4]

Antidepressants, especially selective serotonin reuptake inhibitors, and NSAIDs are each thought to increase the risk of abnormal bleeding.[5 6] According to the results of a meta-analysis in 2008, the odds ratio of upper gastrointestinal haemorrhage was 2.36 (95% confidence interval 1.44 to 3.85) for selective serotonin reuptake inhibitors alone and 6.33 (3.40 to 11.82) with concomitant NSAIDs,[7] although controversy exists about whether the risk of gastrointestinal bleeding increases when they are prescribed together, compared with their use alone.[8 9]

Unlike for gastrointestinal bleeding, neither selective serotonin reuptake inhibitors nor NSAIDs alone have been found to be associated with an increased risk of intracranial haemorrhage.[10-13] However, little is known about the risk of intracranial haemorrhage associated with the combined use of antidepressants and NSAIDs. We sought to estimate the risk of intracranial haemorrhage among patients who were treated with both antidepressants and NSAIDs, compared with the risk among those treated with antidepressants without NSAIDs.

Methods

Data source

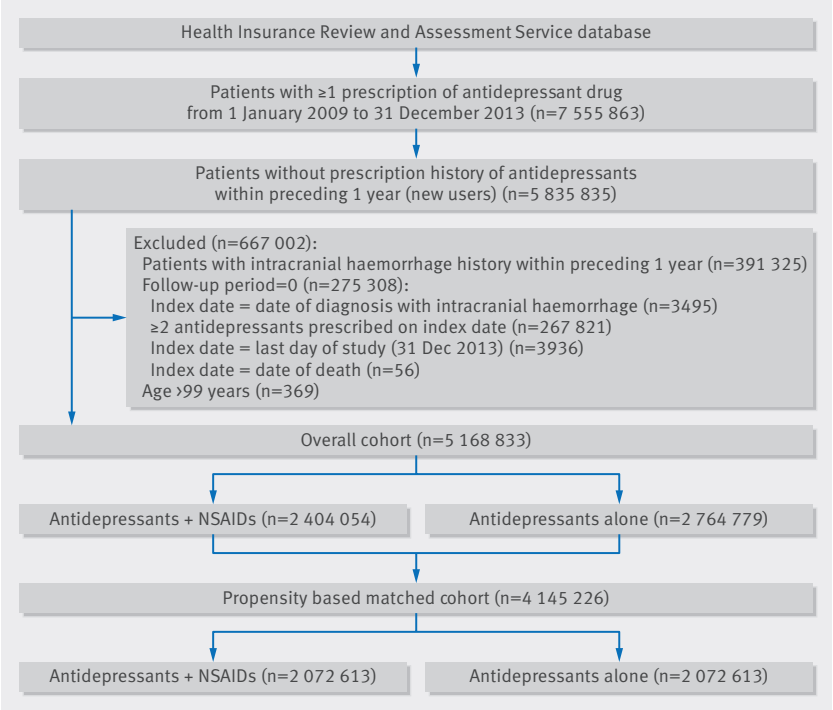
We used the Korean Health Insurance Review and Assessment Service database for this study. The National Health Insurance programme started in Korea in 1977 and achieved universal coverage of the population by 1989.[14] All Koreans are covered by the programme. Accordingly, the database contains all information on healthcare use and prescribed drugs for approximately 50 million Koreans.

We obtained the claims data for the patients who were prescribed at least one antidepressant drug from 1 January 2009 to 31 December 2013. The database included an unidentifiable code representing each patient together with age, sex, diagnosis, ambulatory

care, hospital admissions, and dates of visits.[15] In addition, prescribed drug information included the generic name, prescription date, and duration. The diagnosis was coded according to the international classification of disease, 10th revision (ICD-10). A previous validation study compared the diagnoses derived from the database with the actual diagnoses in the patients' medical records. The overall positive predictive value of the diagnoses was 83.4%.[16]

Patient involvement and study population

There was no patient involvement in this study. The study population was composed of antidepressant treated patients. We included new users of antidepressants who took antidepressants for the first time between 1 January 2010 and 31 December 2013 (index date) without a history of having received a prescription for antidepressants during the preceding year. By including only new users, we could ignore the influence of previous antidepressant treatment. We excluded patients who had been diagnosed as having cerebrovascular diseases (ICD-10: I60-I68, G45, G46) as their primary or secondary diagnosis within a year before the index date. We also excluded patients who were over the age of 99, had a diagnosis of intracranial haemorrhage on the index date, or took prescriptions for more than one antidepressant on the index date and those whose index date was the last day of the study. In addition, we excluded patients whose index date came after the date of death (ICD-10: I46.1, I46.9, R96, R98, R99) (figure). Antidepressants included tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and others.[17] Antidepressants included in "others" were bupropion, hypericin, mirtazapine, tianeptine, and trazodone.



Selection of study participants from Health Insurance Review and Assessment Service database in retrospective cohort design. NSAID=non-steroidal anti-inflammatory drug

Combined use of antidepressants and NSAIDs

Among antidepressant treated patients, we obtained their NSAID prescriptions by using the Anatomical Therapeutic Chemical codes (M01A, N02BA). We defined combined use of antidepressants and NSAIDs as the prescription of at least one NSAID during the defined 30 day follow-up of antidepressants.

Follow-up to intracranial haemorrhage

We defined the outcome as time to first hospital admission with intracranial haemorrhage (ICD-10: I60-62) as the primary or secondary diagnosis within 30 days' follow-up after the index date. The index date was the date of newly prescribed antidepressants. We assumed follow-up of antidepressant to last for seven days after the final prescription in a continuous course of treatment. We considered follow-up to have started on the index date and to have ended on the date of first hospital admission with intracranial haemorrhage within 30 days, the date the patient switched to another antidepressant, the date of discontinuation, or the last day of the study. We treated death as a competing risk.

Potential confounders

Age, sex, comorbidity, and co-medication are all possible confounders of the association between antidepressant use and intracranial haemorrhage. We defined information on comorbidity and co-medication according to previous diagnoses and the use of drugs within one year before the index date. We calculated the modified Charlson index to estimate the severity of disease according to previous diagnoses within one year before the index date.[18] We selected as confounders any comorbidities that may influence the risk of intracranial haemorrhage, which included diabetes, chronic obstructive pulmonary disease, hypertension, osteoarthritis, rheumatoid arthritis, osteoporosis, alcohol related disorder, ischaemic heart disease, chronic kidney disease, peptic ulcer, dementia, non-alcoholic liver disease, schizophrenia, neoplasm, HIV infection, transplantation, atrial fibrillation, heart failure, disease of arteries, and disease of veins. Low dose acetylsalicylic acid (Anatomical Therapeutic Chemical code: B01AC06), steroids (H02AB), warfarin (B01AA03), heparin (B01AB), platelet aggregation inhibitors (B01AC), antithrombotic enzymes (B01AD), direct thrombin inhibitors (B01AE), direct factor Xa inhibitors (B01AF), and other antithrombotic agents (B01AX) were also selected as confounders because they might increase the risk of intracranial haemorrhage through their action on haemostasis.

Statistical analysis

We estimated the propensity scores for adding NSAIDs to antidepressants without regard to outcomes by multiple logistic regression analysis using the following variables: age category, sex, Charlson index category, comorbidity, and co-medication (table 1). We assessed

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Table 1 | Baseline characteristics of people with combined use of antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs), compared with those using antidepressants alone, in overall cohort and propensity based matched cohort. Values are numbers (percentages) unless stated otherwise

	Overall cohort			Propensity based matched cohort		
Characteristic	Antidepressants only (n=2 764 779)	Antidepressants + NSAIDs (n=2 404 054)	Standardised difference	Antidepressants only (n=2 072 613)	Antidepressants + NSAIDs (n=2 072 613)	Standardised difference
Demographics						
Age group (years):						
Mean (SD) age	48.4 (18.4)	54.2 (16.6)		52.2 (16.6)	52.3 (16.6)	
0-19	204 367 (7.4)	61 672 (2.6)		61 071 (2.9)	61 656 (3.0)	
20-39	654 648 (23.7)	400 720 (16.7)	0.328	397 027 (19.2)	396 371 (19.1)	0.006
40-64	1 329 547 (48.1)	1 228 226 (51.1)		1 103 536 (53.2)	1 097 930 (53.0)	
65-84	538 863 (19.5)	675 080 (28.1)		480 887 (23.2)	487 269 (23.5)	
≥85	37 354 (1.4)	38 356 (1.6)		30 092 (1.5)	29 387 (1.4)	
Male sex	1 114 940 (40.3)	869 041 (36.1)	−0.013	805 365 (38.9)	795 345 (38.4)	0.001
Charlson comorbidity index:						
Median (interquartile range)	(0 (0-1)	1 (0-1)		1 (0-1)	1 (0-1)	
0	1 394 275 (50.4)	1 068 932 (44.5)		981 641 (47.4)	978 534 (47.2)	
1	1 103 031 (39.9)	1 091 536 (45.4)	0.073	884 536 (42.7)	887 641 (42.8)	0.002
2	67 160 (2.4)	54 683 (2.3)		51 125 (2.5)	49 966 (2.4)	
3	174 408 (6.3)	168 568 (7.0)		136 768 (6.6)	137 769 (6.6)	
≥4	25 905 (0.9)	20 335 (0.8)		18 543 (0.9)	18 703 (0.9)	
History of comorbidities in previous year						
Diabetes	317 803 (11.5)	328 821 (13.7)	0.066	259 458 (12.5)	262 238 (12.7)	0.004
Chronic obstructive pulmonary disease	365 336 (13.2)	389 601 (16.2)	0.085	309 763 (14.9)	311 016 (15.0)	0.002
Hypertension	639 433 (23.1)	722 923 (30.1)	0.158	550 910 (26.6)	556 677 (26.9)	0.006
Dyslipidaemia	93 395 (3.4)	96 412 (4.0)	0.034	77 404 (3.7)	77 529 (3.7)	0.000
Osteoarthritis	426 466 (15.4)	734 486 (30.6)	0.365	422 387 (20.4)	426 940 (20.6)	0.005
Rheumatoid arthritis	40 484 (1.5)	90 765 (3.8)	0.145	40 156 (1.9)	41 115 (2.0)	0.003
Osteoporosis	167 656 (6.1)	256 709 (10.7)	0.167	159 519 (7.7)	162 192 (7.8)	0.005
Alcohol related disorder	63 306 (2.3)	40 934 (1.7)	−0.042	36 575 (1.8)	38 482 (1.9)	0.007
Ischaemic heart disease	139 364 (5.0)	138 095 (5.7)	0.031	110 828 (5.3)	112 211 (5.4)	0.003
Chronic kidney disease	43 487 (1.6)	31 496 (1.3)	−0.022	27 789 (1.3)	28 242 (1.4)	0.002
Peptic ulcer	477 039 (17.3)	475 766 (19.8)	0.065	384 642 (18.6)	388 098 (18.7)	0.004
Dementia	39 397 (1.4)	24 019 (1.0)	−0.039	21 360 (1.0)	22 918 (1.1)	0.007
Non-alcoholic liver disease	237 558 (8.6)	215 575 (9.0)	0.013	182 140 (8.8)	182 549 (8.8)	0.001
Schizophrenia	40 604 (1.5)	11 454 (0.5)	−0.101	10 559 (0.5)	11 432 (0.6)	0.006
Neoplasm	390 653 (14.1)	352 173 (14.6)	0.015	306 991 (14.8)	304 632 (14.7)	−0.003
HIV infection	160 (0.0)	92 (0.0)	−0.003	81 (0.0)	87 (0.0)	0.000
Transplantation	2406 (0.1)	1012 (0.0)	−0.018	1094 (0.1)	1010 (0.0)	−0.002
Atrial fibrillation	2383 (0.1)	2168 (0.1)	0.001	1786 (0.1)	1820 (0.1)	0.001
Heart failure	27 399 (1.0)	29 118 (1.2)	0.021	22 068 (1.1)	22 548 (1.1)	0.002
Disease of arteries	144 540 (5.2)	181 391 (7.5)	0.095	130 172 (6.3)	131 913 (6.4)	0.003
Disease of veins	125 143 (4.5)	130 618 (5.4)	0.042	105 024 (5.1)	105 291 (5.1)	0.001
Drug use in previous year						
Low dose aspirin (B01AC06)	307 216 (11.1)	339 112 (14.1)	0.090	259 218 (12.5)	262 403 (12.7)	0.005
Warfarin (B01AA)	1 345 295 (48.7)	1 466 106 (61.0)	0.250	1 174 364 (56.7)	1 180 344 (56.9)	0.006
Heparin group (B01AB)	13 362 (0.5)	11 076 (0.5)	−0.003	9 507 (0.5)	9 623 (0.5)	0.001
Platelet aggregation inhibitors (B01AC)	61 082 (2.2)	56 828 (2.4)	0.010	45 986 (2.2)	46 428 (2.2)	0.001
Antithrombotic enzymes (B01AD)	149 681 (5.4)	168 921 (7.0)	0.067	125 779 (6.1)	127 661 (6.2)	0.003
Direct thrombin inhibitors (B01AE)	1 002 (0.0)	711 (0.0)	−0.004	662 (0.0)	656 (0.0)	0.000
Direct factor Xa inhibitors (B01AF)	72 (0.0)	54 (0.0)	−0.001	50 (0.0)	50 (0.0)	0.000
Other antithrombotic agents (B01AX)	1294 (0.0)	4388 (0.2)	0.040	1289 (0.1)	1360 (0.1)	0.001
Steroids (H02AB)	272 (0.0)	679 (0.0)	0.013	268 (0.0)	268 (0.0)	0.000
Index year						
2010	709 825 (25.7)	629 977 (26.2)		536 952 (25.9)	538 817 (26.0)	
2011	726 262 (26.3)	631 551 (26.3)	−0.013	541 168 (26.1)	542 479 (26.2)	−0.003
2012	705 962 (25.5)	609 967 (25.4)		527 004 (25.4)	526 486 (25.4)	
2013	622 730 (22.5)	532 559 (22.2)		467 489 (22.6)	464 831 (22.4)	

model discrimination with the c statistic. Matching was done using the Greedy 5→1 digit matching macro with the estimated propensity score.[19] We used a standardised difference to compare baseline characteristics between patients who were treated with antidepressants without NSAIDs and those treated with antidepressants and NSAIDs.[20] We calculated Cohen's d as the difference between two sample means divided by a pooled standard deviation for the data. We defined imbalance as an absolute value greater than 0.1.[21]

We calculated the incidence rate per 1000 person years by dividing the number of intracranial haemorrhage events by the total number of person years at risk and multiplying the result by 1000 and calculated the 95% confidence interval assuming a Poisson distribution. For construction of the multivariable model, we included variables that achieved statistical significance in the likelihood ratio test. The final model included dementia, warfarin, heparin group, and steroids as the adjusting variables. We assessed the status of combined use of NSAIDs and covariates on a daily basis during the follow-up period for the time varying covariates. We used matched Cox regression models to estimate hazard ratios and their 95% confidence intervals for intracranial haemorrhage with time varying covariates in the propensity based matched cohort. By using this model, we could obtain an unbiased estimate of the change in the hazard of intracranial haemorrhage because of the concomitant use of antidepressants and NSAIDs.[22] Competing risks arise when patients are exposed to several causes and failure due to one cause excludes failure due to other causes.[23] In our study, we treated death as a competing risk rather than censoring it owing to its potential causal effect on the outcome of interest.

We also did a subgroup analysis according to antidepressant class, age category, sex, type of intracranial haemorrhage, comorbidity, and co-medication. We did subgroup analysis using a single model with interaction terms to see whether the association with the concurrent use of NSAIDs among antidepressant users differed significantly. We used the SAS statistical application program (release 9.3) for all statistical analyses. We considered a two tailed value of P<0.05 to be statistically significant.

Results

From the 7 555 863 people who received prescriptions for at least one antidepressant drug during the study period, we identified 5 835 835 new users of antidepressants. A total of 5 168 833 people met the study inclusion criteria. After propensity score estimation and matching in a one to one ratio, the cohort used in the analysis of antidepressant with NSAIDs versus without NSAIDs included 4 145 226 people. The c statistic was 0.686. The figure shows the cohort selection process. Among 5 168 833 people who used the antidepressant and NSAIDs combination, the mean follow-up was 18 (SD 8) days and the median was 14 (range 2-30; interquartile range 12-28).

Table 1 shows the baseline characteristics of people with antidepressant use with and without NSAIDs in the overall cohort and propensity based matched cohort. All of the standardised difference scores in the propensity based matched cohort were less than 0.1 as an absolute value.

Table 2 shows the hazard ratios for intracranial haemorrhage associated with the use of NSAIDs compared with no use of NSAIDs in antidepressant treated patients. We found that the risk of intracranial haemorrhage was higher for the combined use of antidepressants and NSAIDs than for antidepressant use without NSAIDs (hazard ratio 1.6, 95% confidence interval 1.32 to 1.85). We found no statistically meaningful differences in risk of intracranial haemorrhage between the antidepressant drug classes. The differences in adjusted hazard ratios for tricyclic antidepressants (1.7 (1.33 to 2.13) *v* 1.6 (1.27 to 2.03)), selective serotonin reuptake inhibitors (1.4 (1.17 to 1.72) *v* 1.5 (1.27 to 1.86)), and serotonin-norepinephrine reuptake inhibitors (0.4 (0.32 to 0.46) *v* 1.5 (1.31 to 1.83)), each compared with the rest, were not statistically significant. The P values greater than 0.05 for subgroup analysis of different antidepressant classes showed that no particular class increased the risk of intracranial haemorrhage.

Table 3 shows the risk of intracranial haemorrhage in subgroups according to age, sex, subtype of intracranial haemorrhage, comorbidity, and co-medication. We found no difference in risk associated with age and subtype. The hazard ratio associated with concomitant use of NSAIDs was higher among male than female patients (2.6 (1.93 to 3.42) *v* 1.2 (0.89 to 1.57)). Comorbidities and co-medications did not seem to increase the risk of intracranial haemorrhage with combined use of antidepressants and NSAIDs.

Table 2 | Risk of 30 day intracranial haemorrhage with combined use of antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs), compared with antidepressant use without NSAIDs, in propensity based matched cohort

	Antidepressants only			Antidepressants + NSAIDs			Hazard ratio (95% CI)		
Subgroup	Sum of person years	No of events	Incidence rate per 1000 person years* (95% CI)	Sum of person years	No of events	Incidence rate per 1000 person years* (95% CI)	Unadjusted	Adjusted†	P value
Overall	106 858	169	1.6 (1.36 to 1.84)	99 978	573	5.7 (5.28 to 6.22)	1.9 (1.69 to 2.24)	1.6 (1.32 to 1.85)	<0.001
Antidepressant exposure									
TCA	37 803	57	1.5 (1.16 to 1.95)	53 017	307	5.8 (5.18 to 6.48)	2.2 (1.75 to 2.66)	1.7 (1.33 to 2.13)	0.770‡
The rest	69 055	112	1.6 (1.35 to 1.95)	46 961	266	5.7 (5.02 to 6.39)	2.3 (1.86 to 2.83)	1.6 (1.27 to 2.03)	
SSRI	27 165	35	1.3 (0.93 to 1.79)	12 002	82	6.8 (5.50 to 8.48)	3.4 (2.86 to 3.98)	1.4 (1.17 to 1.72)	0.678‡
The rest	79 693	134	1.7 (1.42 to 1.99)	87 977	491	5.6 (5.11 to 6.10)	2.5 (2.14 to 2.98)	1.5 (1.27 to 1.86)	
SNRI	3255	14	4.3 (2.55 to 7.26)	2715	12	4.4 (2.51 to 7.78)	0.5 (0.43 to 0.58)	0.4 (0.32 to 0.46)	0.190‡
The rest	103 603	155	1.5 (1.28 to 1.75)	97 264	561	5.8 (5.31 to 6.27)	2.3 (2.02 to 2.70)	1.5 (1.31 to 1.83)	

SNRI=serotonin-norepinephrine reuptake inhibitors (including duloxetine, milnacipran, and venlafaxine); SSRI=selective serotonin reuptake inhibitors (including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline); TCA=tricyclic antidepressants (including amitriptyline, amoxapine, clomipramine, dothiepin (dosulepin), imipramine, nortriptyline, and quinupramine).
*Incidence rate=(No of events/sum of person years)×1000; 95% CI calculated assuming Poisson distribution.
†Adjusted for dementia, warfarin, heparin group, and steroids as time varying covariates, using matched Cox regression models; death was treated as competing risk.
‡P value for interaction.

Table 3 | Subgroup analyses of risk of intracranial haemorrhage with combined use of antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs), compared with antidepressants use without NSAIDs, in propensity based matched cohort

Subgroup	Hazard ratio (95% CI)*	P value for interaction
Age		
<45 years (n=1 285 011)	2.2 (1.24 to 3.80)	0.234
≥45 years (n=2 860 215)	1.5 (0.87 to 2.67)	
Sex		
Male (n=1 600 710)	2.6 (1.93 to 3.42)	<0.001
Female (n=2 544 516)	1.2 (0.89 to 1.57)	
Subtype of intracranial haemorrhage (n=4 145 226)		
Subarachnoid haemorrhage (I60) (n=262)	1.3 (1.05 to 1.52)	†
Intracerebral haemorrhage (I61) (n=313)	1.3 (1.08 to 1.55)	
Other non-traumatic intracranial haemorrhage (I62) (n=167)	1.3 (1.08 to 1.57)	
History of comorbidities in previous year		
Diabetes:		
Yes (n=521 696)	1.1 (0.86 to 1.30)	0.002
No (n=3 623 530)	1.9 (1.53 to 2.29)	
Chronic obstructive pulmonary disease:		
Yes (n=620 779)	3.7 (3.13 to 4.46)	0.003
No (n=3 524 447)	1.4 (1.21 to 1.72)	
Hypertension:		
Yes (n=1 107 587)	1.0 (0.80 to 1.30)	<0.001
No (n=3 037 639)	2.4 (1.87 to3.03)	
Dyslipidaemia:		
Yes (n=154 933)	2.1 (1.75 to 2.46)	0.455
No (n=3 990 293)	1.5 (1.30-1.84)	
Osteoarthritis:		
Yes (n=849 327)	1.2 (0.98 to 1.44)	0.052
No (n=3 295 899)	1.7 (1.42 to 2.10)	
Rheumatoid arthritis:		
Yes (n=81 271)	0.2 (0.18 to 0.25)	0.010
No (n=4 063 955)	1.6 (1.38 to 1.94)	
Osteoporosis:		
Yes (n=321 711)	0.8 (0.69 to 0.98)	0.009
No (n=3 823 515)	1.7 (1.42 to 2.04)	
Alcohol related disorder:		
Yes (n=75 057)	1.7 (1.40 to 1.98)	0.868
No (n=4 070 169)	1.6 (1.31 to 1.86)	
Ischaemic heart disease:		
Yes (n=223 039)	0.8 (0.69 to 0.99)	<0.001
No (n=3 922 187)	1.8 (1.48 to 2.13)	
Chronic kidney disease:		
Yes (n=56 031)	0.5 (0.43 to 0.60)	0.026
No (n=4 089 195)	1.6 (1.38 to 1.94)	
Peptic ulcer:		
Yes (n=772 740)	1.1 (0.90 to 1.32)	0.023
No (n=3 372 486)	1.7 (1.43 to 2.08)	
Non-alcoholic liver disease:		
Yes (n=364 689)	1.6 (1.38 to 1.97)	0.823
No (n=3 780 537)	1.6 (1.30 to 1.86)	
Neoplasm:		
Yes (n=611 623)	1.5 (1.22 to 1.78)	0.692
No (n=3 533 603)	1.6 (1.32 to 1.93)	
Heart failure:		
Yes (n=44 616)	9.9 (8.30 to 11.68)	0.071
No (n=4 100 610)	1.5 (1.28 to 1.80)	
Disease of arteries:		
Yes (n=262 085)	0.6 (0.47 to 0.66)	0.021
No (n=3 883 141)	1.6 (1.38 to 1.95)	
Disease of veins:		
Yes (n=210 315)	1.0 (0.84 to 1.18)	0.149
No (n=3 934 911)	1.6 (1.36 to 1.93)	

(*Continued*)

Table 3 | (Continued) Subgroup analyses of risk of intracranial haemorrhage with combined use of antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs), compared with antidepressants use without NSAIDs, in propensity based matched cohort

Subgroup	Hazard ratio (95% CI)*	P value for interaction
Drug use in previous year		
Low dose aspirin:		
Yes (n=521 621)	1.3 (1.10 to 1.59)	0.317
No (n=3 623 605)	1.6 (1.35 to 1.96)	
Platelet aggregation inhibitors:		
Yes (n=253 222)	0.7 (0.59 to 0.84)	0.0026
No (n=3 892 004)	1.7 (1.44 to 2.05)	

*Adjusted for dementia, warfarin, heparin group, and steroids as time varying covariates, using matched Cox regression models.
†P value for interaction not calculated, because subtype of intracranial haemorrhage was an outcome variable.

Discussion

In this population based cohort study, we evaluated the association between the combined use of antidepressants and NSAIDs, compared with the use of antidepressants alone, and the risk of intracranial haemorrhage. Compared with the use of antidepressants alone, the combined use of antidepressants and NSAIDs was associated with an increased risk of intracranial haemorrhage.

Comparison with other studies

These results are in line with those of a nested case-control study of the risk of intracranial haemorrhage in users of selective serotonin reuptake inhibitors, which found a trend towards an increased risk of intracranial haemorrhage in people with current exposure to both selective serotonin reuptake inhibitors and NSAIDs.[10] The odds ratio of intracranial haemorrhage for current use of selective serotonin reuptake inhibitors and never use of NSAIDs was 0.7 (95% confidence interval 0.3 to 1.7) and the odds ratio for current use of both drug types was 2.4 (0.9 to 6.2), compared with never use of either drug type. Our study included all the classes of antidepressants, and we found no difference between them.

Advancing age and antithrombotic agents are well known risk factors for intracranial haemorrhage,[10 12] but the hazard ratio for intracranial haemorrhage associated with the combined use of antidepressants and NSAIDs did not differ significantly in the patients who used antithrombotic agents or in older patients. The combined use of antidepressants and NSAIDs seems not to have had a major effect on patients who already had risk factors for intracranial haemorrhage. However, male sex was the most common risk factor for a higher hazard ratio for intracranial haemorrhage with combined use of antidepressants and NSAIDs. We verified our study design by including myocardial infarction, which is not related to bleeding. The endpoint not related to bleeding did not increase the risk of intracranial haemorrhage compared with the endpoints related to bleeding (hazard ratio 0.9, 0.65 to 1.32). Our results showed that the study design was adequate to detect the increase in risk of bleeding with combined use of antidepressant and NSAIDs (data not shown).

Antidepressants, particularly selective serotonin reuptake inhibitors, block platelet uptake, and use of these agents results in bleeding complications.[5] NSAIDs are also known to inhibit normal platelet function.[6] However, a previous population based study did not find a significant association of use of each drug with intracranial haemorrhage.[13] Our study found the additional effect according to the drug-drug interaction based on the population based data. Serotonin-norepinephrine reuptake inhibitors work by inhibiting the reuptake of not only serotonin but also norepinephrine. Elevation of norepinephrine concentrations may be associated with an increased risk of intracranial haemorrhage. A high risk with venlafaxine was reported by De Abajo and Garcia-Rodriguez, who estimated the risk of upper gastrointestinal tract bleeding.[24] This may be because, as they noted, venlafaxine has a lower affinity for the serotonin receptor than do most selective serotonin reuptake inhibitors,[25] but to compensate for its lower potency in vitro, a threefold to sevenfold greater daily dose is usually prescribed.

To the best of our knowledge, this is the first population based cohort study focusing on the risk of intracranial haemorrhage associated with the combined use of antidepressants and NSAIDs. Most existing studies have been case-control studies and have focused on abnormal bleeding risk from selective serotonin reuptake inhibitors. This study included all antidepressant prescriptions in Korea during a five year period. We focused on changes in risk due to addition of NSAIDs to antidepressants, which could provide information about drug interaction.

Strengths and limitations of study

Our finding should be interpreted with caution. This study has potential inaccuracy of coding and incompleteness of records. The outcome measures were also limited to patients admitted to hospital with intracranial haemorrhage, which does not capture events outside hospital. However, patients with fatal events are likely to be in hospital, which minimises the possibility of us missing fatal cases. A validation study compared the diagnosis derived from the Health Insurance Review and Assessment Service database with the actual diagnosis in patients' medical records in Korea. The overall positive predictive value of the diagnoses was 83.4% in the case of patients admitted to hospital.[16] Computed tomography and magnetic resonance imaging are routinely used in the diagnosis of intracranial haemorrhage, and a radiologist's reading is required for

insurance claims in Korea.[26] According to a nationwide survey of 152 representative hospitals, computed tomography or magnetic resonance imaging was used in 89% of hospital admissions for intracranial haemorrhage. Agreement on diagnosis of intracranial haemorrhage is generally high in Korea and in other countries.[16 26-30] We defined death by ICD-10 codes (I46.1, I46.9, R96, R98, and R99) without further records after the date of coding.

Our findings are subject to selection bias and confounding with respect to the relative difference in the baseline for the risk of intracranial haemorrhage between the comparison groups. However, we used propensity score matching, which should eliminate a greater proportion of the baseline differences than would stratification or covariate adjustment. Although we used a propensity score matched design, this does not preclude findings being influenced by potential confounders. Hidden bias may remain because of the influence of unmeasured confounders.

Conclusion

The addition of NSAIDs to antidepressant treatment increased the risk of intracranial haemorrhage within 30 days of the combination starting, especially in men. This result adds to evidence confirming the increase of risk with combination use of antidepressants and NSAIDs. Special attention is needed when patients use both these drugs together.

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Ethical approval: This study was approved by the institutional review board of the Korea Institute of Drug Safety and Risk Management, Seoul (study ID: KIDS-IRB-2013-007).

Data sharing: No additional data available.

Transparency declaration: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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