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Current Prescription Status of Contraindicated Drug Combinations Causing Serotonin Syndrome: Analysis of HIRA-NPS Data

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ABSTRACT

Background: Serotonin syndrome is a life-threatening disease if not appropriately treated. This study aimed to investigate the prescription status of contraindicated drug combinations that cause serotonin syndrome and identify the related factors. **Methods:** A cross-sectional study was conducted using nationwide claims data. Adult patients taking serotonergic drugs with Parkinson's disease or mental disorders were selected. Based on international medical databases (MDBs) and the Korean Drug Utilization Review (DUR), the status of prescribing contraindicated drug combinations that induce serotonin syndrome, the related factors, and the difference between international MDBs and the Korean DUR were analyzed. **Results:** Of the 49,773 study subjects, 163 (0.3%) were prescribed contraindicated serotonergic drug combinations based on international MDBs, and among them, only 105 (64.4%) were contraindicated by the Korean DUR. Positive influencing factors for prescribing contraindicated drug combinations include patient age between 65 and 74 and physician's specialties (neurologists, and orthopedists). Negative influencing factors were physician's specialty (internists) and medical institution (primary institutions). **Conclusion:** Despite the implementation of DUR, 3 out of 1,000 study subjects received contraindicated drug combinations that caused serotonin syndrome. Hence, it is necessary to comply with the DUR and improve it in accordance with international MDBs.

KEYWORDS: serotonin syndrome, serotonin agents, contraindications, drug combinations, drug utilization review

Serotonin syndrome is caused by excessive activation of serotonin receptors in the central nervous system.[1)] This may occur when an overdose of a drug that increases serotonin levels is utilized or when two serotonergic drugs are used concurrently.[2)] Serotonergic drugs include monoamine oxidase inhibitors (MAOIs), selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antipsychotics, opiate analgesics, etc.[1,3-13)] The symptoms of serotonin syndrome vary in severity. Mild cases may only experience tachycardia without fever and in some occasions autonomic findings such as diaphoresis, shivering, or mydriasis can be recognized on physical examination.[2)] Severe cases can be life-threatening, with high blood pressure and tachycardia, sustained clonus, muscle hypertonicity, and a

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high fever exceeding 41°C.[2] The onset of symptoms is usually rapid with clinical findings, and approximately 60% of the patients with serotonin syndrome present symptoms within six hours after initiating medication, an overdose, or a change in drug dose.[14] However, epidemiological investigation of serotonin syndrome has not been easily carried out because the symptoms are nonspecific and hardly noticeable in clinical situations.[15]

The prevalence of serotonin syndrome in Korea is unknown; therefore, our best estimate is obtained from the results of a study using US insurance claims data.[16] In a retrospective cohort study of 15 million patients exposed to serotonergic agents, the incidence of serotonin syndrome ranged between 0.9 and 2.3 per 1000 patients.[17] Based on the above findings and the number of patients exposed to serotonergic agents, the estimated number of patients with serotonin syndrome in Korea ranges from 81 to 208 per year.[16,17]

The main purpose of the drug utilization review (DUR) is to prevent the inappropriate use of drugs, thereby preventing side effects, improving the quality of care provided to patients, and creating an environment in which drugs can be safely used. A real-time computerized DUR has been implemented nationwide in Korea since December 2010.[18] DUR criteria include contraindicated drug-drug interactions (DDIs), therapeutic duplications, drug-age precautions, and drug-pregnancy contraindications.[19] The major consequences of contraindicated DDIs include the increased risk of QTc prolongation, intracranial hypertension, rhabdomyolysis, etc., as well as that of serotonin syndrome. If a prescription does not meet the DUR criteria, the DUR program provides an alert message to the physician when prescribing, and he/she must write a reason to override the alert or fix the prescription.[19] As a result of the implementation of the DUR program, the adverse effects due to DDIs were reduced in patients using a combination of benzodiazepine and an enzyme inhibitor to prevent the side effects due to increased benzodiazepine concentration.[20] Moreover, the number of prescriptions of drug-age precautions significantly decreased in the entire elderly patient group.[21] The Ministry of Health and Welfare reported that, as a result of DUR, adverse drug reactions was prevented in advance by canceling or changing inappropriate prescriptions or dispensing in 5.2% of all prescriptions during the first three quarters of 2015.[22] Therefore, it is essential to ensure compliance with the DUR and systematic organization of the DUR contraindicated list.

To date, most studies on serotonin syndrome have been case-based in Korea.[23-25] To the best of our knowledge, there are no prior studies examining the prescribing status of contraindicated drug combinations that have the potential to cause serotonin syndrome in Korea. Therefore, we aimed to analyze the prescribing status of contraindicated serotonergic drug combinations using nationally representative data and to identify factors influencing this.

Methods

Data source

The Health Insurance Review and Assessment Service National Patient Sample (HIRA-NPS-2020) was used for retrospective analysis. The sample data corresponded to approximately 1 million patients, with a random sampling rate of 2% of the total number of patients. In Korea, citizens must obtain the National Health Insurance; hence, it represents data for all Koreans.[26,27] After personal information was deleted, secondary data was extracted for patients stratified by sex and age for one year from the start date of treatment.

Patient population

Data on patients with psycho-behavioral disorders (F**) or Parkinson's disease (G20) were extracted using the Korean Standard Classification of Diseases 7 (KCD7). Among them, patients with a history of at least one prescription for a drug that causes serotonin syndrome were selected as study subjects. The serotonergic drugs and codes are listed in Appendix 1.

Contraindicated drugs in combination

Among the study subjects, those who were prescribed contraindicated serotonergic drug combinations that could cause serotonin syndrome were identified. For this purpose, two international medical databases (MDBs), Lexicomp Online™ and Micromedex®, were referred. A list of contraindicated drug combinations generated based on the two MDBs is presented in Appendix 2. We also checked the list of contraindicated serotonergic drug pairs in current Korean DUR system which was provided and updated by the Korea Institute of Drug Safety and Risk Management (KIDS). Contraindications between and within prescriptions were identified. Contraindications between prescriptions were defined as cases in which contraindicated drugs were included

in two prescriptions that overlapped for ≥1 day. In this experiment, when a patient had various contraindications, the first prescribed contraindicated drug combination was analyzed as the standard in the 'patient' analysis. However, all contraindicated serotonergic combinations were included in the 'contraindicated combination' analysis.

Statistical analysis

The baseline characteristics of the patients were presented using frequency analysis, and *P*-values for the prescription of contraindicated serotonergic drug combinations were determined using chi-squared tests. Using multiple logistic regression analysis, we examined the relationship between demographic factors, social factors, prescriber specialties, type of medical institution, comorbidities, and the prescription of contraindicated drug combinations causing serotonin syndrome. The Hosmer-Lemeshow test was performed to determine the model fit of the multiple logistic regression.

Demographic factors include age and sex, and social factors include insurance type and region. Korea has three main types of insurance: National Health Insurance (NHI), Medical Aid (MedAid), and Patriots and Veterans Insurance (PVI). We divided the study regions into three categories: capital, metropolitan, and rural areas. The capital area included Seoul and its surrounding areas. The metropolitan area included non-capital cities, with over 1 million people, and the remaining areas were categorized as rural. The specialties of physicians were classified as general practitioners, neurologists, orthopedists, psychiatrists, internists, and others. Medical institutions were grouped as primary, secondary, and tertiary hospitals. Primary institutions, such as clinics, community health centers, and single-specialty hospitals, have fewer than 30 beds. A secondary institution is a medical institution with more than 30 beds and greater than seven departments. In the case of a Korean tertiary institution, university hospitals must have more than 500 beds, and general hospitals must have more than 700 beds and nine or more departments. Comorbidities included hypertension, diabetes mellitus, hyperlipidemia, osteoarthritis, and rheumatic arthritis.

Statistical analyses were performed using R software (version 3.5.1), and $p<0.05$ was considered statistically significant.

Results

Characteristics of study subjects

The HIRA-NPS-2020 included 72,570 adult patients with Parkinson's disease or mental disorders. Among them, 49,773 patients who were prescribed at least one serotonergic drug were selected as study subjects. The demographics and other characteristics of the study subjects are summarized in Table 1. Among the study subjects, women were almost twice as many as men, and those aged ≥75 years accounted for about a quarter.

Prescribing status of contraindicated serotonergic drug combinations

A total of 163 (0.3%) study subjects were prescribed contraindicated serotonergic drug combinations (Fig. 1). When the Korean DUR criteria were applied, the number of patients who were prescribed contraindicated pairs was reduced to 105, approximately two-thirds. The rate of contraindicated drug combinations prescribed tended to be relatively high in males and highest in patients aged 65-74 years. In the specialty category, the neurologists prescribed the highest number of contraindicated drug combinations. Patients with Parkinson's disease as the main diagnosis only accounted for approximately 4% of the study subjects, but they were prescribed the most contraindicated drug combinations (Table 1).

Factors related to prescribing contraindicated drug combinations

Table 2 presents the results of the multiple logistic regression analysis. Patients between 65-74 years were positively associated with the prescription of contraindicated drug combinations (OR=2.120; confidence interval [CI]=1.096-4.343). Neurologists (OR=4.916; CI=2.732-9.186) and orthopedists (OR=2.227; CI=1.155-4.346) had higher odds of prescribing contraindicated drug combinations than general practitioners, whereas internists had lower odds (OR=0.228; CI=0.082-0.554). The prescription of contraindicated drug combinations was lower in primary institutions than that in tertiary hospitals (OR=0.410; CI=0.255-0.666).

Table 1. Demographic characteristics and frequency of prescribing contraindicated drug combinations

Explanatory variables	n	(%)	Prescribing contraindicated drug combinations		*P*-value
Overall	49773	(100.0)	163	(0.3)	
Sex					0.055
Male	17794	(35.8)	70	(0.4)	
Female	31979	(64.3)	93	(0.3)	
Age (years)					<0.001
20-39	9405	(18.9)	13	(0.1)	
40-54	9090	(18.3)	11	(0.1)	
55-64	8934	(17.9)	35	(0.4)	
65-74	9214	(18.5)	52	(0.6)	
≥75	13130	(26.4)	52	(0.4)	
Insurance type					0.447
NHI	44264	(88.9)	148	(0.3)	
Non-NHI	5509	(11.1)	15	(0.3)	
Main diagnosis					<0.001
Mental disorder	47704	(95.8)	24	(0.1)	
Parkinson	1418	(2.8)	99	(7.0)	
Both	651	(1.3)	40	(6.1)	
Physician specialty					<0.001
General practitioner	9164	(18.4)	17	(0.2)	
Neurologist	5025	(10.1)	85	(1.7)	
Orthopedist	3898	(7.8)	21	(0.5)	
Psychiatrist	6809	(13.7)	18	(0.3)	
Internist	11852	(23.8)	6	(0.1)	
Others	13025	(26.2)	16	(0.1)	
Region					0.361
Capital	23188	(46.6)	85	(0.4)	
Metropolitan	10428	(21.0)	31	(0.3)	
Rural	16157	(32.5)	47	(0.3)	
Institution					<0.001
Tertiary	3122	(6.3)	35	(1.1)	
Secondary	6232	(12.5)	55	(0.9)	
Primary	40419	(81.2)	73	(0.2)	
Comorbidities					
Hypertension	22265	(44.7)	91	(0.4)	0.004
Diabetes mellitus	14581	(29.3)	60	(0.4)	0.035
Hyperlipidemia	26286	(52.8)	107	(0.4)	0.001
Osteoarthritis	19964	(40.1)	82	(0.4)	0.008
Rheumatic arthritis	2477	(5.0)	15	(0.6)	0.013
DUR contraindication					<0.001
No	49668	(99.8)	58	(0.1)	
Yes	105	(0.2)	105	(100.0)	

NHI, National health insurance; DUR, Drug Utilization Review.

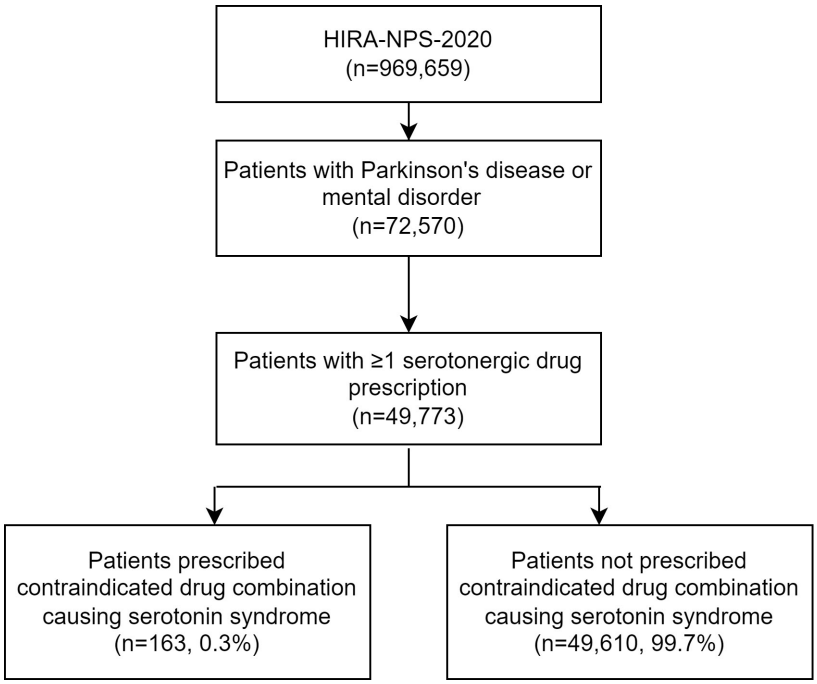

Fig. 1. Extraction of study subject. HIRA-NPS, Health Insurance Review and Assessment Service National Patient Sample.

Frequency of prescribing contraindicated drugs in combinations

Table 3 shows the top ten commonly prescribed contraindicated drug combinations that cause serotonin syndrome. The first was the combination of rasagiline and tramadol (299, 23.6%), followed by rasagiline and escitalopram (184, 14.6%), and rasagiline and trazodone (97, 7.6%). Of the top 10 combinations, rasagiline was the most abundant. In the top 10, the two combinations without rasagiline were ziprasidone plus trazodone and ziprasidone plus fluoxetine.

Discussion

We investigated the prescription status of contraindicated serotonergic drug combinations using real-world data (HIRA-NPS-2020). Among the 49,773 study participants, 163 (0.3%) were prescribed contraindicated serotonergic drug combinations. Multiple logistic regression showed that patients between 65-74 years had the highest odds of being prescribed with contraindicated serotonergic drug combinations. This is presumably because most prescribed serotonergic drug pairs contain rasagiline, an antiparkinson agent. Rasagiline can be used as an initial monotherapy or add-on therapy in patients taking dopaminergic agents.[28,29] Epidemiology studies show that patients with Parkinson's disease usually start pharmacotherapy when they are diagnosed or when symptoms of the disease interfere with daily life.[30,31] The mean age at diagnosis of Parkinson's disease was known to be between 65 and 70 years old.[32-34]

The reason for the high OR among neurologist is also thought to be related with rasagiline. As shown in Table 3, among the 1,268 cases of contraindicated drug combinations, 858 cases involving rasagiline account for approximately two-thirds. Rasagiline is one of the main drugs of choice for the initial treatment of patients with mild Parkinson's disease. Therefore, it is widely used despite the high risk of drug interactions, and it is necessary to pay more attention to these interactions when using other drugs. Nevertheless, many combinations designated as contraindicated with rasagiline in both MDBs were not included in the DUR list in Korea (Appendix 2). Among the eight drug pairs including rasagiline in Table 3, six (except tramadol and sertraline) were not included in the DUR. Moreover, among the drugs contraindicated for concomitant use with selegiline in the Korean DUR system, some were not designated as contraindicated with rasagiline. Combinations of rasagiline with some psychiatric drugs (i.e., paroxetine, duloxetine,

Table 2. Results of the multiple logistic regression analysis of factors affecting the prescription of contraindicated drug combinations

Explanatory variables		Contraindicated drugs in combinations causing serotonin syndrome		
		Adj. OR	95% CI	*P*-value
Sex	Male (R)			
	Female	0.737	0.537-1.015	0.060
Age (years)	20-39 (R)			
	40-49	0.691	0.300-1.563	0.374
	50-64	1.791	0.928-3.648	0.093
	65-74	2.120	1.096-4.343	0.031
	≥75	1.313	0.671-2.716	0.442
Insurance	NHI (R)			
	Non-NHI	0.716	0.400 -1.191	0.227
Comorbidities	Hypertension	0.915	0.642-1.314	0.628
	Diabetes mellitus	0.972	0.679-1.384	0.874
	Hyperlipidemia	1.212	0.836-1.772	0.314
	Osteoarthritis	1.321	0.946-1.845	0.102
	Rheumatic arthritis	1.752	0.973-2.934	0.045
Region	Capital (R)			
	Metropolitan	0.790	0.513-1.185	0.268
	Rural	0.840	0.577-1.211	0.357
Institution	Tertiary (R)			
	Secondary	0.921	0.596-1.441	0.713
	Primary	0.410	0.255-0.666	<0.001
Physician specialty	General practitioner (R)			
	Neurologist	4.916	2.732-9.186	<0.001
	Orthopedist	2.227	1.155-4.346	0.017
	Psychiatrist	1.060	0.511-2.198	0.875
	Internist	0.228	0.082-0.554	0.002
	Others	0.639	0.318-1.280	0.204
c statistic		0.822		
P-value of Hosmer-Lemeshow test		0.278		

Adj. OR, adjusted odds ratio; CI, confidence interval; NHI, National health insurance; R, reference.

venlafaxine, and vortioxetine) should be reconsidered as potential DUR contraindications, considering that irreversible or nonselective MAOIs are closely associated with severe cases of serotonin syndrome.[2)]

The combination of rasagiline and tramadol accounted for the largest number of prescriptions for contraindicated drug combinations, although it was specified as a contraindication in DUR. Tramadol inhibits the reuptake of noradrenaline and serotonin by binding to the descending pathway neurons and accounts for the remaining analgesic properties.[35)] Between 2003 and 2013, the number of patients using tramadol as a pain reliever increased by approximately 1.5 times in Korea.[36)] Although tramadol is frequently prescribed in clinical practice, there seems to be a lack of awareness regarding its adverse reactions.[37)] For drugs with low awareness of side effects, such as tramadol, a policy that separately classifies and manages them, as in the USA, may be required.

The antipsychotic ziprasidone is contraindicated with

Table 3. Frequency of prescription of each combination of contraindicated drugs causing serotonin syndrome

Contraindicated drugs in combinations			n (%)
Overall			1,268 (100.0)
rasagiline	+	tramadol	299 (23.6)
rasagiline	+	escitalopram	184 (14.6)
rasagiline	+	trazodone	97 (7.6)
ziprasidone	+	trazodone	83 (6.5)
rasagiline	+	paroxetine	80 (6.3)
ziprasidone	+	fluoxetine	77 (6.1)
rasagiline	+	sertraline	58 (4.6)
rasagiline	+	vortioxetine	56 (4.4)
rasagiline	+	duloxetine	48 (3.8)
rasagiline	+	venlafaxine	36 (2.8)
Others			250 (19.7)

trazodone or fluoxetine in MDBs but not in DUR. Ziprasidone is a potent 5-HT1A agonist that inhibits serotonin reuptake with an affinity equivalent to imipramine.[38] In one case, serotonin syndrome occurred using ziprasidone alone.[39] Ziprasidone was positively associated with the incidence of serotonin syndrome among second-generation antipsychotics.[40] Based on the characteristics of ziprasidone, in terms of serotonin function and the presentation of this case, caution should be exercised regarding the occurrence of serotonin syndrome in patients receiving ziprasidone.

This study had several limitations. First, we used claims data which were primarily collected for reimbursement purpose; thus, the actual diagnosis and disease codes may differ. Second, physicians and pharmacists must write a reason for prescribing and dispensing drugs that do not meet the DUR standards. However, because this study used secondary data, the reason for the prescription could not be determined. Lastly, the names of mental disorders are masked; hence, they cannot be classified in detail. The claims data are masked as mental disorders and sensitive diseases because of privacy protection starting from 2021. Therefore, we could not examine the relationship between specific psychiatric disorders and contraindicated drug combinations. However, this study has several implications. This is the first study to identify the current prescription status of contraindicated drug combinations that cause serotonin syndrome in Korea. In addition, the differences between international MDBs and the Korean DUR were reviewed for contraindication drugs related to serotonin syndrome, and improvements in the DUR were suggested.

Conclusion

Despite the implementation of DUR, 3 out of 1,000 study subjects received contraindicated drug combinations that caused serotonin syndrome. And most contraindicated drug pairs identified in this study were not listed in Korean DUR criteria. Therefore, it is necessary to update and supplement current DUR criteria.

Acknowledgments

This study is based on data from the Korea Health Insurance Review and Assessment Service (HIRA-NPS-2020); however, the results are not related to the HIRA or Ministry of Health and Welfare.

Statement of Ethics

This study was approved by the Pusan National University Institutional Review Board (IRB No. 2022_28_HR), and official approval was obtained from the HIRA (Project No. S20220126792). The informed consent was waived because the data used were anonymized and did not contain any personal identification information.

Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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