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의약품부작용보고시스템 데이터베이스를 이용한 fluconazole 및 itraconazole 관련 이상사례 분석

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Real-world Adverse Events Associated with Fluconazole and Itraconazole: Analysis of Nationwide Data Using a Spontaneous Reporting System Database

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ABSTRACT

Objective: This study aimed to investigate the occurrence and types of the adverse events (AEs) associated with oral fluconazole and itraconazole and factors associated with specific types of AEs. **Methods:** We analyzed AEs reported by community pharmacies nationwide over 10 years using the Korea Adverse Event Reporting System database. Various AE terms were categorized into 18 types, and concomitant medications were classified by drug-drug interaction (DDI) severity. The relationship between the specific type of AE and age, sex, and number of concomitant medications was investigated using multiple logistic regression analysis. **Results:** A total of 879 AE reports of fluconazole and 401 reports of itraconazole were analyzed; of these reports, 321 and 83 reports of fluconazole and itraconazole, respectively, described concomitant drug administration categorized as DDI severity of contraindicated or major. Women had a higher risk of psychiatric AEs associated with fluconazole use (OR, 1.587; p=0.042). Polypharmacy increased the risk for psychiatric AEs (OR, 3.598; p<0.001 for fluconazole and OR, 2.308; p=0.046 for itraconazole). In dermatologic AEs, the mean age of patients who received itraconazole was lower than that of patients who received fluconazole (46.3±16.8 *vs.* 54.9±15.4; p<0.001). Co-administration of fluconazole with 1-3 drugs increased the risk of neurological AEs (OR, 1.764; p=0.028). **Conclusion:** When using fluconazole and itraconazole, psychiatric AEs should be noted, particularly in women and in case of polypharmacy; moreover, when fluconazole is co-administered with other drugs, attention should be paid to the occurrence of neurological AEs.

KEYWORDS: Adverse events, drug-drug interaction, fluconazole, itraconazole

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Fungal diseases are prevalent worldwide and are a huge burden on healthcare system. Globally, more than 1 billion people are estimated to have superficial fungal infections, including dermatomycosis and mucosal candidiasis, whereas over 150 million people have serious infections, leading to approximately 1.7 million deaths per year.[1,2] In South Korea, about 6.6-7.4% of the population was treated for fungal diseases, and the prevalence of trichophytosis was 8.6% in individuals in their 60s during 2009-2013.[3] According to the Korea Health Insurance Review & Assessment Service (HIRA), from 2016 to 2020, the pharmaceutical expenditure of National Health Insurance Service (NHIS) amounted to approximately 424 million USD for fluconazole and 187 million USD for itraconazole.[4]

Fluconazole and itraconazole are the most commonly used antifungal agents because of their broad-spectrum antifungal activities and efficacy in the management of various fungal diseases.[5,6] They are triazole derivatives and possess fungistatic activity by inhibiting the fungal cytochrome P450-dependent enzyme lanosterol 14-α-demethylase (CYP51A1), thereby suppressing the synthesis of ergosterol, a major component of cell membrane, leading to accumulation of toxic 14-α-methylated sterols in fungal cell membranes.[7] Most human cytochrome P450 (CYP) isoenzymes belong to the CYP family 1-3 and metabolize 70-80% of clinically used drugs. However, fluconazole inhibits CYP 2C9, 2C19 and 3A4, whereas itraconazole is a substrate and strong inhibitor of CYP 3A4, which requires attention to drug-drug interactions (DDIs). DDIs may have major impact on clinical conditions and healthcare costs, and even increase morbidity and mortality.[8,9]

Although caution about DDIs and adverse events (AEs) cannot be overemphasized in triazole antifungal therapy, to the best of our knowledge, recent studies reporting AEs using long-term real-world data are limited. Furthermore, a clear understanding of specific types of AEs associated with fluconazole and itraconazole will be helpful to develop strategies for individualized patient medication counseling. We investigated the occurrence and types of the AEs related to oral fluconazole and itraconazole treatment using the Korea Adverse Event Reporting System (KAERS) database of the Korean Pharmaceutical Association (KPA) for Patient and Drug Safety Regional Pharmacovigilance Center (RPVC). KAERS is a system developed by the Korea Institute of Drug Safety and Risk Management (KIDS) to facilitate reporting and management of AE reports. The RPVC is a nationwide center that collects AE reports from approximately 20,000-24,000 community pharmacies in South Korea.[10,11]

This study aimed to investigate the occurrence and types of the AEs associated with oral fluconazole and itraconazole and factors associated with specific types of AEs using real-world data.

Methods

Data source

We searched the KAERS of the KPA for Patient and Drug Safety RPVC for AEs associated with oral fluconazole and itraconazole. All reports registered in the database over a 10-year period (January 2013-April 2022) were examined. Each report contained information on patient characteristics, drug(s) administered, AE term(s), and region reporting the AE(s). Before 2021, the AEs were categorized by the World Health Organization Adverse Reaction Terminology (WHO-ART) 092; however, from 2021, the AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). This study was approved by the Institutional Review Board of Inje University (IRB File Number: INJE 2022-03-027).

Analysis of AE reports

The characteristics of AE reports were analyzed. The various AE terms were categorized into 18 types according to the “Information on pharmaceuticals” provided by the Ministry of Food and Drug Safety of Korea, which is mainly based on the System Organ Class (SOC).[12] (Appendix 1). When a report had topical preparation(s), the topical drug(s) were excluded and the AEs in the skin were not analyzed, because the dermatologic AEs could be due to the topical medications. If a report had more than one AE term, each term was independently categorized into the AE types. The number of medications administered a day was categorized into four groups: 1, 2-4, 5-9 and ≥10. We defined polypharmacy when a report had a total of 5-9 medications including 4-8 concomitant medications, and excessive polypharmacy was defined by ≥9 concomitant medications.[13] Concomitant medications were classified according to DDI severity of Micromedex®: contraindicated, major, or moderate. Finally, we analyzed the relationship between the specific type of AE and age, sex, and the number of concomitant medications.

Statistical analysis

The characteristics of the AE reports were summarized using descriptive statistics. Statistical significance was determined using the chi-square test for categorical variables and independent-samples *t* test for continuous variables. Fisher's exact test was used when more than 20% of the cells had expected frequencies <5. When estimating the probability of the occurrence of each type of AEs, we performed multiple logistic regression analysis using the 18 types of AEs as the outcome and age, sex, and number of concomitant medications as explanatory variables. Data analysis was performed using SPSS version 25 (IBM Corporation, New York) and *p* values <0.05 were considered statistically significant.

Results

Number of AE reports

During the period (January 2013-April 2022), 901 AE reports of fluconazole and 422 AE reports of itraconazole were collected. In 2013, there were 28 AE reports of fluconazole and 10 of iraconazole. After 2013, these numbers gradually increased, peaking at 141 reports of fluconazole in 2018 and 61 reports of itraconazole in 2019. However, in 2021, there were 86 and 46 AE reports of fluconazole and itraconazole, respectively. The reports reporting age and sex of the patients, concomitant medication(s), AE term(s), and the regions reporting the AEs were included and analyzed in this study; these were 879 reports of fluconazole and 401 reports of itraconazole (Fig. 1).

Characteristics of AE reports and patients

Most AEs were reported by patients aged 20-64 years of age for both fluconazole and itraconazole. Although the number of female patients reporting AEs was more than that of male patients, the proportion of female patients was higher for fluconazole than that for itraconazole (75.2% vs. 59.4%, $p<0.001$). More than 50% of AEs were reported in Seoul and the six major metropolitan cities. Although most reports showed concomitant medications, the proportion of co-administration was higher for fluconazole than for itraconazole (74.4% vs. 66.1%, $p<0.001$). Of 827 reports reporting the doses of fluconazole, 96.7% described 50 mg/day or 150 mg/week, whereas of 347 such reports of itraconazole, 49.3, 32.7, and 17.2% described doses of 200, 400, and 100 mg/day, respectively (Table 1).

Of 130 reports reporting indications for fluconazole and itraconazole, tinea pedis/corporis/unguium were the most frequent (63.1%), followed by candida vaginitis, aspergillosis, and oropharyngeal/esophageal candidiasis.

Of 115 reports of fluconazole, the most commonly reported comorbidity was hypertension (23.5%), followed by diabetes (19.1%), skin disease, cancer, prostatic hyperplasia, and gastrointestinal disturbances. Of 77 reports of itraconazole use, the most frequent comorbidity was skin disease (33.8%), followed by pulmonary diseases (19.5%) and prostatic hyperplasia.

DDI severity of the concomitant medications

Of the 879 reports of fluconazole, 21 reports reported

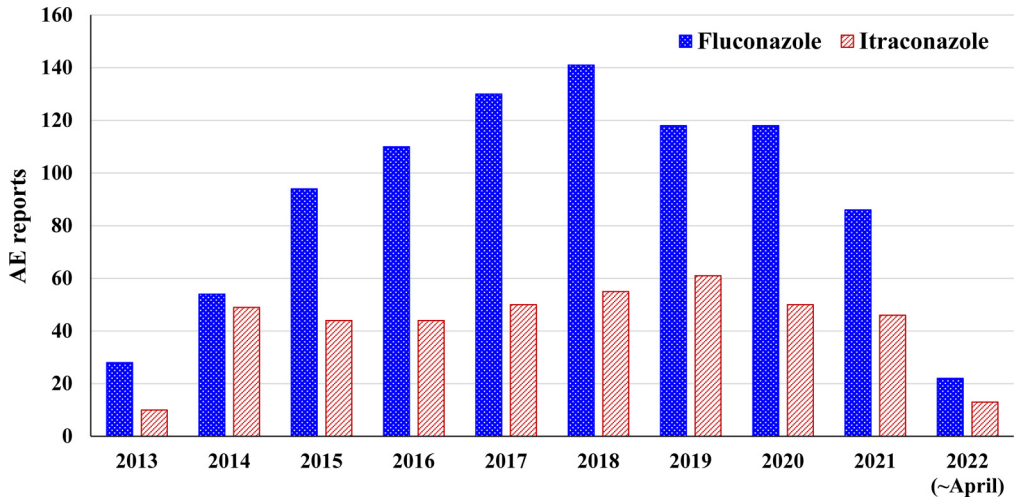

Fig. 1. The number of fluconazole- and itraconazole-related adverse events reported to the Korean Pharmaceutical Association for Patient and Drug Safety Regional Pharmacovigilance Center over a 10-year period (January 2013-April 2022).

Table 1. Characteristics of adverse event reports associated with fluconazole and itraconazole

	Cases of AEs		*p* value
	Fluconazole N (%)	Itraconazole N (%)	
Overall[a]	879 (100)	401 (100)	<0.001
Age group			0.262
<20	16 (1.8)	8 (2.0)	
20-64	655 (74.5)	318 (79.3)	
65-74	142 (16.2)	50 (12.5)	
≥75	66 (7.5)	25 (6.2)	
Sex			<0.001
Male	218 (24.8)	163 (40.6)	
Female	661 (75.2)	238 (59.4)	
Region reporting AEs			<0.001
Capital	179 (20.4)	156 (38.9)	
Metropolitan	311 (35.4)	92 (22.9)	
Others[b]	389 (44.3)	153 (38.2)	
Medications administered a day			<0.001
1	225 (25.6)	136 (33.9)	
2-4	366 (41.6)	200 (49.9)	
5-9	189 (21.5)	52 (13.0)	
≥10	99 (11.3)	13 (3.2)	
Dose[c]			NA
40 mg/day	1 (0.1)	0 (0)	
50 mg/day, 150 mg/week	800 (96.7)	1 (0.3)	
100 mg/day	15 (1.8)	60 (17.2)	
200 mg/day	4 (0.5)	172 (49.3)	
300 mg/day	3 (0.4)	2 (0.6)	
400 mg/day	3 (0.4)	114 (32.7)	
600 mg/day	1 (0.1)	0 (0)	

AE, adverse event; Capital, Seoul; Metropolitan includes Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan.
[a]Number of the reports reporting age, gender, the region where the AEs occurred, concomitant medication and the type(s) of AE.
[b]Others include Gangwon-do, Gyeonggi-do, Chuncheong-do, Gyeongsan-do, Jeolla-do, and Jeju-do.
[c]The percentage was calculated by taking 827 for fluconazole and 347 for itraconazole as 100.

concomitant medications classified as contraindicated (CI) DDI severity, and 85.7% were polypharmacy. Only two reports of itraconazole described CI medications. Of 280 reports describing fluconazole and concomitant medications classified as major DDI severity but not CI, more than 85% included women, polypharmacy was observed in 61.4% of these reports. Of 59 reports describing itraconazole and concomitant medications classified as major but not CI, nearly 60% included women and 53.6% reported polypharmacy. Of reports reporting moderate DDI severity (59 of fluconazole and 44 of itraconazole), which was neither CI nor major, 67.8 and 54.6% reported polypharmacy, respectively (Table 2).

The most frequently reported drug contraindicated with fluconazole was solifenacin (11 reports), followed by clarithromycin (4). Alfuzosin, amiodarone, buprenorphine, domperidone, donepezil and itraconazole were co-administered in one report each. The drugs classified as having major DDI severity were co-administered with

Table 2. Characteristics of adverse event reports describing concomitant drug(s) categorized into moderate, major, and contraindicated according to drug-drug interaction severity of Micromedex

	Fluconazole			Itraconazole		
	Moderate only, N=59	Major w/o CI, N=280	CI, N=21	Moderate only, N=44	Major w/o CI, N=59	CI, N=2
Age group						
<65	44 (74.6)	236 (84.3)	13 (61.9)	32 (72.7)	45 (76.3)	2 (100)
≥65	15 (25.4)	44 (15.7)	8 (38.1)	12 (27.3)	14 (23.7)	0 (0)
Sex						
Male	25 (42.4)	40 (14.3)	6 (28.6)	20 (45.5)	26 (44.1)	1 (100)
Female	34 (57.6)	240 (85.7)	15 (71.4)	24 (54.5)	33 (55.9)	0 (0)
Medications administered a day						
2-4	19 (32.2)	108 (38.6)	3 (14.3)	20 (45.5)	28 (47.5)	0 (0)
5-9	35 (59.3)	91 (32.5)	14 (66.7)	20 (45.5)	22 (38.3)	2 (100)
≥10	5 (8.5)	81 (28.9)	4 (19.0)	4 (9.1)	9 (15.3)	0 (0)
Region reporting AE						
Capital	17 (28.8)	39 (13.9)	2 (9.5)	20 (45.5)	33 (55.9)	1 (50)
Metropolitan	21 (35.6)	63 (22.5)	8 (38.1)	12 (27.3)	11 (18.6)	1 (50)
Others[a]	21 (35.6)	178 (63.6)	11 (52.4)	12 (27.3)	15 (25.4)	0 (0)

AE, adverse event; CI, contraindicated; w/o, without; Capital, Seoul; Metropolitan includes Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan.
[a]Others include Gangwon-do, Gyeonggi-do, Chuncheong-do, Gyeongsan-do, Jeolla-do, and Jeju-do.
The percentages calculated by assuming the number of cases in each severity category as 100.

fluconazole for 300 times because 10 reports reported drugs classified as CI and major DDI together, and some reports contained more than one major drugs. Among drugs having major DDI severity when co-administered with fluconazole, ebastine (112), metronidazole (54), hydroxyzine (30), tramadol (23), fluoroquinolones such as ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin (17), and statins such as atorvastatin and simvastatin (16) were frequent, followed by dihydrocodeine (8), alprazolam (6), famotidine (6), cilostazol (5), azithromycin (4), clopidogrel (3), formoterol (3), sulfamethoxazole/trimethoprim (3) and nortriptyline (2). Colchicine, cyclosporine, hydroxychloroquine, irbesartan, paroxetine, sildenafil, theophylline and tolterodine were co-administered in one report each.

Among drugs having moderate DDI severity when co-administered with fluconazole for 138 times, rosuvastatin (31), proton pump inhibitors such as esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole (29), aceclofenac (17), cimetidine (14), losartan (12), and prednisolone (11) were frequent, followed by celecoxib (8), zolpidem (6), dutasteride (4), buspirone (2), diltiazem (2) and propranolol (2).

The drugs classified as CI when co-administered with itraconazole were simvastatin (1) and alfuzosin (1). Among drugs showing major DDI severity when co-administered with itraconazole for 81 times, metronidazole (21), hydroxyzine (20), and codeine and dihydrocodeine (10) were frequent, followed by clofazimine (6), tamsulosin (5), and fluoroquinolones such as moxifloxacin and levofloxacin (4). Atorvastatin, cyclosporine, hydroxychloroquine, rifabutin were co-administered in two reports each and clarithromycin, digoxin, domperidone, fesoterodine, nifedipine, sildenafil and tadalafil were co-administered in one report each. Among drugs with moderate DDI severity when co-administered with itraconazole for 69 times, H2-receptor antagonists such as cimetidine, famotidine, nizatidine and ranitidine (35) and proton pump inhibitors such as esomeprazole, lansoprazole, omeprazole and pantoprazole (18) were frequent, followed by calclium carbonate (9), ciprofloxacin (4), magnesium oxide (2) and rosuvastatin (1).

Types of AEs

A total of 1011 AE terms were reported from the 879 reports of fluconazole, whereas 480 AE terms were reported from the 401 reports of itraconazole. Gastrointestinal AEs were the most frequent, followed by psychiatric, dermatologic, and neurologic AEs.

In dermatologic AEs, the mean age of patients who received itraconazole was lower than that of patients who received fluconazole (46.3±16.8 *vs.* 54.9±15.4; $p<0.001$). Regarding gastrointestinal, psychiatric, and dermatologic AEs, the proportion of women was higher in reports of fluconazole than in reports of itraconazole (Table 3).

Types of AEs stratified by DDI severity

After co-administration of CI drugs with fluconazole, gastrointestinal AEs were the most frequent, followed by psychiatric and neurologic AEs and edema. After co-administration of major DDI severity drug(s) with fluconazole, gastrointestinal AEs were the most common, followed by psychiatric, neurologic, and dermatological AEs and edema. After co-administration CI drugs with itraconazole, dermatological AE and edema were reported in one report each. After co-administration of major DDI severity drug(s) with itraconazole, gastrointestinal and neurologic AEs were the most frequently reported, followed by psychiatric AEs, fatigue/fever, skin and edema (Fig. 2).

Factors involved in the occurrence of the specific type of AEs

After administration of fluconazole, the risk of psychiatric AEs was lower in the patients aged 65 years or older (adjusted odds ratio [aOR], 0.364; $p<0.001$). Women had a higher risk of psychiatric AEs (aOR, 1.587; $p=0.042$) but a lower risk of neurologic AEs (aOR, 0.596; $p=0.015$) and fatigue/fever (aOR, 0.484; $p=0.004$). The risk for psychiatric AEs increased with concomitant drugs (aOR, 4.215 for 1-3 drugs; 3.598 for 4-8 drugs; 7.553 for ≥9 drugs, $p<0.001$ for all). Co-administration of fluconazole with 1-3 drugs increased the risk of neurological AEs (aOR, 1.764; $p=0.028$). In contrast, the risk of gastrointestinal AEs was decreased with 1-3 concomitant drugs (aOR, 0.664; $p=0.011$). Furthermore, the risk of fatigue/fever decreased as the number of concomitant medications increased (aOR, 0.399 for 1-3 drugs, $p=0.001$; 0.262 for 4-8 drugs, $p<0.001$; 0.121 for ≥ 9 drugs, $p=0.004$).

In case of itraconazole, there was no significant relationship between the 18 types of AEs and age and sex. However, co-administration of itraconazole with 4-8 drugs increased the risk of psychiatric AEs (aOR, 2.308; $p=0.046$) (Table 4).

Discussion

Using the KAERS of the KPA for Patient and Drug Safety RPVC, we investigated fluconazole- and itraconazole-related AE reports collected by a nationwide center of community pharmacies in Korea over 10 years. As the center started collecting AE reports in 2013, there were few reports in that year. The number of reports gradually increased, peaking in 2018 for fluconazole and in 2019 for itraconazole. However, since then, the number of reports started to decrease, and in 2021, it was 61% of the peak number in 2018 for fluconazole and 75% of the peak in 2019 for itraconazole. In a year with a large number of AE reports, there were many reports describing concomitant drug administration categorized as DDI severity of moderate or higher. This relationship was explained based on the results of a previous study, where DDI was the most common concern in AEs of fluconazole and itraconazole.[14] In Korea, HIRA provides nationwide Drug Utilization Review (DUR) system that provides real-time alerts to physician and pharmacists through HIRA's system linked computers regarding prescriptions containing drugs with age and pregnancy contraindications and contraindicated DDI. In 2019, the system started reviewing drugs categorized into the same efficacy group and prescribed repeatedly between prescriptions.[15] The DUR system is believed to have contributed to the decrease in the number of AE reports since 2019.

The number of AE reports was higher in women than that in men. This result is in accordance with those of previous studies demonstrating the women had a higher risk of adverse drug reactions (ADRs), and the proportion of women experiencing ADRs after taking antifungal agent was 1.7 times of that of men.[16,17] Furthermore, we observed that the proportion of women included in AE reports of fluconazole was approximately 2 times of that of itraconazole.

Compared to reports with singly antifungal agent, those with concomitant drugs were three times for fluconazole and two times for itraconazole. This is in line with the result of a previous study reporting that 13 and 38% of patients taking two and five medications, respectively, were at risk of adverse drug interaction.[18]

Table 3. Differences in mean age and sex between fluconazole and itraconazole groups when stratified by the type of adverse events

Types of AEs	Drug	AEs, N (%)	Age, mean±SD	*p* value	Female, N (%)	*p* value
Gastrointestinal system	fluconazole	388 (38.4)	51.6±17.2	0.876	302 (77.8)	0.001
	itraconazole	125 (26.0)	51.9±15.3		78 (62.4)	
Psychiatric system	fluconazole	146 (14.4)	44.1±15.8	0.156	119 (81.5)	0.001
	itraconazole	61 (12.7)	47.4±14.0		36 (59.0)	
Skin	fluconazole	105 (10.4)	54.9±15.4	<0.001	83 (79.0)	0.028
	itraconazole	82 (17.1)	46.3±16.8		53 (64.6)	
Nervous system	fluconazole	112 (11.1)	53.4±17.8	0.332	73 (65.2)	0.728
	itraconazole	53 (11.0)	50.6±16.1		36 (67.9)	
Fatigue/Fever	fluconazole	73 (7.2)	49.1±15.6	0.622	44 (60.3)	0.240
	itraconazole	58 (12.1)	50.4±14.4		29 (50.0)	
Edema	fluconazole	55 (5.4)	57.8±14.5	0.165	38 (69.1)	0.055
	itraconazole	33 (6.9)	53.24±15.2		16 (48.5)	
Reproductive system	fluconazole	29 (2.9)	46.3±16.2	0.683	25 (86.2)	0.235
	itraconazole	15 (3.1)	48.3±18.6		10 (66.7)	
Heart	fluconazole	20 (2.0)	49.3±13.3	0.768	18 (90.0)	0.075
	itraconazole	11 (2.3)	51.3±24.8		7 (63.6)	
Musculoskeletal system	fluconazole	23 (2.3)	59.8±15.4	0.013	18 (78.3)	1.000
	itraconazole	7 (1.5)	42.3±15.2		5 (71.4)	
Mouth	fluconazole	13 (1.3)	50.9±21.5	-	8 (61.5)	-
	itraconazole	4 (0.8)	40.3±13.8		2 (50.0)	
Renal system	fluconazole	11 (1.1)	52.6±18.8	-	7 (63.6)	-
	itraconazole	0	NA		0	
Respiratory system	fluconazole	10 (1.0)	50.0±10.7	-	3 (42.9)	-
	itraconazole	8 (1.7)	59.2±10.6		3 (40.0)	
Hepatobiliary system	fluconazole	7 (0.7)	58.1±9.7	-	5 (71.4)	-
	itraconazole	7 (1.5)	55.6±13.3		3 (42.9)	
Blood pressure	fluconazole	7 (0.7)	61.4±16.9	-	3 (42.9)	-
	itraconazole	2 (0.4)	53.5±16.3		2 (100)	
Metabolism	fluconazole	5 (0.5)	48.2±19.1	-	2 (40.0)	-
	itraconazole	7 (1.5)	48.7±17.2		2 (16.7)	
Auditory system	fluconazole	5 (0.5)	46.2±15.3	-	4 (80.0)	-
	itraconazole	2 (0.4)	51.5±5.0		2 (100)	
Eye	fluconazole	1 (0.1)	36.0±0.0	-	1 (100)	-
	itraconazole	4 (0.8)	54.3±14.7		2 (50.0)	
Blood/lymphatic system	fluconazole	1 (0.1)	56.0±0.0	-	1 (100)	-
	itraconazole	1 (0.2)	39.0±0.0		1 (100)	

AEs, adverse events
The percentage of AEs was calculated by taking 1011 for fluconazole and 480 for itraconazole as 100.
The percentage of female was calculated by assuming the number of adverse events associated with each drug as 100.

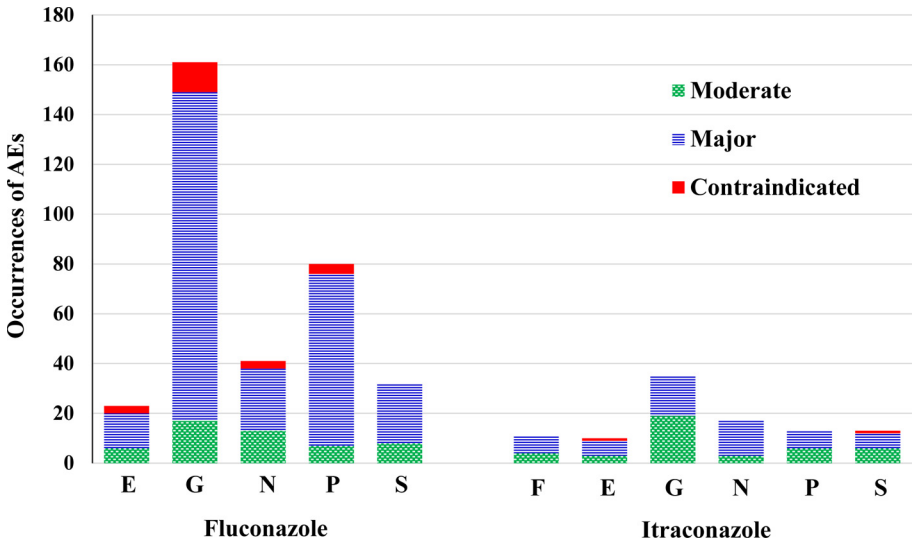

Fig. 2. The occurrence of each type of adverse events stratified by the drug-drug interaction severity of the concomitant medications. E, edema; G, gastrointestinal system; N, nervous system; P, psychiatric system; S, skin; F, fatigue/fever

Concomitant medications classified as moderate or higher severity were more frequent in women and patients aged < 65 years. This might be attributed to that most reports were of patients aged <65 years (76.3% for fluconazole and 81.3% for itraconazole) and that the proportion of women was higher than that of men (75.2% for fluconazole and 59.4% for itraconazole).

It is well documented that antimicrobials such as azithromycin, clarithromycin, metronidazole and some fluoroquinolones, formoterol, and hydroxyzine increase the risk of QT prolongation and/or arrhythmia when co-administered with fluconazole or itraconazole.[19,20] In this study, chest discomfort/pain, shortness of breath, and tachycardia were reported in 20 AE reports of fluconazole: 5 reports had the above-mentioned antimicrobials, one had formoterol and one had hydroxyzine.

However, 11 reports of itraconazole reported these terms: one report had hydroxyzine. No reports showed "QT prolongation". In a previous study, during the period 1995-2015, the cases of torsade de pointes reported to the WHO monitoring center were more frequently associated with fluconazole than with itraconazole (130 cases *vs.* 22cases).[21]

Micromedex categorizes the DDI of ebastine and fluconazole into major severity because of the risk of QT prolongation. However, in this study, no AEs related to QT prolongation were reported with ebastine, highlighting the need for further studies to determine the DDI severity of ebastine-fluconazole. In a previous study, ebastine did not produce clinically relevant changes in the QT interval at doses less than five times the recommended therapeutic dose.[22]

In total, AEs associated with fluconazole and itraconazole, gastrointestinal, psychiatric, neurologic, and dermatologic AEs, and fatigue/fever were frequently reported. Similarly, in a recent study that analyzed the U.S. FAERS database, during the period 1993-2019, dermatological AEs were the most frequent for fluconazole and itraconazole, followed by fatigue/fever and gastrointestinal and neurologic AEs.[14]

In most AEs, no differences in the mean ages were observed between fluconazole and itraconazole groups. However, the mean age in itraconazole group was lower than that in fluconazole group for dermatologic and musculoskeletal AEs.

Hepatic dysfunction, but not severe liver injury, was reported in 7 reports of fluconazole and in 7 reports of itraconazole. In six reports, fluconazole was co-administered with 1-4 drugs at a dose of 150 mg/week, whereas in five reports, itraconazole was co-administered with more than 10 drugs at various doses of 100-400 mg/day. The administration period ranged from 7 to 90 days. None of the patients had chronic liver disease. On the basis of these findings, hepatic dysfunction associated with itraconazole and fluconazole is considered uncommon. This is supported by the results of a previous study.[23]

In this study, women had a higher the risk of psychiatric AEs associated with fluconazole than that of men. Previous

Table 4. The relationship between the specific type of adverse event and age, sex, and number of concomitant medications

	Fluconazole							
	Gastrointestinal system		Psychiatric system		Nervous system		Fatigue/Fever	
	aOR	*p* value	aOR	*p* value	aOR	*p* value	aOR	*p* value
Age								
<65	R		R		R		R	
≥65	1.257	0.125	0.364	<0.001	1.473	0.076	0.652	0.174
Sex								
Male	R		R		R		R	
Female	1.318	0.069	1.587	0.042	0.596	0.015	0.484	0.004
Concomitant medications								
0	R		R		R		R	
1-3	0.664	0.011	4.215	<0.001	1.764	0.028	0.399	0.001
4-8	0.728	0.091	3.598	<0.001	0.961	0.903	0.262	<0.001
≥9	1.143	0.566	7.553	<0.001	0.737	0.497	0.121	0.004
	Itraconazole							
	Gastrointestinal system		Psychiatric system		Nervous system		Fatigue/Fever	
	aOR	*p* value	aOR	*p* value	aOR	*p* value	aOR	*p* value
Age								
<65	R							
≥65	1.364	0.225	0.435	0.063	1.154	0.692	0.663	0.305
Sex								
Male	R		R		R		R	
Female	1.146	0.524	0.954	0.867	1.471	0.214	0.629	0.099
Concomitant medications								
0	R		R		R		R	
1-3	1.361	0.188	1.634	0.136	0.956	0.888	1.1102	0.752
4-8	1.023	0.948	2.308	0.046	0.795	0.642	0.750	0.558
≥9	1.114	0.859	0.667	0.704	1.098	0.907	0.483	0.493

aOR, adjusted odds ratio; R, reference

studies have consistently shown that women were more frequently affected by psychiatric AEs than men.[17,24] In contrast, the present study found that women had a lower risk of neurologic AEs and fatigue/fever than that of men, although more women reported fluconazole-related nervous AEs (65.2%) and fatigue/fever (60.3%), suggesting the need further research. The mean age of the patients experiencing psychiatric AEs associated with fluconazole was 44 years, and patients aged 65 years or older had a lower risk of psychiatric AEs. Similarly, in a previous study conducted in Sweden, the median age was 44 years, and only 15% patients were at the age of ≥65 years.[24] Although it is uncommon, psychiatric AEs such as sleepiness, insomnia, and mood swings have been reported in patients taking fluconazole.[25] The risk of psychiatric AEs increased when fluconazole was co-administered with other drug(s) compared with that of fluconazole monotherapy. When itraconazole was used with 4-8 concomitant drugs, the risk of psychiatric AEs was higher than that of itraconazole monotherapy. This finding is consistent with the result of the Netherlands study, where psychiatric AEs were more frequent in excessive polypharmacy.[17] Despite these results, among AE reports of fluconazole, gastrointestinal AEs were less likely to occur following co-administration with 1-3 drug(s). Furthermore, the risk for

fatigue/fever decreased as the number of concomitant medications increased. To the best of our knowledge, our study is the first to reveal above results, warranting further research.

The strength of this study is that it analyzed real-world AE reports associated of fluconazole and itraconazole collected from more than 20,000 community pharmacies nationwide over 10 years. However, this study had some limitations. First, it is difficult to preclude that AEs were likely to be more strongly related to concomitant drug(s) in the reports describing administration of concomitant drug(s). Second, in this study, AEs reported by consumers through community pharmacies were analyzed; therefore, serious AEs involving hospital visits were not analyzed. Third, the demographic characteristics of the patients reporting AEs were analyzed based on each AE report rather than each patient. Lastly, sufficient data were not available on the exact numbers of doses administered before reporting AEs, which may have affected the occurrence of AEs. Despite these limitations, the KAERS database is valuable for understanding the occurrence and types of AEs related to medications.

Conclusion

Polypharmacy was observed to be associated with increased risk of psychiatric AEs of fluconazole and itraconazole. According to the reports of fluconazole, women had a higher risk of psychiatric AEs but a lower risk of neurologic AEs and fatigue/fever than those of men. Co-administration of fluconazole with 1-3 drug(s) increased the risk of neurologic AEs but decreased the risk of gastrointestinal AEs.

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Conflict of interest

The authors have no conflicts of interests to declare with regards to the content of this article.

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