Drugs - Real World Outcomes
https://doi.org/10.1007/s40801-024-00450-1

ORIGINAL RESEARCH ARTICLE

Prescription Patterns of Inducers and Inhibitors of Cytochrome P450 and Their Potential Drug Interactions in the Real World: A Cross-Sectional Study

Luis Fernando Valladales-Restrepo[1,2,3] · **Juan Alberto Ospina-Cano**[1] · **Brayan Stiven Aristizábal-Carmona**[3] · **Jorge Enrique Machado-Alba**[1]

Accepted: 22 August 2024

Abstract

Introduction Both the induction and inhibition of cytochrome P450 are associated with multiple pharmacological interactions, which can lead to loss of efficacy or increase the risk of adverse drug reactions.

Objective The aim was to determine the prescription patterns of cytochrome P450-inducing and -inhibiting drugs and their contraindicated and major pharmacological interactions in a group of patients from Colombia.

Methods This cross-sectional observational study included patients who received drugs that induce or inhibit metabolism and examined their contraindicated and major pharmacological interactions. The patients were identified from a population-based database of drug dispensing. Patients were included between December 1 and December 31, 2021. Inhibitors and inducers of cytochrome P450 were classified based on FDA (Food and Drug Administration) guidelines. Drug interactions were identified using the Micromedex® database. Descriptive, bivariate and multivariable analysis was performed.

Results A total of 63,433 patients were analyzed. Antiseizure medications (35.9%) and antifungals (27.6%) were the most used inducers and inhibitors. A total of 30.1% of patients had potential contraindicated or greater interactions. The following factors were associated with a higher probability of presenting a potential pharmacological interaction: being male (OR 1.14; 95% CI 1.10–1.19), aged 18–39 years (OR 1.77; 95% CI 1.67–1.89) or 40–64 years (OR 1.64; 95% CI 1.56–1.72), having neurological diseases (OR 1.28; 95% CI 1.21–1.35), having psychiatric diseases (OR 3.84; 95% CI 3.58–4.13), having rheumatologic diseases (OR 1.32; 95% CI 1.23–1.41), receiving comedications with statins (OR 1.14; 95% CI 1.08–1.19), receiving comedications with analgesics (OR 1.33; 95% CI 1.27–1.38), receiving comedications with antiparasitics (OR 2.88; 95% CI 2.66–3.11) and an increase in the number of medications (OR 1.24; 95% CI 1.23–1.25).

Conclusion Among the users of cytochrome P450 inhibitors and inducers, potential contraindications and greater interactions are very common, especially in men under 65 years of age with comorbidities and polypharmacy.

1 Introduction

Medications play an important role in the prevention of diseases and in the promotion, maintenance and recovery of the health of the patient, thus contributing to improving quality of life and increasing life expectancy [1]. Despite these benefits, problems related to the use of medications are increasingly frequent and involve inadequate prescriptions, adverse drug reactions and pharmacological interactions [1]. Pharmacological interactions are understood as the change in the effect of a drug as a result of the association with one or more drugs, which can generate adverse reactions or therapeutic failure [2]. It has been documented that the prevalence of adverse drug reactions as a result of drug–drug

✉ Jorge Enrique Machado-Alba
machado@utp.edu.co

1 Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia, Universidad Tecnológica de Pereira-Audifarma S.A, Calle 105 No. 14-140, 660003 Pereira, Risaralda, Colombia

2 Grupo de Investigación Biomedicina, Facultad de Medicina, Fundación Universitaria Autónoma de las Américas, Pereira, Colombia

3 Semillero de Investigación en Farmacología Geriátrica, Grupo de Investigación Biomedicina, Facultad de Medicina, Fundación Universitaria Autónoma de las Américas, Pereira, Colombia

Published online: 07 September 2024

Key Summary Points

The prevalence of users with inhibitors was 26.5 per 1000 people with drug dispensing and the prevalence of users with inducers was 15.1 per 1000 people with drug dispensing.

Potential drug interactions occurred in almost a third of patients and the prevalence was 12.4 per 1000 people with drug dispensing.

Possible drug interactions were predominant in patients receiving antiseizure medications (39.7%) and antifungal medications (31.5%).

interactions ranges between 1.2% and 64.0% [1], thus indicating that it is an important cause of hospitalization and deaths related to the use of medications [3].

The cytochrome P450 family of enzymes is the most important enzymatic system that catalyzes the phase 1 metabolism of pharmaceutical products and other xenobiotics, such as herbal substances and toxic compounds, in the environment [4–6]. To date, 57 genes encoding different isoforms of cytochrome P450 have been identified [5]. Most of the drugs approved by the US Food and Drug Administration (FDA) are metabolized mainly by CYP3A4, followed by CYP2D6, CYP2C8, CYP2C19, CYP2C9, CYP2B6 and CYP1A1/2 [3, 5]. The main mechanisms that cause clinically significant pharmacokinetic interactions between drugs are the inhibition and induction of cytochrome P450 [3, 4, 6]. Its inhibition can lead to adverse drug reactions by increasing the serum concentrations of the drug administered concomitantly, while its induction could significantly reduce the efficacy of some treatments by decreasing the serum concentrations of the drug [2, 3, 5].

According to the FDA, some medications, such as antiseizure medications, antiretrovirals, oncologicals, immunosuppressants, antifungals, macrolides, nondihydropyridine calcium channel blockers and antituberculous agents, among others, inhibit or induce cytochrome P450 [7]. However, there are no pharmacoepidemiologic studies on patterns of use and pharmacological interactions involving different inducers and inhibitors. There are studies on specific drugs but no studies including all or most of these drugs. The Colombian Health System offers universal coverage to the entire population through two affiliation regimes that have a similar gender and age distribution: the contributory system that is paid by workers and employers (n = 22,757,343; 46.6%) and the subsidized system that is responsible for the insurance of all people without the ability to pay (n = 26,082,344; 53.4%) [8] and includes a benefit plan that involves a large number of drugs that may have inhibitory and metabolism-inducing properties. The objective of this study was to determine the prescription patterns of cytochrome P450-inducing and -inhibiting drugs and their contraindicated and major pharmacological interactions in a group of patients from Colombia.

2 Materials and Methods

2.1 Study Design and Patients

A cross-sectional observational study was conducted to establish the prescription patterns of drugs with potent and moderate inducing and inhibiting properties of cytochrome P450 and potential contraindicated and major pharmacological interactions in outpatients. The subjects were identified from a population database of drug dispensing that collects information from approximately 9.5 million people affiliated with the Colombian Health System across five health insurance companies (Salud Total, Nueva EPS, Mutual Ser, Compensar and Coomeva), corresponding to approximately 19.5% of the Colombian population, including 29.2% (6.6 million) of the individuals in the contributory or health care system and 11.1% (2.9 million) of the individuals in the state-subsidized system. The drug dispensing database contains sociodemographic variables (age, sex, city of dispensing and affiliation regime), pharmacological variables (medication, pharmaceutical form, dose and prescribing physician) and primary and secondary diagnoses [9, 10]. This database is the most widely used source of secondary information for studies with evidence in the real world in Colombia, which allows research on the use and safety of medications [10]. To date, more than 200 investigations have been carried out and published [9].

Patients were included if they were prescribed drugs with potent and moderate inducing and inhibiting properties of cytochrome P450 between December 1 and 31 of 2021. Patients of any sex, aged 18 years or older, seen in medical consultation were selected. Patients with incomplete information were excluded.

2.2 Variables

Based on the information on drug consumption of the affiliated population that was systematically obtained by the dispensing company (Audifarma SA), a database was designed that allowed the following groups of patient variables to be collected:

1. Sociodemographic: age, sex, affiliation regime to the health system (contributory or subsidized) and origin. The place of origin was categorized according to the regions of Colombia, taking into account the classification of the National Administrative Department of Statistics—DANE of Colombia, as follows: Bogotá-Cundinamarca region, Caribbean region, Central region, Eastern region, Pacific region and Amazonia-Orinoquía region.
2. Chronic pathologies: identified from the main and secondary diagnoses reported by the International Classification of Diseases, 10th version (ICD-10) codes of the selected patients from October 1 to December 31, 2021. They were categorized into cardiovascular, respiratory, digestive, rheumatological, neurological, psychiatric and endocrine disorders (Supplementary Table 1, see electronic supplementary material [ESM]).
3. Inhibitors and inducers of cytochrome P450: classified based on FDA guidelines [7] (Supplementary Table 2, see ESM). They were grouped into antiseizure medications, antifungals, antihypertensives, antiarrhythmics, immunosuppressants, macrolides, antiretrovirals, oncologicals, drugs for pulmonary hypertension, antituberculosis drugs, psychostimulants, antiemetics and drugs for cystic fibrosis (Supplementary Table 3, see ESM).
4. Relevant pharmacological interactions: classified by their severity according to the Micromedex® database. Contraindicated interactions (do not use simultaneously) and major interactions (may cause death or require medical intervention to minimize or avoid serious adverse effects) were evaluated [11].
5. Type of prescriber: general practitioner, medical specialties (internal medicine, pediatrics, among others), surgical specialties (general surgery, orthopedics, among others) and dentistry.
6. Number of medications: categorized into polypharmacy (5–9 medications), excessive polypharmacy (10–19 medications) and extreme polypharmacy (20 or more medications) [12, 13].
7. Comedications grouped into the following categories: (a) antidiabetics, (b) antihypertensives and diuretics, (c) lipid-lowering drugs, (d) antiulcers, (e) antidepressants, (f) analgesics and anti-inflammatories, (g) antipsychotics, (h) antiseizure medications, (i) antihistamines, (j) antiparkinsonian drugs, (k) antidementia medications, (l) micronutrients, (m) antiparasitics and (n) anxiolytics.

2.3 Ethics Statement

The protocol was endorsed by the Bioethics Committee of the Technological University of Pereira under the category of 'research without risk' (approval code or number of the certification: CBE.48-280621. Date: July 2, 2021). The principles of confidentiality of information established by the Declaration of Helsinki were respected.

2.4 Data Analysis

The data were analyzed with the statistical package SPSS Statistics, version 26.0 for Windows (IBM, USA). Descriptive analysis was performed with frequencies and proportions for the qualitative variables and measures of central tendency and dispersion for the quantitative variables through medians and interquartile ranges (IQRs). Prevalences of users of inhibitors or inducers and of users with drug interactions were determined for every 1000 people with drug dispensing. The comparison of quantitative variables was performed using the Mann–Whitney U test, and X^2 or Fisher's exact test for categorical variables. An exploratory multivariable analysis was performed using binary logistic regression. The dependent variable was relevant pharmacological interactions (contraindicated and major) (yes/no). The independent variables (covariates) (candidates to be part of the logistic regression) were those that showed statistical significance with the dependent variable in the bivariate analyses as well as those with sufficient plausibility or reported association (e.g., sex and age). The intro method was used to select the variables. A p-value <0.05 indicated statistical significance.

3 Results

During the month of December, 2021, 1,535,488 people aged ≥18 years had prescribed medication (62.9% were women, the median age was 61 years [IQR 35–68] and 67.7% were affiliated to the contributory regime). Of these patients, 4.1% (n = 63,433) were prescribed a drug with properties to either inhibit or induce cytochrome P450, distributed over 189 different cities. A total of 63.1% (n = 39,997) of the patients were women, and the median age was 61.0 years (range: 19.0–105.0). A total of 20.2% (n = 12,841) were <40 years of age, 37.6% (n = 23,858) were between 40–64 years and 42.1% (n = 26,734) were 65 years or older. The majority of patients were in the Caribbean region (n = 27,747; 43.7%). A total of 65.3% (n = 41,447) were affiliated with the contributory regime of the Colombian Health System, and 34.7% (n = 21,986) were affiliated with the subsidized regime (Table 1).

Cardiovascular diseases were the most prevalent (n = 29,282; 46.2%) in this group of patients, followed by endocrine (n = 18,637; 29.4%), neurological (n = 11,296; 17.8%), rheumatological (n = 4622; 7.3%) and psychiatric diseases (n = 4228; 6.7%). Most cases were being managed by general practitioners (n = 60,182; 94.9%), and the median number of medications prescribed per patient was 5.0 (IQR:

3.0–8.0). A total of 55.3% ($n = 35,080$) of patients had five or more medications, of which antihypertensives and diuretics ($n = 30,384$; 47.9%), lipid-lowering drugs ($n = 24,444$; 38.5%) and analgesics predominated ($n = 21,120$; 33.3%) (Table 1).

Forty-four different drugs that induce or inhibit cytochrome P450 were identified. Inhibitors were prescribed to 64.4% ($n = 40,744$) of patients, most of which were moderate ($n = 36,492$; 57.4% of all subjects with inducing or inhibiting drugs) rather than potent ($n = 4431$; 7.0%). Inducers were prescribed to 36.6% ($n = 23,233$) of patients, most of which were potent ($n = 22,988$; 36.2%) rather than moderate ($n = 246$; 0.4%). A total of 544 (0.9%) patients received both inducer and inhibitor drugs simultaneously. The prevalence of users with inhibitors or inducers per 1000 people with drug dispensing was 26.5 and 15.1, respectively. Verapamil and fluconazole were the most frequently prescribed inhibitors, while carbamazepine and phenytoin were the most common inducers (Table 2). Antiseizure medications were the most common group of drugs ($n = 22,787$; 35.9% of all patients), followed by antifungals ($n = 17,519$; 27.6%), antihypertensives ($n = 17,386$; 27.4%), antiarrhythmics ($n = 3294$; 5.2%), immunosuppressants ($n = 640$; 1.0%), macrolides ($n = 1418$; 2.2%), antiretrovirals ($n = 499$; 0.8%), oncological medications ($n = 370$; 0.6%), medications for pulmonary hypertension ($n = 142$; 0.2%), antituberculosis drugs ($n = 49$, 0.1%), psychostimulants ($n = 25$; 0.0%), antiemetics ($n = 5$; 0.0%) and medications for cystic fibrosis ($n = 1$; 0.0%).

A total of 26,443 potential drug interactions were identified in 30.1% of patients ($n = 19,086$). The prevalence

Table 1 Comparison of some sociodemographic and pharmacological variables according to the prescription of drugs that induce or inhibit cytochrome P450 in Colombia

Variables	Total		Inhibitors		Inductors		Inhibitors–inductors	
	$n = 63,433$	%	$n = 40,200$	%	$n = 22,689$	%	$n = 544$	%
Woman	39,997	63.1	27,246	67.8	12,416	54.7	335	61.6
Age, median (interquartile range)	61.0 (44.0–73.0)		62.0 (43.0–74.0)		58.0 (44.0–70.0)		67.0 (54.5–77.0)	
Origin								
Caribbean region	27,747	43.7	16,094	40.0	11,392	50.2	291	48.0
Pacific region	12,357	19.5	8518	21.2	3692	16.3	147	27.0
Bogotá-Cundinamarca region	12,038	19.0	8376	20.8	3606	15.9	56	10.3
Central region	9430	14.9	5995	14.9	3365	14.8	70	12.9
Eastern region	1697	2.7	1097	2.7	590	2.6	10	1.8
Amazon region	164	0.3	120	0.3	44	0.2	0	0.0
Comorbidities								
Arterial hypertension	28,430	44.8	19,876	49.4	8267	36.4	287	52.8
Diabetes mellitus	11,692	18.4	7092	17.6	4436	19.6	164	30.1
Hypothyroidism	7253	11.4	4881	12.1	2281	10.1	91	16.7
Epilepsy	6346	10.0	193	0.5	6098	26.9	55	10.1
Chronic kidney disease	2624	4.1	1982	4.9	603	2.7	39	7.2
Number of drugs per patient, median (interquartile range)	5.0 (3.0–8.0)		5.0 (3.0–7.0)		5.0 (2.0–8.0)		9.0 (6.0–11.0)	
No polypharmacy	28,353	44.7	17,399	43.3	10,894	48.0	60	11.0
Polypharmacy	26,002	41.0	17,861	44.4	7877	34.7	264	48.5
Excessive polypharmacy	8743	13.8	4796	11.9	3743	16.5	204	37.5
Extreme polypharmacy	335	0.5	144	0.4	175	0.8	16	2.9
Comedications	55,562	87.6	35,485	88.3	19,547	86.2	530	97.4
Antihypertensives and diuretics	30,384	47.9	21,074	52.4	8932	39.4	378	69.5
Lipid-lowering	24,444	38.5	16,582	41.2	7554	33.3	308	56.6
Analgesics and anti-inflammatories	21,120	33.3	12,624	31.4	8223	36.2	273	50.2
Anti-ulcer	17,915	28.2	11,198	27.9	6481	28.6	236	43.4
Micronutrients	13,509	21.3	7859	19.5	5452	24.0	198	36.4
Pharmacokinetic interactions	19,086	30.1	11,420	28.4	7164	31.6	502	92.3
Major	18,679	29.4	11,016	27.4	7162	31.6	501	92.1
Contraindicated	821	1.3	794	2.0	3	0.0	24	4.4

was 12.4 per 1000 people with drug dispensing. Potential drug interactions predominated in the antiseizure medications (n = 7576/19,086; 39.7%) group, followed by the antifungal (n = 6006; 31.5%), antihypertensive (n = 2930; 15.4%), antiarrhythmic (n = 1913; 10.0%) and macrolide (n = 740; 3.9%) groups. Potential major interactions were identified in 18,679 patients (29.4% of all patients; prevalence 12.2 per 1000 people) and contraindicated in 821 patients (1.3%; prevalence 0.5 per 1000 people). Among the most common potential major interactions, the association of fluconazole with metronidazole or atorvastatin was found, while the most common contraindicated interaction was the combination of fluconazole with trazodone or with ketoconazole (Table 3). A total of 34.9% (n = 5208/14,944) of the patients who were prescribed fluconazole had some potential pharmacological interaction. Table 2 shows the proportion of potential interactions by type of inhibitory or inducing action of the drug.

3.1 Multivariable Analysis

The binary logistic regression found that male patients, those under 65 years of age, or those with neurological, psychiatric or rheumatological pathologies had a higher probability of potential contraindicated or major pharmacological interactions. Similarly, patients who were prescribed cytochrome P450 inhibitors, statins, analgesics or antiparasitics and an increase in the number of medications (24.2% higher risk for each, from two drugs) were risk factors for a potential contraindicated or major pharmacological interaction. No variable reduced this risk (Table 4).

4 Discussion

This analysis revealed potential contraindicated and major pharmacological interactions in patients treated with inhibitors and inducers of metabolism. The findings were based on real-world evidence from a group of patients affiliated with an insurer of the Colombian Health System. These findings can be useful for health care, academic and scientific personnel in making decisions regarding the risks among patients and can contribute to strengthening the practices of rational use of medications among physicians as a way to reduce adverse drug reactions in the country and improve drug safety [14].

The median age of the patients was similar to that found in other studies on drug interactions (57.3–58.5 years) [15, 16], but differs from other reports in which the average age was higher (69.0–83.0 years). However, other studies had only an older adult population in their inclusion criteria [17–21]. On the other hand, a predominance of women was found, as identified in all the referenced studies (54.0–67.6%) [15, 17–20, 22]. Similarly, cardiovascular comorbidities were common, consistent with the findings of other studies [15, 18, 19, 21].

Almost one-third of the patients presented some potential drug interaction that was contraindicated or greater. However, it was not possible to make a reliable comparison with other studies because there were no studies that used a methodology similar to that used in our analysis. In has been found that potential drug interactions can range between 10.8% and 96.0% [15–19, 21, 23, 24]. Due to the heterogeneity present in the inclusion criteria, the results may vary based on age, the number of medications prescribed, the presence or absence of comorbidities, whether it is an outpatient or hospital prescription [15, 17, 18, 21, 23, 24] and the type of database used to identify and categorize pharmacological interactions [25, 26]. However, comparing our findings with previous reports of potential drug interactions that are contraindicated (X) or greater (D) in patients with outpatient prescriptions, the findings reveal that patients with inducers or inhibitors of cytochrome P450 have a higher proportion of interactions (30.1% vs 7.9–15.4%, respectively) [14–16, 23, 27], which could lead to an increased risk of adverse drug reactions or therapeutic failures [28].

Antiseizure medications and antifungals were the most commonly used inducers and inhibitors, respectively, with the presence of potential interactions in approximately one-third of them, which is in line with other reports [29–32]. In the USA, Faught et al. examined patients with epilepsy and found that in 39.0% of cases, antiseizure medications affected the efficacy of other medications, and in 29.3% of cases, comedications affected the efficacy of the antiseizure medications [29]. Similarly, in Poland, Bosak et al., also studied patients with epilepsy and found that 30.1% of them had potential pharmacological interactions [30]. On the other hand, in the USA, Andes et al. identified that 87.6% of hospitalized patients who had received triazoles (itraconazole, voriconazole or posaconazole) had contraindicated, major or moderate drug interactions [31]. In the United Kingdom, Niazi-Ali et al. examined patients who received antifungals (including triazoles) and found interactions occurred in 15.9% of them [32].

It was found that the most common drug–drug interactions were the association of fluconazole with metronidazole or with atorvastatin, in contrast with other studies in which the interaction between ciprofloxacin and metronidazole predominated [23], followed by carbamazepine with acetaminophen [20], verapamil with atorvastatin [14], pioglitazone with glimepiride [16] and methotrexate with nonsteroidal anti-inflammatory drugs [24]. This is probably due to the different clinical conditions in which the studies

Table 2 Prescription pattern of drugs with cytochrome P450-inducing and -inhibitory properties and the proportion of relevant pharmacological interactions in Colombia

Drugs	Patients with inhibitors or inducers	%[a]	%[b]	Prevalence[c]	Patients with interactions	%[d]	Prevalence[c]
Cytochrome P450 inhibitors	40,744	64.4	100.0	26.5	12,225	30.0	8.0
Verapamil[m]	15,542	24.5	38.1	10.1	1774	11.4	1.2
Fluconazol[m]	14,944	23.6	36.7	9.7	5208	34.9	3.4
Amiodarone[m]	3246	5.1	8.0	2.1	1880	57.9	1.2
Ketoconazole[s]	2586	4.1	6.3	1.7	893	34.5	0.6
Diltiazem[m]	1855	2.9	4.6	1.2	1162	62.6	0.8
Clarithromycin[s]	1274	2.0	3.1	0.8	698	54.8	0.5
Ciclosporin[m]	640	1.0	1.6	0.4	356	55.6	0.2
Darunavir[s]	231	0.4	0.6	0.2	44	19.0	<0.1
Erythromycina[m]	144	0.2	0.4	0.1	42	29.2	<0.1
Cobicistat[s] (associated[1])	125	0.2	0.3	0.1	25	20.0	<0.1
Imatinib[m]	99	0.2	0.2	0.1	13	13.1	<0.1
Itraconazole[s]	90	0.1	0.2	0.1	22	24.4	<0.1
Nilotinib[m]	68	0.1	0.2	<0.1	14	20.6	<0.1
Dronedarona[m]	48	0.1	0.1	<0.1	33	68.8	<0.1
Darunavir/ritonavir[s]	46	0.1	0.1	<0.1	5	10.9	<0.1
Ribociclib[m]	42	0.1	0.1	<0.1	1	2.4	<0.1
Darunavir/cobicistat[s]	26	0.0	0.1	<0.1	12	46.2	<0.1
Voriconazole[s]	18	0.0	0.0	<0.1	13	72.2	<0.1
Posaconazole[s]	16	0.0	0.0	<0.1	7	43.8	<0.1
Ritonavir[s]	12	0.0	0.0	<0.1	6	50.0	<0.1
Atazanavir/ritonavir[s]	11	0.0	0.0	<0.1	11	100.0	<0.1
Lopinavir/ritonavir[s]	6	0.0	0.0	<0.1	3	50.0	<0.1
Aprepitant[m]	5	0.0	0.0	<0.1	0	0.0	<0.1
Atazanavir[s]	3	0.0	0.0	<0.1	1	33.3	<0.1
Crizotinib[m]	2	0.0	0.0	<0.1	2	100.0	<0.1
Isavuconazol[m]	2	0.0	0.0	<0.1	0	0.0	<0.1
Cytochrome P450 inducers	23,233	36.6	100.0	15.1	7872	33.9	5.1
Carbamazepine[s]	18,874	29.8	81.2	12.3	6668	35.3	4.3
Phenytoin[s]	2634	4.2	11.3	1.7	759	28.8	0.5
Phenobarbital[s]	1667	2.6	7.2	1.1	348	20.9	0.2
Bosentan[m]	142	0.2	0.6	0.1	26	18.3	<0.1
Enzalutamide[s]	102	0.2	0.4	0.1	23	22.5	<0.1
Rifampicin[s] (alone or associated)	49	0.1	0.2	<0.1	16	32.7	<0.1
Apalutamide[s]	48	0.1	0.2	<0.1	4	8.3	<0.1
Etravirina[m]	42	0.1	0.2	<0.1	14	33.3	<0.1
Modafinil[m]	25	0.0	0.1	<0.1	1	4.0	<0.1
Primidone[s]	18	0.0	0.1	<0.1	4	22.2	<0.1
Efavirenz[m] (alone or associated[2])	31	0.0	0.1	<0.1	9	29.0	<0.1
Dabrafenib[m]	7	0.0	0.0	<0.1	0	0.0	<0.1
Mitotan[s]	2	0.0	0.0	<0.1	0	0.0	<0.1
Lumacaftor/ivacaftor[s]	1	0.0	0.0	<0.1	0	0.0	<0.1

[s]Strong; [m]Moderate; [1]Tenofovir/emtricitabine/elvitegravir; [2]Tenofovir/emtricitabine or lamivudine

[a]Percentage of patients with inhibitors or inducers calculated on total number of people ($n = 63,433$)

[b]Percentage of patients with inhibitors or inducers calculated on all inhibitors ($n = 40,744$) or inducers ($n = 23,233$)

[c]Prevalence per 1000 people with medication dispensing

[d]Percentage of patients with interactions calculated on the totality of each inhibitor or inducer

Table 3 Most frequent relevant pharmacological interactions in patients who received inducers and/or inhibitors of cytochrome P450 in Colombia

Interactions	*n*	%[a]	Prevalence[b]
Major	18,679	100.0	12.2
Fluconazole—Metronidazole	1661	8.9	1.1
Fluconazole—Atorvastatin	1467	7.9	1.0
Amiodarone—Carvedilol	1146	6.1	0.7
Diltiazem—Atorvastatin	808	4.3	0.5
Carbamazepine—Sertraline	735	3.9	0.5
Carbamazepine—Tramadol	701	3.8	0.5
Carbamazepine—Quetiapine	683	3.7	0.4
Carbamazepine—Trazodone	649	3.5	0.4
Carbamazepine—Codeine	603	3.2	0.4
Carbamazepine—Fluoxetine	490	2.6	0.3
Carbamazepine—Clonazepam	489	2.6	0.3
Carbamazepine—Nimodipine	458	2.5	0.3
Carbamazepine—Linagliptin	448	2.4	0.3
Fluconazole—Ciprofloxacin	435	2.3	0.3
Carbamazepine—Dexamethasone	420	2.2	0.3
Contraindicated	821	100.0	0.5
Fluconazole—Trazodone	167	20.3	0.1
Fluconazole—Ketoconazole	135	16.4	0.1
Fluconazole—Quetiapine	123	15.0	0.1
Verapamil—Colchicine	76	9.3	<0.1
Clarithromycin—Colchicine	35	4.3	<0.1
Ketoconazole—Ergotamine	33	4.0	<0.1
Amiodarone—Colchicine	29	3.5	<0.1
Ketoconazole—Nimodipine	26	3.2	<0.1
Fluconazole—Domperidone	21	2.6	<0.1
Clarithromycin—Fluconazole	15	1.8	<0.1
Fluconazole—Clozapine	15	1.8	<0.1
Ketoconazole—Trazodone	13	1.6	<0.1
Diltiazem—Colchicine	10	1.2	<0.1
Fluconazole—Mirtazapine	9	1.1	<0.1
Ketoconazole—Colchicine	9	1.1	<0.1

[a]Percentage calculated on the number of patients with major or contraindicated interactions

[b]Prevalence per 1000 people with medication dispensing

were developed, the inclusion criteria that were used, and the availability of the drugs in each country [14, 16, 20, 23, 24]. The simultaneous use of fluconazole with metronidazole can increase the risk of QT interval prolongation and generate arrhythmias, while the simultaneous prescription of fluconazole and atorvastatin can lead to an increase in the risk of myopathy and rhabdomyolysis when these interactions occur. Patients may require some medical intervention to minimize or avoid serious adverse effects or even death [11].

Different variables related to increasing the risk of potential drug interactions were found. In this analysis, it was found that men had a higher risk, consistent with what was previously found in Colombia [14] and in China [16], which contrasts with other publications in which there were no significant differences between the sexes [17, 22, 29]. Several studies have found that the risk of interactions increases with increasing age [14, 16–18, 22]. However, in this report, it was found that those under 65 years of age were at higher risk. This is probably because many of the inhibitors or inducers of cytochrome P450 are widely used in adolescence or adulthood and can even be considered potentially inappropriate prescriptions in elderly individuals, as is the case for some calcium channel blockers, antiarrhythmics, barbiturates and antiseizure medications [33]. On the other hand, it has been described that various cardiovascular diseases [18, 21], endocrine diseases [14, 21] and psychiatric diseases [22, 27] increase the risk of interactions, which is consistent with some results found in this report. Similarly, the increase in the number of medications increased the probability of drug–drug interactions, which is consistent with other studies [16–18, 21, 22, 27]. Among the most involved therapeutic groups were statins, analgesics and antiparasitics, due to their wide use [14, 34, 35] and their hepatic metabolism [36].

Some limitations are recognized in the interpretation of certain results. There was no access to medical records to identify the true adherence of patients who were receiving these medications. Additionally, some drugs could be acquired outside the health system (that is, medicines paid for with their own money and not acquired through the contributory/subsidized regime), but the proportion of patients who do so is very low, and herbal substances are not reported in the drug dispensing database on which the study was based. Additionally, only the potential risk of producing an adverse reaction or a reduction in efficacy as a result of a risk interaction could be considered. Finally, one of the main limitations of cross-sectional studies is that they do not allow a clear time sequence to be determined between the dependent variable and the independent variables (covariates). This is because the measurement of both types of variables is done simultaneously. However, they provide preliminary evidence on associations between variables. Among the strengths of the study is the large number of patients and their extensive distribution throughout the country. The database covers the dispensations of all the users made by the different ambulatory medical institutions. It is necessary to conduct other studies aimed at the early identification of adverse reactions, as well as to evaluate strategies that avoid risky pharmacological interactions, thus preventing unwanted outcomes in patients.

Table 4 Binary logistic regression on the variables related to the presence of contraindicated or major pharmacological interactions among users of inhibitors and inducers of cytochrome P450 in Colombia

Variables	cOR	95% CI		*p*-Value	aOR	95% CI		*p*-Value
		Lower	Upper			Lower	Upper	
Male (yes/no)	1.016	0.981	1.052	0.385	1.148	1.104	1.194	<0.001
Age ≥65 years	1.023	0.988	1.058	0.200	Ref.	Ref.	Ref.	
Age 18–39 years	0.830	0.795	0.866	<0.001	1.778	1.670	1.894	<0.001
Age 40–64 years	1.107	1.069	1.146	<0.001	1.643	1.569	1.720	<0.001
Bogotá-Cundinamarca region (yes/no)	0.864	0.827	0.903	<0.001	0.999	0.952	1.049	0.964
Cardiovascular disorders (yes/no)	1.312	1.268	1.358	<0.001	0.975	0.932	1.020	0.269
Neurological disorders (yes/no)	1.181	1.131	1.233	<0.001	1.283	1.215	1.354	<0.001
Rheumatologic disorders (yes/no)	2.066	1.945	2.195	<0.001	1.324	1.235	1.419	<0.001
Psychiatric disorders (yes/no)	4.028	3.777	4.296	<0.001	3.847	3.583	4.131	<0.001
Medication quantity (continued)	1.233	1.227	1.240	<0.001	1.242[a]	1.234	1.251	<0.001
Cytochrome inhibitors (yes/no)	0.896	0.865	0.929	<0.001	1.079	1.033	1.128	0.001
Statins (co-medication) (yes/no)	1.641	1.585	1.699	<0.001	1.142	1.089	1.197	<0.001
Opioid and non-opioid analgesics (co-medication) (yes/no)	2.213	2.137	2.293	<0.001	1.331	1.277	1.388	<0.001
Antiparasitics (co-medication) (yes/no)	2.498	2.331	2.677	<0.001	2.883	2.667	3.117	<0.001

aOR adjusted odds ratio; *CI* confidence interval; *cOR* crude odds ratio; *Ref.* reference

[a]24.2% higher risk for each drug, from two drugs

5 Conclusions

This study identified potential risk interactions with other drugs in users of inhibitors and inducers of cytochrome P450, as well as their classification, in a population in Colombia. The results revealed that these interactions are more frequent in men, in patients younger than 65 years, in patients with comorbidities, and in patients with a greater number of medications, especially statins, analgesics and antiparasitics. The results of this study will allow us to review the treatment approaches of patients with a higher risk of interactions and thus use pharmacovigilance strategies to implement interventions to reduce the rate of such interactions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-024-00450-1.

Acknowledgments Soffy Claritza López for her work in creating the database.

Declarations

Funding The present study did not receive funding.

Conflict of Interest Jorge Enrique Machado-Alba is an Editorial Board member of Drugs—Real World Outcomes. Jorge Enrique Machado-Alba was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Luis Fernando Valladales-Restrepo, Juan Alberto Ospina-Cano and Brayan Stiven Aristizábal-Carmona declare no conflicts of interest.

Ethics Approval The protocol was endorsed by the Bioethics Committee of the Technological University of Pereira in the category of 'research without risk' (approval code: CBE.48-280621). The principles of confidentiality of information established by the Declaration of Helsinki were respected.

Consent to Participate Not applicable; this is a retrospective observational study.

Writing Assistance The manuscript was translated to English by American Journal Experts.

Availability of Data and Material (Name of Repository) Protocols.io. In the repository you will find the anonymized database of all the variables of the patients included in the study.

Code Availability https://doi.org/10.17504/protocols.io.bp2l61mrkvqe/v1.

Author Contributions LFVR: conceptualization, methodology, formal analysis, investigation, data curation and writing the original draft. JAOC: formal analysis, investigation, data curation. BSAC: formal analysis, investigation, data curation; JEMA: methodology, validation, formal analysis, resources, writing, review and editing and supervision. All authors read and approved the final version.

References

1. Gonzagade Andrade Santos TN, Mendonça da Cruz Macieira G, CardosoSodréAlves BM, et al. Prevalence of clinically manifested drug interactions in hospitalized patients: a systematic review and meta-analysis. PLoS ONE. 2020;15(7): e0235353. https://doi.org/10.1371/journal.pone.0235353.
2. Guengerich FP. A history of the roles of cytochrome P450 enzymes in the toxicity of drugs. Toxicol Res. 2020;37(1):1–23. https://doi.org/10.1007/s43188-020-00056-z.
3. Guengerich FP. Inhibition of cytochrome P450 enzymes by drugs-molecular basis and practical applications. Biomol Ther (Seoul). 2022;30(1):1–18. https://doi.org/10.4062/biomolther.2021.102.
4. Hakkola J, Hukkanen J, Turpeinen M, et al. Inhibition and induction of CYP enzymes in humans: an update. Arch Toxicol. 2020;94(11):3671–722. https://doi.org/10.1007/s00204-020-02936-7.
5. Kato H. Computational prediction of cytochrome P450 inhibition and induction. Drug Metab Pharmacokinet. 2020;35(1):30–44. https://doi.org/10.1016/j.dmpk.2019.11.006.
6. Pelkonen O, Hakkola J, Hukkanen J, et al. CYP-associated drug–drug interactions: a mission accomplished? Arch Toxicol. 2020;94(11):3931–4. https://doi.org/10.1007/s00204-020-02912-1.
7. US Food & Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. Available at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 1 November 2021.
8. Base de Datos Única de Afiliados (BDUA). Administradora de los Recursos del Sistema General de Seguridad Social en Salud. Ministerio de Salud y Protección Social. Available at https://www.adres.gov.co/eps/bdua/reportes. Accessed 3 April 2023.
9. Fármaco Online, Audifarma SA. Available at https://www.audifarma.com.co/farmaco-online/. Accessed 3 April 2023.
10. Franco JS, Vizcaya D. Availability of secondary healthcare data for conducting pharmacoepidemiology studies in Colombia: a systematic review. Pharmacol Res Perspect. 2020;8(5): e00661.
11. IBM Corporation. 2022. Drug interactions. In: Drug point summary [database on the Internet]. Greenwood Village (CO). Available on www.micromedexsolutions.com. Subscription required to view. Accessed 1 February 2022.
12. Masnoon N, Shakib S, Kalisch-Ellett L, et al. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230. https://doi.org/10.1186/s12877-017-0621-2.
13. Machado-Alba JE, Machado-Duque ME, Gaviria-Mendoza A. Extreme polypharmacy: the need to mint a new term. Pharmacoepidemiol Drug Saf. 2020;29(2):224–5. https://doi.org/10.1002/pds.4942.
14. Valladales-Restrepo LF, Medina-Morales DA, Giraldo-Giraldo C, et al. Prescription of statins and pharmacokinetic interactions in Colombian patients. Expert Opin Drug Metab Toxicol. 2021;17(5):627–34. https://doi.org/10.1080/17425255.2021.1908261.
15. Nusair MB, Al-Azzam SI, Arabyat RM, et al. The prevalence and severity of potential drug–drug interactions among adult polypharmacy patients at outpatient clinics in Jordan. Saudi Pharm J. 2020;28(2):155–60. https://doi.org/10.1016/j.jsps.2019.11.009.
16. Ren W, Liu Y, Zhang J, et al. Prevalence of potential drug–drug interactions in outpatients of a general hospital in China: a retrospective investigation. Int J Clin Pharm. 2020;42(4):1190–6. https://doi.org/10.1007/s11096-020-01068-3.
17. Doan J, Zakrzewski-Jakubiak H, Roy J, et al. Prevalence and risk of potential cytochrome P450-mediated drug–drug interactions in older hospitalized patients with polypharmacy. Ann Pharmacother. 2013;47(3):324–32. https://doi.org/10.1345/aph.1R621.
18. Doubova Dubova SV, Reyes-Morales H, Torres-Arreola Ldel P, et al. Potential drug-drug and drug-disease interactions in prescriptions for ambulatory patients over 50 years of age in family medicine clinics in Mexico City. BMC Health Serv Res. 2007;7:147. https://doi.org/10.1186/1472-6963-7-147.
19. Hermann M, Carstens N, Kvinge L, et al. Polypharmacy and potential drug–drug interactions in home-dwelling older people—a cross-sectional study. J Multidiscip Healthc. 2021;14:589–97. https://doi.org/10.2147/JMDH.S297423.
20. Bojuwoye AO, Suleman F, Perumal-Pillay VA. Polypharmacy and the occurrence of potential drug–drug interactions among geriatric patients at the outpatient pharmacy department of a regional hospital in Durban, South Africa. J Pharm Policy Pract. 2022;15(1):1. https://doi.org/10.1186/s40545-021-00401-z.
21. Secoli SR, Figueras A, Lebrão ML, et al. Risk of potential drug–drug interactions among Brazilian elderly: a population-based, cross-sectional study. Drugs Aging. 2010;27(9):759–70. https://doi.org/10.2165/11538460-000000000-00000.
22. Hughes JE, Russo V, Walsh C, et al. Prevalence and factors associated with potential drug–drug interactions in older community-dwelling adults: a prospective cohort study. Drugs Aging. 2021;38(11):1025–37. https://doi.org/10.1007/s40266-021-00898-8.
23. Ismail M, Noor S, Harram U, et al. Potential drug-drug interactions in outpatient department of a tertiary care hospital in Pakistan: a cross-sectional study. BMC Health Serv Res. 2018;18(1):762. https://doi.org/10.1186/s12913-018-3579-7.
24. Toivo TM, Mikkola JA, Laine K, et al. Identifying high risk medications causing potential drug–drug interactions in outpatients: a prescription database study based on an online surveillance system. Res Social Adm Pharm. 2016;12(4):559–68. https://doi.org/10.1016/j.sapharm.2015.09.004.
25. Sancar M, Kaşik A, Okuyan B, et al. Determination of potential drug–drug interactions using various software programs in a community pharmacy setting. Turk J Pharm Sci. 2019;16(1):14–9. https://doi.org/10.4274/tjps.30932.
26. Kheshti R, Aalipour M, Namazi S. A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. J Res Pharm Pract. 2016;5(4):257–63. https://doi.org/10.4103/2279-042X.192461.
27. Rogero-Blanco E, Del-Cura-González I, Aza-Pascual-Salcedo M, et al. Group MULTIPAP. Drug interactions detected by a computer-assisted prescription system in primary care patients in Spain: MULTIPAP study. Eur J Gen Pract. 2021;27(1):90–6. https://doi.org/10.1080/13814788.2021.1917543.
28. Dechanont S, Maphanta S, Butthum B, et al. Hospital admissions/visits associated with drug–drug interactions: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2014;23(5):489–97. https://doi.org/10.1002/pds.3592.
29. Faught E, Szaflarski JP, Richman J, et al. Risk of pharmacokinetic interactions between antiepileptic and other drugs in older persons and factors associated with risk. Epilepsia. 2018;59(3):715–23. https://doi.org/10.1111/epi.14010.
30. Bosak M, Słowik A, Iwańska A, et al. Co-medication and potential drug interactions among patients with epilepsy. Seizure. 2019;66:47–52. https://doi.org/10.1016/j.seizure.2019.01.014.
31. Andes D, Azie N, Yang H, et al. Drug–drug interaction associated with mold-active triazoles among hospitalized patients.

Antimicrob Agents Chemother. 2016;60(6):3398–406. https://doi.org/10.1128/AAC.00054-16.
32. Niazi-Ali S, Atherton GT, Walczak M, et al. Drug–drug interaction database for safe prescribing of systemic antifungal agents. Ther Adv Infect Dis. 2021;8:20499361211010604. https://doi.org/10.1177/20499361211010605.
33. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674–94. https://doi.org/10.1111/jgs.15767.
34. Lindrose AR, Fraser JA, Hickey PW, et al. Costs and prescribing patterns of anthelmintics in the United States military: a retrospective analysis. Open Forum Infect Dis. 2022;9(3):ofac040. https://doi.org/10.1093/ofid/ofac040.
35. Schieber LZ, Guy GP Jr, Seth P, et al. Trends and patterns of geographic variation in opioid prescribing practices by state, United States, 2006–2017. JAMA Netw Open. 2019;2(3): e190665. https://doi.org/10.1001/jamanetworkopen.2019.0665.
36. Almazroo OA, Miah MK, Venkataramanan R. Drug metabolism in the liver. Clin Liver Dis. 2017;21(1):1–20. https://doi.org/10.1016/j.cld.2016.08.001.