DOI: 10.1002/pul2.12114

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Prevalence of potential drug–drug interactions with disease-specific treatments in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension: A registry study

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Funding information
None

Abstract

Polypharmacy increases the risk of drug–drug interactions that may disturb treatment effects. The aim of this study was to investigate the frequency of codispensing of potentially interacting or contraindicated drugs related to PH-specific treatment in the Swedish pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) population. All prescribed drugs, on an individual level, dispensed 2016–2017 at pharmacies to patients with PAH or CTEPH were obtained from The National Board of Health and Welfare's pharmaceutical registry. Potential drug–drug interactions were investigated using the Drug Interaction tool in the IBM Micromedex® database. There were 4785 different dispensed drugs from 572 patients (mean age 61 ± 16 years, 61% female, mean number of drugs per patient 8.4 ± 4.2) resulting in 1842 different drug combinations involving a PH-specific treatment. Of these drug combinations, 67 (3.5%) had a potential drug–drug interaction considered clinically relevant and it affected 232 patients (41%). The PH-specific drugs with the highest number of potential drug–drug interactions was bosentan ($n = 23$, affected patients = 171) while the most commonly codispensed, potentially interacting drug combination was sildenafil/furosemide (119 patients affected). Other common codispensed and potentially interacting drugs were anticoagulants ($n = 11$, affected patients = 100) and antibiotic treatment ($n = 12$, affected patients = 26). In conclusion, codispensing of PH-specific therapy and potentially interacting drugs was common, but codispensing of potentially contraindicated drugs was rare.

KEYWORDS
clinical relevance, lexicomp, micromedex, patient safety, polypharmacy

INTRODUCTION

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are rare and serious cardiopulmonary diseases that frequently require lifelong pharmacological treatment.[1] Disease-specific treatment includes endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE-5i), soluble guanylate cyclase stimulators (SGCs) as well as selective prostacyclin receptor agonists and prostacyclin analogs. Combination therapy is recommended to improve quality of life and outcome but monotherapy is not uncommon.[2–5]

An improved survival and an older population being diagnosed have increased the presence of comorbidities and thus, polypharmacy is common in this population.[6–10] Further, side effects from pulmonary hypertension (PH)-specific drugs such as headache, nausea, diarrhea, or constipation often require additional medical treatment.

With polypharmacy, the potential of a drug–drug interaction causing adverse effects on treatment outcomes increases.[9] Drug–drug interactions can be caused by pharmacokinetic (PK) changes such as altered drug metabolism, or by pharmacodynamic (PD) changes such as additive effects. Combination of drugs that use the same metabolizing enzymes, for example, cytochrome P450, may cause reduced or enhanced systemic drug concentrations.[11,12] To avoid unwanted treatment effects, identification and understanding the risk of potential drug–drug interactions are important. The primary aim of this study was to investigate the frequency of codispensing of potentially interacting combinations of drugs or contraindicated drugs related to PH-specific drugs in the Swedish PAH and CTEPH population. A secondary aim was to increase the awareness outside the PH specialist clinics of potential drug–drug interactions related to PH-specific drugs.

METHODS

Study population

In Sweden, individual-level data for all residents can be linked across national databases. The current study was a retrospective observational study including all drug prescriptions registered by the Swedish prescribed drug registry and dispensed by patients with PAH or CTEPH, aged ≥18 years, alive January 2016 through December 2017 and registered in the Swedish PAH & CTEPH registry (SPAHR[13]).

The National Board of Health and Welfare's (Socialstyrelsen) pharmaceutical registry (Swedish Prescribed Drug Registry[14]) covers all medicines that have been dispensed at pharmacies in Sweden on an individual level.

SPAHR[13] constitutes an open continuous registry of patients diagnosed with PAH or CTEPH. All Swedish PAH/CTEPH-expert centers participate in SPAHR and the national coverage of patients diagnosed with PAH or CTEPH in the registry is >90%. SPAHR is approved by the National Board of Health and Welfare and by the Swedish Data Protection Authority. All patients were informed about their participation in SPAHR and had the right to decline.

The study was approved by the Regional Ethics Committee in Lund, Sweden (LU 2016/766), and performed in accordance with the Declaration of Helsinki.

Drug interactions

The Swedish Prescribed Drug Registry use the anatomical therapeutic chemical (ATC) classification system. The drug interaction tool in the IBM Micromedex® database[15] was used to search for known interacting combinations of drugs or contraindicated drug combinations. If drugs could not be found in the Micromedex® database, the Lexicomp® Interactions database was used.[16] Seven drugs were not found in either database. Using the Swedish interaction database Janusmed Interaktioner,[17] these seven drugs were determined not to have any recorded drug–drug interaction in combinations found in the present study. The classifications of drug–drug interactions from Micromedex® and Lexicomp® Interactions can be found in Table 1. Micromedex® classifications moderate, major, and contraindicated correspond to Lexicomp® classifications C, D, and X, respectively. Interactions were considered clinically relevant if moderate to severe in Micromedex® (C in Lexicomp®). Drugs that did not have a systemic uptake were excluded from the study. The reliability and quality of documentation that formed basis on the potential drug–drug interactions that was found ranged between fair, good, and excellent.[15,16]

PH-specific treatment

All PH-specific treatments approved in Sweden at the time of the study were included in the analyses[18] and are listed here by ATC code and generic name in parenthesis; B01AC09 (epoprostenol), B01AC11 (iloprost), B01AC21 (treprostinil), B01AC27 (selexipag), C02KX01

TABLE 1 Classification of drug–drug interactions in Micromedex® and Lexicomp® interaction tools

Micromedex® drug interactions		
Unknown		Unknown (none found)
Minor		Limited clinical effects, where interactions may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy
Moderate		Interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy
Major		Interaction could prove life-threatening and/or require medical intervention to minimize or prevent serious adverse effects
Contraindicated		Drugs contraindicated for concurrent use
Lexicomp® interactions		
A	*No known interaction*	No demonstrated pharmacodynamic or pharmacokinetic interactions
B	*No action needed*	Potential interaction, with little to no evidence of clinical concern from concomitant use
C	*Monitor therapy*	Potential interaction in a clinically significant manner. Benefits of concomitant use usually outweigh risks. Appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments may be needed in minority of patients
D	*Consider therapy modification*	Potential interaction in a clinically significant manner. Patient-specific assessment must be conducted to determine if benefits of concomitant therapy outweigh the risks. Actions (e.g., aggressive monitoring, empiric dosage changes, or choosing alternative agents) must be taken to realize the benefits and/or minimize the toxicity resulting from concomitant use
X	*Avoid combination*	Potential interaction in a clinically significant manner. Risks associated with concomitant use usually outweigh benefits. Generally considered contraindicated

Note: Micromedex® classifications moderate, major and contraindicated correspond to Lexicomp® classifications C, D, and X, respectively.

(bosentan), C02KX02 (ambrisentan), C02KX04 (macitentan), C02KX05 (riociguat), G04BE03 (sildenafil), and G04BE08 (tadalafil).

Statistical analyses and data management

Lists of drug combinations were exported from the SAS statistical software to Microsoft Excel® (Microsoft 365) and potential drug–drug interactions were analyzed with using the drug interaction tools described earlier. Descriptive statistics were used to characterize the data. The SAS statistical software (The SAS system for Windows 9.4. SAS Institute Inc.) was used for all analyses.

RESULTS

Study population

There were 4785 different drugs with filled prescriptions from 572 patients included in the analyses. Of those, 433 patients were treated with a PH-specific treatment. The average number of drugs per patient was 8.4 ± 4.2, including PH-specific treatment (Table 2). Mean age of the study cohort was 61 ± 16 years and 61% were female (Table 2). A prescription of ERA was filled by 61% of the patients, PDE-5i by 60%, SGCs by 6%, and PRO by 12% (Table 3). The most common combinations of PH-specific treatments were macitentan/sildenafil (17%) and macitentan/tadalafil (14%). There were no potential drug–drug interactions related to these drug combinations.

The study population was evenly distributed between patients <65 years (50%) and ≥65 years (50%). ERA and PRO were prescribed more often to patients <65 years (ERA 65% vs. 58% and PRO 16% vs. 9%) while PDE-5i and SGCs were more often prescribed to patients ≥65 years (PDE-5i 57% vs. 64% and SGCs 4% vs. 8%).

Drug–drug interactions

There were 1842 different drug combinations involving a PH-specific treatment. Of those drug combinations, 67 (3.5%) had a potential drug–drug interaction affecting 232 patients (41%), whereof 25 combinations were classified as moderate (183 patients), 41 combinations as major (97 patients), and one combination as contraindicated (2 patients) (Table 2). The codispensed contraindicated drug combination was tadalafil/isosorbide

TABLE 2 Study population characteristics ($n = 572$), drug combinations including a PH-specific drug and their drug–drug interaction severity

Age (years)	61 ± 16
Sex (% women)	61
Time since diagnosis (years)	5.3 ± 4.7
Drugs per patient (polypharmacy, *n*)	8.4 ± 4.2
Drug combinations including PH-specific drugs (*n*)	1842
Potential drug–drug interactions (*n*)	65
Moderate (*n*)	23
Major (*n*)	41
Contraindicated (*n*)	1
Patients that codispensing potentially interacting drugs or contraindicated drugs (*n*)	232
Moderate (*n*)	183
Major (*n*)	97
Contraindicated (*n*)	2
Patients with no potential drug–drug interaction (*n*)	201
Patients with 1 potential drug–drug interaction (*n*)	132
Patients with 2 potential drug–drug interaction (*n*)	51
Patients with 3 potential drug–drug interaction (*n*)	32
Patients with ≥4 potential drug–drug interaction (*n*)	17

Note: Data are shown as mean ± SD, as number, or as proportion (%).
PH indicates pulmonary hypertension.

dinitrate that may lead to hypotension. Details of all codispensed, potentially interacting drugs or contraindicated drugs found in the present study are displayed in Table 3. No potential interactions were found for epoprostenol.

The PH-specific drugs with the highest number of potential drug–drug interactions were bosentan ($n = 23$ interactions, affecting 171 patients) and sildenafil ($n = 10$ interactions, affecting 144 patients). Combination treatment between bosentan and sildenafil or bosentan and tadalafil that can lead to increased plasma levels of the PDE5-5i was seen in 35 and 19 patients, respectively (Table 3).

The most commonly codispensed, potentially interacting drug combination was sildenafil/furosemide (119 patients), which may lead to hearing loss (Table 3). Other common codispensed and potentially interacting drugs were anticoagulants ($n = 11$ interactions, affecting 100 patients) and antidepressant treatments ($n = 7$ interactions, affecting nine patients) that might increase the risk of bleeding, and to antibiotic treatment ($n = 12$ interactions, affecting 26 patients) that might increase the bioavailability of PH-specific drugs (Table 4).

Patients <65 years had more different drug combinations involving a PH-specific treatment than patients ≥65 years (1318 vs. 1281). Potential drug–drug interactions affected 125 patients (44%) <65 years and 157 patients (55%) ≥65 years. This difference between the age groups related to a higher proportion of drug combinations classified as moderate among patients ≥65 years.

DISCUSSION

Forty-one percent of the patients treated with a PH-specific treatment were simultaneously codispensed potentially interacting drugs or contraindicated drugs. The most common potential interaction was between sildenafil and furosemide, whereas bosentan had the highest total number of related potential interactions and affected the largest number of patients. Anticoagulants, antibiotics, and antidepressants were commonly dispensed in combination with a PH-specific treatment and presented with major potential drug–drug interactions.

Potential drug–drug interactions between PH-specific treatment and other concomitant drug treatments are common. It has been reported to affect 67% in a PAH and CTEPH population, whereof 16% of potential drug–drug interactions were considered contraindicated.[19] The prevalence of potentially interacting or contraindicated drugs among codispensed drugs in the present study was low, only one contraindicated potential drug–drug interaction was dispensed, and it affected only two patients. The declining use of bosentan in Sweden during the studied time period is likely a contributing factor to this. Another contributing factor might be the direct communication link that exists between the Swedish medical records systems and the Janus Interactions database.[17] This provides an easy access, one-click-tool that allow the prescriber to consider the presence of drug–drug interaction already at the time of writing the prescription. In addition, using the tool will likely increase the familiarity with common drug–drug interactions that can then be avoided in upcoming prescriptions.

A third of the study population in the present study was treated with sildenafil and two-thirds with diuretics, rendering the single most common potential drug–drug interaction to be between sildenafil and furosemide. The hypotensive effect of this drug combination is well known and careful monitoring of patients will likely be sufficient.[9,12] A less known effect is ototoxicity that can cause hearing loss.[20] The mechanism behind this may be further enhanced as an additive effect, as hearing loss can be induced temporarily by diuretics[21] and as a sensorineural effect induced by sildenafil.[22] The

TABLE 3 Potential drug–drug interactions in shown by PH-specific drugs

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
Ambrisentan ($n = 95$) (C02KX02)	Hepatic metabolism by uridine 5′-diphosphate glucuronosyltransferases (UGTs) UGT1A9S, -2B7S, -1A3S), and by CYP450 enzymes CYP3A4, -3A5, and -2C19	Ciclosporin	L04AD01	1	Moderate	Inhibition of ambrisentan metabolism by cyclosporine, a strong CYP3A4 inhibitor	↑ Ambrisentan exposure
Bosentan ($n = 87$) (C02KX01)	Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19	Oxycodone	N02AA05	13	Major	Bosentan induces CYP3A4 which reduces oxycodone exposure	↓ Oxycodone exposure
		Tramadol	N02AX02	7	Major	Bosentan induces CYP3A4 which reduces tramadol exposure	↓ Tramadol exposure
		Paracetamol + codeine	N02AJ06	5	Major	Bosentan induces CYP3A4 which reduces codeine efficacy and may increase withdrawal	↓ Opioid efficacy, risk opioid withdrawal
		Medroxyprogest acetate	G03DA02	3	Major	Bosentan induces CYP3A4 which reduces medroxyprogest. acetate exposure	↓ Medroxyprogesterone concentrations
		Estradiol	G03CA03	3	Major	Bosentan induces CYP3A4 which reduces estradiol plasma levels	↓ Hormonal contraceptive plasma levels
		Buprenorphine	N02AE01	2	Major	Bosentan induces CYP3A4 which reduces buprenorphine exposure	↓ Buprenorphine plasma levels
		Medroxyprogest acetate	G03AC06	1	Major	Bosentan induces CYP3A4 which reduces medroxyprogest. acetate exposure	↓Medroxyprogesterone concentrations

(Continues)

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Desogestrel	G03AC09	1	Major	Bosentan induces CYP3A4 which reduces desogestrel plasma levels	↓ Hormonal contraceptive plasma levels
		Estrogen + norethindrone	G03FB05	1	Major	Bosentan induces CYP3A4 which reduces norethindrone plasma levels	↓ Hormonal contraceptive plasma levels
		Codeine	N05DA04	1	Major	Bosentan induces CYP3A4 which reduces codeine efficacy and may increase withdrawal	↓ Opioid efficacy, opioid withdrawal
		Aspirin + caffeine + codeine	N02AJ09	1	Major	Bosentan induces CYP3A4 which reduces codeine efficacy and may increase withdrawal	↓ Opioid efficacy, opioid withdrawal
		Warfarin	B01AA03	55	Moderate	Bosentan induces CYP3A4 (and possibly 2C9) which reduces warfarin exposure	↓ Warfarin efficacy
		Sildenafil	G04BE03	35	Moderate	Sildenafil induces increased bosentan exposure due to CYP3A4 metabolism	↑ Bosentan, ↓ sildenafil plasma levels
		Tadalafil	G04BE08	19	Moderate	Bosentan induces CYP3A4 which reduces tadalafil exposure	↓ Tadalafil plasma levels
		Atorvastatin	C10AA05	7	Moderate	Bosentan induces CYP3A4 which reduces atorvastatin exposure	↓ Atorvastatin plasma levels and efficacy
		Simvastatin	C10AA01	7	Moderate	Bosentan induces CYP3A4 which reduces simvastatin exposure	↓ Simvastatin plasma levels and efficacy

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Diclofenac	M02AA15	3	Moderate	Bosentan induces CYP2C9 which reduces diclofenac exposure	↓ Diclofenac exposure
		Verapamil	C08DA01	2	Moderate	Inhibition of CYP3A4-mediated bosentan metabolism by verapamil	↑ Bosentan plasma levels
		Ebastin	R06AX22	1	Moderate	Bosentan induces CYP3A4 which reduces ebastin exposure (increased ebastin metabolism)	↓ Ebastin plasma levels
		Fluconazole	J02AC01	1	Moderate	Fluconazole is a CYP2C9 inhibitor which may reduce bosentan metabolism	↑ Bosentan plasma levels
		Diclofenac	M01AB05	1	Moderate	Bosentan induces CYP2C9-mediated diclofenac metabolism	↓ Diclofenac plasma levels
		Amiodarone	C01BD01	1	Moderate	Bosentan induces CYP3A4 which reduces amiodarone exposure; reduced CYP3A4- and CYP2C9-mediated bosentan metabolism	↓ Amiodarone and/or ↓ bosentan exposure
		Clarithromycin	J01FA09	1	Moderate	Clarithromycin is a CYP2C9 inhibitor which may reduce bosentan metabolism	↑ Bosentan plasma levels
Macitentan (n = 169) (C02KX04)	Hepatic metabolism by CYP3A4, -2C8, -2C9, -2C19	Fluconazole	J02AC01	2	Major	Fluconazole is a dual CYP3A4- and CYP2C9-inhibitor and may inhibit macitentan metabolism	↑ Macitentan plasma levels, toxicity

(Continues)

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Esomeprazole + amoxicillin + clarithromycin	A02BD06	2	Major	Clarithromycin is a strong CYP3A4 inhibitor and may inhibit macitentan metabolism	↑ Macitentan plasma levels
		Clarithromycin	J01FA09	1	Major	Clarithromycin is a strong CYP3A4 inhibitor and may inhibit macitentan metabolism	↑ Macitentan plasma levels
		Carbamazepine	N03AF01	1	Major	Carbamazepine is a strong CYP3A4 inducer and may increase macitentan metabolism	↑ Macitentan plasma levels
Iloprost (n = 14) (B01AC11)	β-oxidation	Warfarin	B01AA03	5	Major	Additive effects on hemostasis combining antiplatelet agents (iloprost) and warfarin	Bleeding
		Dalteparin	B01AB04	4	Major	Additive effects on hemostasis combining antiplatelet agents (iloprost) and low molecular weight heparin (dalteparin)	Bleeding
		Apixaban	B01AF02	2	Major	Additive effects on hemostasis combining antiplatelet agents (iloprost) and apixaban	Bleeding
		Sertraline	N06AB06	1	Major	Additive effects combining antiplatelet agents (iloprost) with sertraline	Bleeding
		Duloxetine	N06AX21	1	Major	Additive effects on hemostasis combining antiplatelet agents (iloprost) and duloxetine	Bleeding

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Tinzaparin	B01AB10	1	Major	Additive effects combining antiplatelet agents (iloprost) and low molecular weight heparin (tinzaparin)	Bleeding
		Diclofenac	M02AA15	1	Major	Additive effects on hemostasis combining antiplatelet agents (iloprost) with NSAID (diclofenac)	Bleeding
		Dipyridamole	B01AC07	1	Moderate	Additive antiplatelet effects	Bleeding
Riociguat (n = 32) (C02KX05)	Hepatic metabolism by CYP1A1, -3A4, -3A5, -2J2 and -2C8	Calcium carbonate	A12AX	4	Moderate	Decreased riociguat absorption due to calcium carbonate	↓ Riociguat exposure
		Sodium picosulfate	A06AB08	1	Moderate	Decreased riociguat absorption due to sodium picosulfate (prepopik)	↓ Riociguat exposure
		Magnesium hydroxide	G04BX01	1	Moderate	Decreased riociguat absorption due to magnesium hydroxide	↓ Riociguat exposure
Selexipag (n = 29) (B01AC27)	Hepatic metabolite activation by carboxylesterase 1 Hepatic metabolism by CYP3A4 and -2C8 Glucuronidation of metabolite by UGT1A3 and -2B7	Apixaban	B01AF02	4	Major	Additive effects combining antiplatelet agents (selexipag) with apixaban	Bleeding

(Continues)

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Sertraline	N06AB06	2	Major	Combining antiplatelet agents (selexipag) with SSRIs (sertraline) may alter platelet function and induce bleeding	Bleeding
		Citalopram	N06AB04	1	Major	Combining antiplatelet agents (selexipag) with SSRIs (citalopram) may alter platelet function and induce bleeding	Bleeding
		Paroxetine	N06AB05	1	Major	Additive effects combining antiplatelet agents (iloprost) with paroxetine	Bleeding
Sildenafil (n = 199) (G04BE03)	Hepatic metabolism primarily by CYP3A4, to lesser extent -2C9	Fluconazole	J02AC01	3	Major	CYP3A4- and CYP2C9-mediated sildenafil metabolism inhibition by fluconazole	↑ Sildenafil exposure, toxicity risk
		Esomeprazole + amoxicillin + clarithromycin	A02BD06	2	Major	CYP3A4-mediated sildenafil metabolism inhibition by clarithromycin	↑ Sildenafil exposure
		Clarithromycin	J01FA09	2	Major	CYP3A4-mediated sildenafil metabolism inhibition by clarithromycin	↑ Sildenafil exposure
		Itraconazole	J02AC02	1	Major	Itraconazole is a CYP3A4 inhibitor which may increase sildenafil exposure	↑ Sildenafil exposure
		Furosemide	C03CA01	119	Moderate	Additive ototoxicity, potentiation of antihypertensive activities of furosemide	Ototoxicity (hearing loss)

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Bosentan	G04BE03	35	Moderate	CYP3A4 metabolism alterations (increased bosentan and decreased sildenafil exposure)	↓ Sildenafil, ↑ bosentan, plasma levels
		Ciprofloxacin	J01MA02	9	Moderate	CYP3A-mediated sildenafil metabolism inhibition by ciprofloxacin	↑ Sildenafil exposure and plasma levels
		Alfuzosin	G04CA01	4	Moderate	Sildenafil inhibits PDE5-mediated degradation of cyclic guanosine monophosphate (cGMP) which could cause peripheral vasodilation that may be additive with alfuzosin effects	Potentiation hypotensive effects
		Erythromycin	J01FA01	3	Moderate	Erythromycin is a CYP3A4 inhibitor and may inhibit sildenafil metabolism	Sildenafil adverse effects ↑ ; hypotension, visual changes, priapism
		Ciprofloxacin	S02AA15	1	Moderate	Ciprofloxacin is a CYP3A4 inhibitor and may inhibit sildenafil metabolism	↑ Sildenafil exposure and plasma levels
Tadalafil (n = 146) (G04BE08)	Hepatic metabolism by CYP3A4	Isosorbide dinitrate	C01DA14	2	Contraindicated	increased levels of cGMP from tadalafil and nitrates	Potentiation hypotensive effects
		Simvastatin	C10AA01	21	Major	Unknown; may be due to CYP3A4	Myopathy
		Alfuzosin	G04CA01	1	Major	Additive hypotensive effects (vasodilation and lowered blood pressure)	Potentiation hypotensive effects

(Continues)

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Esomeprazole + amoxicillin + clarithromycin	A02BD06	1	Major	CYP3A4-mediated tadalafil metabolism inhibition by clarithromycin	↑ Tadalafil bioavailability
		Clarithromycin	J01FA09	1	Major	CYP3A4-mediated tadalafil metabolism inhibition by clarithromycin	↑ Tadalafil bioavailability
		Itraconazole	J02AC02	1	Major	CYP3A4-mediated tadalafil metabolism inhibition by itraconazole	↑ Tadalafil bioavailability
		Bosentan	G04BE08	19	Moderate	CYP3A4-mediated metabolism of tadalafil by bosentan	↓ Tadalafil plasma levels
Treprostinil (n = 27) (B01AC21)	Hepatic metabolism, primarily by CYP2C8	Warfarin	B01AA03	20	Major	Additive effects on hemostasis combining antiplatelet agents (treprostinil) with warfarin	Bleeding
		Dalteparin	B01AB04	6	Major	Additive effects combining antiplatelet agents (treprostinil) and low molecular weight heparin (dalteparin)	Bleeding
		Sertraline	N06AB06	2	Major	Combining antiplatelet agents (treprostinil) with SSRIs (sertraline) may alter platelet function and induce bleeding	Bleeding
		Citalopram	N06AB04	1	Major	Combining antiplatelet agents (treprostinil) with SSRIs (citalopram) may alter platelet function and induce bleeding	Bleeding

TABLE 3 (Continued)

PH-drug (n = patients at risk, i.e., treated with the PH-drug)	PH drug metabolism	Codispensed drug	ATC codispensed drug	Patients on combination treatment (n)	Severity	Probable mechanism (PK/PD)	Risk
		Aspirin	B01AC06	1	Major	Additive effects on hemostasis combining antiplatelet agents (treprostinil) with aspirin	Bleeding
		Apixaban	B01AF02	1	Major	Additive effects on hemostasis combining antiplatelet agents (treprostinil) with apixaban	Bleeding
		Trimethoprim	J01EA01	1	Moderate	Trimethoprim is a CYP2C8 inhibitor and may inhibit treprostinil metabolism	↑ Trimethoprim exposure

Note: No potential interactions for epoprostenol were found in this population. Abbreviations: ATC, anatomical therapeutic chemical classification system; PH, pulmonary hypertension; ↑, increased; ↓, decreased.

synergistic ototoxic effect might also be further enhanced if combined with other drugs inhibiting cytochrome P450 enzymes.[12] Underreporting of this drug–drug interaction is plausible since hearing loss is commonly attributed to ageing[23] both by the patients themselves and by the health care staff.

Anticoagulant treatment with the vitamin K antagonist warfarin is recommended for patients with CTEPH,[1] and though no longer recommended for patients with PAH,[1] it is still commonly used in this population.[10] In the present study, a vast majority of patients with CTEPH and almost half of the patients with PAH were treated with warfarin. The combination with bosentan may induce hepatic metabolism (cytochrome P2C9) and reduce warfarin plasma concentration.[12,14] Combination of warfarin with prostacyclin analogs may cause additive effects of antiplatelets and result in bleeding, however, reports in the literature are conflicting.[24,25] Careful monitoring of the prothrombin time in patients with warfarin should thus be undertaken when initiating or discontinuing PH-treatments.

Antibiotic treatment was common and more than half of the study population filled a prescription at least once during the study period. Some antibiotic and antifungal treatments may increase plasma concentrations of sildenafil, tadalafil, bosentan and macitentan due to decreased systemic clearance by cytochrome P3A4.[12] Interactions between antibiotic drugs and PH-specific treatment are well-known but its effect limited as antibiotics are generally administered occasionally and for short periods at a time. This allows for dose adjustment or, if warranted, even discontinuation of the PH-specific treatment during antibiotic treatment when needed. For long-term treatment with antibiotics, adjustments of PH-specific drugs might be warranted.

While it is recommended that patients with PAH and CTEPH are cared for by PH-specialist centers,[1] other health care facilities will often meet the need for care of comorbidities and common colds and flues. Awareness of potential drug–drug interactions between PH-specific treatment and commonly prescribed treatments like diuretics, anticoagulants, and antibiotics are warranted, but awareness of less common drug–drug interactions also needs attention. In addition, nonprescriptions drugs and supplements such as vitamins or herbal products should also be closely monitored as they might contribute to unwanted drug–drug interactions. Close collaboration between the PH-specialist centres and other care facilities as well as easy access to available and reliable drug–drug interaction databases are important to increase patient safety.

TABLE 4 Potential drug–drug interactions and their related risks observed between PH-specific drugs and treatments with anticoagulants, antibiotics, or antidepressants

Drug class	Codispensed drug	ATC codispensed drug	PH-drug	PH-drug ATC	Patients on combination treatment (*n*)	Severity	Risk
Anticoagulants (B01)	Warfarin	(B01AA03)	Bosentan	(C02KX01)	55	Moderate	↓ Warfarin efficacy
	Warfarin	(B01AA03)	Treprostinil	(B01AC21)	20	Major	Bleeding
	Dalteparin	(B01AB04)	Treprostinil	(B01AC21)	6	Major	Bleeding
	Warfarin	(B01AA03)	Iloprost	(B01AC11)	5	Major	Bleeding
	Dalteparin	(B01AB04)	Iloprost	(B01AC11)	4	Major	Bleeding
	Apixaban	(B01AF02)	Selexipag	(B01AC27)	4	Major	Bleeding
	Apixaban	(B01AF02)	Iloprost	(B01AC11)	2	Major	Bleeding
	Tinzaparin	(B01AB10)	Iloprost	(B01AC11)	1	Major	Bleeding
	Aspirin	(B01AC06)	Treprostinil	(B01AC21)	1	Major	Bleeding
	Apixaban	(B01AF02)	Treprostinil	(B01AC21)	1	Major	Bleeding
	Dipyridamole	(B01AC07)	Iloprost	(B01AC11)	1	Moderate	Bleeding
Antibiotics (J01, J02, J04)	Ciprofloxacin	(J01MA02)	Sildenafil	(G04BE03)	9	Moderate	↑ Sildenafil plasma concentration
	Erythromycin	(J01FA01)	Sildenafil	(G04BE03)	3	Moderate	Ssildenafil adverse effects; hypotension, visual changes, priapism
	Fluconazole	(J02AC01)	Sildenafil	(G04BE03)	3	Major	↑ Sildenafil exposure, toxicity risk
	Fluconazole	(J02AC01)	Macitentan	(C02KX04)	2	Major	↑ Macitentan exposure, toxicity risk
	Clarithromycin	(J01FA09)	Sildenafil	(G04BE03)	2	Major	↑ Sildenafil exposure
	Clarithromycin	(J01FA09)	Macitentan	(C02KX04)	1	Major	↑ Macitentan exposure
	Itraconazole	(J02AC02)	Sildenafil	(G04BE03)	1	Major	↑ Sildenafil exposure
	Fluconazole	(J02AC01)	Bosentan	(C02KX01)	1	Moderate	↑ Bosentan plasma concentrations
	Clarithromycin	(J01FA09)	Tadalafil	(B01AC21)	1	Major	↑ Tadalafil bioavailability
	Itraconazole	(J02AC02)	Tadalafil	(B01AC21)	1	Major	↑ Tadalafil bioavailability
	Trimethoprim	(J01EA01)	Treprostinil	(B01AC21)	1	Moderate	↑ Treprostinil exposure
	Clarithromycin	(J01FA09)	Bosentan	(C02KX01)	1	Moderate	↑ Bosentan plasma concentrations

TABLE 4 (Continued)

Drug class	Codispensed drug	ATC codispensed drug	PH-drug	PH-drug ATC	Patients on combination treatment (*n*)	Severity	Risk
Antidepressants (N06A)	Sertraline	(N06AB06)	Treprostinil	(B01AC21)	2	Major	Bleeding
	Sertraline	(N06AB06)	Selexipag	(B01AC27)	2	Major	Bleeding
	Citalopram	(N06AB04)	Treprostinil	(B01AC21)	1	Major	Bleeding
	Sertraline	(N06AB06)	Iloprost	(B01AC11)	1	Major	Bleeding
	Citalopram	(N06AB04)	Selexipag	(B01AC27)	1	Major	Bleeding
	Paroxetine	(N06AB05)	Selexipag	(B01AC27)	1	Major	Bleeding
	Duloxetine	(N06AX21)	Iloprost	(B01AC11)	1	Major	Bleeding

Abbreviations: ATC, anatomical therapeutic chemical classification system; PH, pulmonary hypertension; ↑, increased; ↓, decreased.

Strengths and limitations

Drug interaction databases have different capacities to detect and classify severities of drug–drug interaction that might affect the results of a study investigating interactions between drugs.[26] The decision to use Micromedex® as the primary database might have affected the results.

The study population consisted of all patients with PAH or CTEPH registered in SPAHR[13] and alive during the study period of 2016–2017. Due to the high national coverage of SPAHR (>90%), the study population ably represents patients with PAH and CTEPH in Sweden. The study included all prescriptions filled by patients with PAH or CTEPH in Sweden, available from the National Board of Health and Welfare's pharmaceutical registry (Swedish Prescribed Drug Registry). Limitations are that dose adjustments or drug discontinuation of prescribed drugs are not available and drug adherence was not considered. The registry-based design of the study did not allow for investigation if actual drug–drug interaction occurred.

CONCLUSION

Codispensing of PH-specific therapy and potentially interacting drugs was common in the Swedish PAH and CTEPH population, but codispensing of potentially contraindicated drugs was rare. The most prevalent codispensed and potentially interacting drug combination were between sildenafil and furosemide while bosentan was associated with a higher proportion of potential drug–drug interactions and affected the highest number of patients. Potential drug–drug interactions of major severity were observed between PH-specific treatment and anticoagulants, antibiotics and antidepressants, and should warrant attention.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Puck N. Norell, Bodil Ivarsson, Maria Selin, and Barbro Kjellström. The first draft of the manuscript was written by Puck N. Norell and Barbro Kjellström and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

ACKNOWLEDGMENTS

We acknowledge the work of the SPAHR registrars at the PAH/CTEPH-specialist clinics, the members of the SPAHR steering committee and Uppsala Clinical Research Centre for administrating SPAHR; pharmacist and PhD Anna Sandqvist at Umeå University for support in designing the study, interpretation of the results and drafting the manuscript; and associate professor Per Näsman at the Royal Institute of Technology in Stockholm (KTH) for doing the statistic calculations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the Regional Ethics Committee in Lund, Sweden (LU 2016/766), and performed in accordance with the Declaration of Helsinki. The study used retrospective, anonymized data from Swedish National Registries and in accordance to Swedish law, no informed consent from patients was needed.

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How to cite this article: Norell PN, Ivarsson B, Selin M, Kjellström B. Prevalence of potential drug–drug interactions with disease-specific treatments in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension: a registry study. Pulm Circ. 2022;12:e12114. https://doi.org/10.1002/pul2.12114