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

Puck N. Norell1 | Bodil Ivarsson2 | Maria Selin3 | Barbro Kjellström4,5

1Department of Medicine, Karolinska Institutet, Stockholm, Sweden
2Department of Clinical Sciences, Lund University Lund, Cardiothoracic Surgery, and Medicine Services University Trust, Region Skåne, Lund, Sweden
3Heart Centre, Cardiology, Umeå University Hospital, Umeå, Sweden
4Department of Clinical Sciences Lund, Clinical Physiology and Skåne University Hospital, Lund University, Lund, Sweden
5Cardiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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 (SPAHR13).

The Swedish Prescribed Drug Registry use the anatomical therapeutic chemical (ATC) classification system. The drug interaction tool in the IBM Micromedex® database15 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 analyses18 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® interactions | Lexicomp® 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 |

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

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 (bosentan), C02KX02 (ambrisentan), C02KX04 (macitentan), C02KX05 (riociguat), G04BE03 (sildenafil), and G04BE08 (tadalafil).
TABLE 2   Study population characteristics (n = 572), drug combinations including a PH-specific drug and their drug–drug interaction severity

| Characteristic                              | Value   |
|---------------------------------------------|---------|
| 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.

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, whereas 16% of potential drug–drug interactions were considered contraindicated. 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. 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. A less known effect is ototoxicity that can cause hearing loss. The mechanism behind this may be further enhanced as an additive effect, as hearing loss can be induced temporarily by diuretics and as a sensorineural effect induced by sildenafil. The...
| 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 |
| Ambrisentan (n = 95) (C02KX02)                              | Hepatic metabolism by uridine 5'-diphosphate glucuronosyltransferases (UGTs) UGT1A9S, -2B7S, -1A3S, and by CYP450 enzymes CYP3A4, -3A5, and -2C19 | Oxycodone          | N02AA05              | 13                                   | Major    | Bosentan induces CYP3A4 which reduces oxycodone exposure | ↓ Oxycodone exposure |
| Bosentan (n = 87) (C02KX01)                                 | Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19 | Tramadol           | N02AX02              | 7                                    | Major    | Bosentan induces CYP3A4 which reduces tramadol exposure | ↓ Tramadol exposure |
| Bosentan (n = 87) (C02KX01)                                 | Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19 | Paracetamol + codeine | N02AJ06              | 5                                    | Major    | Bosentan induces CYP3A4 which reduces codeine efficacy and may increase withdrawal | ↓ Opioid efficacy, risk opioid withdrawal |
| Bosentan (n = 87) (C02KX01)                                 | Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19 | Medroxyprogesterone acetate | G03DA02              | 3                                    | Major    | Bosentan induces CYP3A4 which reduces medroxyprogesterone acetate exposure | ↓ Medroxyprogesterone concentrations |
| Bosentan (n = 87) (C02KX01)                                 | Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19 | Estradiol          | G03CA03              | 3                                    | Major    | Bosentan induces CYP3A4 which reduces estradiol plasma levels | ↓ Hormonal contraceptive plasma levels |
| Bosentan (n = 87) (C02KX01)                                 | Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19 | Buprenorphine      | N02AE01              | 2                                    | Major    | Bosentan induces CYP3A4 which reduces buprenorphine exposure | ↓ Buprenorphine plasma levels |
| Bosentan (n = 87) (C02KX01)                                 | Hepatic metabolism by CYP2C9, -3A4 and to lesser extent -2C19 | Medroxyprogesterone acetate | G03AC06              | 1                                    | Major    | Bosentan induces CYP3A4 which reduces medroxyprogesterone acetate exposure | ↓ Medroxyprogesterone concentrations |

(Continues)
| 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 |
| 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 |
|---|---|---|---|---|---|---|---|
| | | Didofenac | 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 |
| | | Didofenac | 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) (C02XX04) | 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)
| 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        |                  |                      |                                      |          | Additive effects on hemostasis combining antiplatelet agents (iloprost) and warfarin | Bleeding |
| Warfarin                                                      |                    | B01AA03          | 5                    | Major                                |          | Additive effects on hemostasis combining antiplatelet agents (iloprost) and low molecular weight heparin (dalteparin) | Bleeding |
| Dalteparin                                                    |                    | B01AB04          | 4                    | Major                                |          | Additive effects on hemostasis combining antiplatelet agents (iloprost) and 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 |
| 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                                                 | Hepatic metabolism by CYP1A1, -3A4, -3A5, -2J2 and -2C8 | B01AB10          | 1                   | Major                               | Additive effects combining antiplatelet agents (iloprost) and low molecular weight heparin (tinzaparin) | Bleeding |
| Didofenac                                                  | Sodium picosulfate  | M02AA15          | 1                   | Major                               | Additive effects on hemostasis combining antiplatelet agents (iloprost) with NSAID (diclofenac) | Bleeding |
| Dipyridamole                                               | 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)                                         | Hepatic metabolite activation by carboxylesterase 1 | B01AF02          | 4                   | Major                               | Additive effects combining antiplatelet agents (selexipag) with apixaban | Bleeding |

(Continues)
| 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) |
| PH-drug                  | 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)
| 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 | Hepatic metabolism, primarily by CYP2C8 | Warfarin | B01AA03 | 20 | Major | Additive effects on hemostasis combining antiplatelet agents (treprostinil) with warfarin | Bleeding |
| Clarithromycin | | Dalteparin | B01AB04 | 6 | Major | Additive effects combining antiplatelet agents (treprostinil) and low molecular weight heparin (dalteparin) | Bleeding |
| Itraconazole | | Sertraline | N06AB06 | 2 | Major | Combining antiplatelet agents (treprostinil) with SSRIs (sertraline) may alter platelet function and induce bleeding | Bleeding |
| Bosentan | | Citalopram | N06AB04 | 1 | Major | Combining antiplatelet agents (treprostinil) with SSRIs (citalopram) may alter platelet function and induce bleeding | Bleeding |
synergistic ototoxic effect might also be further enhanced if combined with other drugs inhibiting cytochrome P450 enzymes. Underreporting of this drug–drug interaction is plausible since hearing loss is commonly attributed to ageing 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, and though no longer recommended for patients with PAH, it is still commonly used in this population. 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. Combination of warfarin with prostacyclin analogs may cause additive effects of antiplatelets and result in bleeding, however, reports in the literature are conflicting. 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. 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, 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                            | Sildenafil adverse effects; hypotension, visual changes, priapism |
| Fluconazole      | (J02AC01)        | Sildenafil            | (G04BE03)      | 3           | Major                               | ↑ Sildenafil exposure, toxicity risk |
| Clarithromycin   | (J01FA09)        | Sildenafil            | (G04BE03)      | 2           | Major                               | ↑ Macitentan exposure, toxicity risk |
| 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 |
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\(^5\) 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.
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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.

ORCID
Barbro Kjellström @ http://orcid.org/0000-0002-7936-1209

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