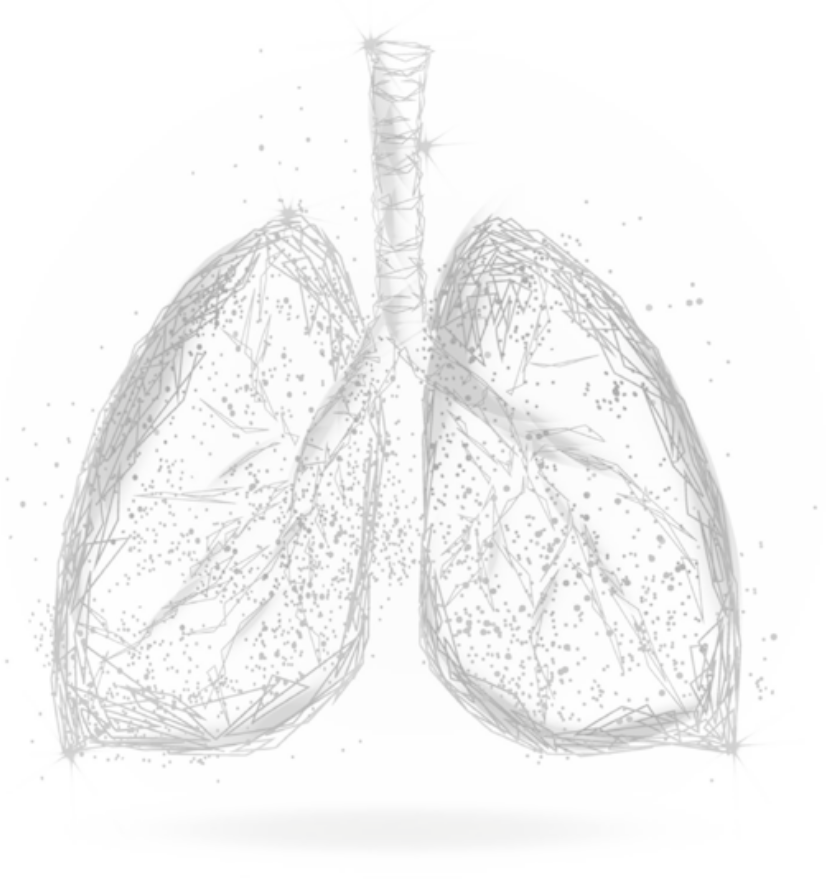
Effectiveness and safety of medicines used in COPD patients

Wang, Yuanyuan

DOI:
10.33612/diss.123921981

CHAPTER 5



Improving antibacterial prescribing safety in the management of COPD exacerbations: systematic review of observational and clinical studies on potential drug interactions associated with frequently prescribed antibacterials among COPD Patients

Yuanyuan Wang
Muh. Akbar Bahar
Anouk M.E. Jansen
Janwillem W.H. Kocks
Jan-Willem C. Alffenaar
Eelko Hak
Bob Wilffert Sander D. Borgsteede

Published as: Wang Y, Bahar MA, Jansen AME, Kocks JWH, Alffenaar JC, Hak E, Wilffert B, Borgsteede SD. Improving antibacterial prescribing safety in the management of COPD exacerbations: systematic review of observational and clinical studies on potential drug interactions associated with frequently prescribed antibacterials among COPD patients. J Antimicrob Chemother. 2019;74(10):2848–2864.

ABSTRACT

Background

Guidelines advice the use of antibacterials (ABs) in the management of COPD exacerbations. COPD patients often have multiple comorbidities like diabetes mellitus and cardiac diseases leading to polypharmacy. Consequently, drug-drug interactions (DDIs) may frequently occur, cause serious adverse events and treatment failure.

Objective

(i) To review DDIs related to frequently prescribed ABs among COPD patients from observational and clinical studies. (ii) To improve AB prescribing safety in clinical practice by structuring DDIs according to comorbidities of COPD.

Methods

We conducted a systematic review by searching Pubmed and Embase up to Feb 8, 2018 for clinical trials, cohort and case-control studies reporting DDIs of ABs used for COPD. Study design, subjects, sample size, pharmacological mechanism of DDI, and effect of interaction were extracted. We evaluated level of DDIs and quality of evidence according to established criteria and structured the data by possible comorbidities.

Results

In all, 318 articles were eligible for review describing a wide range of drugs used for comorbidities and their potential DDIs with ABs. DDIs between ABs and co-administered drugs could be subdivided into: (1) co-administered drugs alter the pharmacokinetics of ABs; and (2) ABs interfere with the pharmacokinetics of co-administered drugs. The DDIs could lead to therapeutic failures or toxicities.

Conclusion

DDIs related to ABs with clinical significance may involve a wide range of indicated drugs to treat comorbidities in COPD. The evidence can support (computer supported) decision-making by health practitioners when prescribing ABs during COPD exacerbations in the case of co-medication.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disorder characterized by persistent respiratory symptoms and airflow limitation.[1] The chronic and progressive course of COPD is frequently aggravated by exacerbation defined as an acute worsening of respiratory symptoms like increased cough, dyspnea and production of sputum.[2] Exacerbations of COPD can be triggered by respiratory tract infections, 40% to 60% of exacerbations are caused by bacteria, especially by *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*.[3] Evidence from randomized controlled trials (RCTs) indicated that use of antibacterials (ABs) may reduce the frequency and severity of COPD exacerbations.[4-6] Therefore, guidelines have recommended involving ABs in the therapeutic and preventive management of COPD exacerbations.[1,7]

Patients with COPD often suffer from multiple morbidities.[8] Hence, polypharmacy is common and contributes to drug-drug interactions (DDIs). Adverse drug reactions (ADRs) or therapeutic failure may be the result of ABs and co-administered drugs interactions. Besides, COPD is an age-related disease and elderly are more susceptible to the effect of DDIs because of gradual physiologic changes affecting pharmacokinetics and pharmacodynamics.[9]

The objective of this study was to (1) systematically review DDIs related to frequently prescribed ABs among COPD patients from observational and clinical studies and (2) improve AB prescribing safety in clinical practice by structuring DDIs according to comorbidities of COPD. Studies without comparison groups, and therefore have low quality of the causal evidence, like case reports about QT-interval prolonging interactions are not included in this review. Hence, a DDI handbook like Stockley's Drug Interactions and the official product information can be referred to see the clinical impact of those kinds of interactions.

METHODS

Searching strategy

We conducted a systematic review following PRISMA guideline. PubMed and Embase databases were searched for related articles published in English up to Feb 8, 2018 using key terms of "drug interactions," "pharmacokinetics", "pharmacodynamics", and a list of most frequently used ABs for COPD (see Table 1). The ABs were selected based on two related Cochrane reviews and their prescription frequency by the University of Groningen prescription database IADB.nl (http://www.iadb.nl/) covering drug prescriptions of approximately 700,000 people.[4,5] Additionally, we checked the primary sources of signals from Dutch DDI alert systems: G-Standard and Pharmabase.[10]

Reference lists from eligible studies were also tracked for additional qualified papers. Searching details are provided in supplementary data.

Study selection criteria

Eligible studies met the following criteria: (1) DDIs in humans; (2) involving the targeted ABs; (3) being clinical trials, RCTs, cohort, or case-control study. We excluded case reports or other descriptive studies. We further excluded studies with subjects whose pharmacokinetics and pharmacodynamics were not comparable to the general COPD patients, *e.g.* newborn babies, pregnant women and patients with severe renal/hepatic impairment. Other exclusion criteria were: (1) unregistered drugs (by FDA or EMA); (2) involving three or more drug interactions; (3) not DDIs (food-drug, gene-drug); (4) not original studies (reviews, letters and editorials). Besides, pharmacodynamic interactions were beyond the scope of this review and then, excluded.

Data extraction and quality assessment

All records were exported to Refworks; title and abstracts were screened by Y.W. and A.M.E.J. independently. Full-text papers were obtained for records that were considered of potential relevance by at least one of the reviewers. Final decisions were made by consensus between two reviewers according to the preset criteria. Discrepancies between reviewers were resolved by discussion, a third reviewer (E.H.) was asked if no consensus was reached. Information about name of ABs and related interacting drug, study design, study subjects, sample size, interacting mechanism, effects of interaction, recommendation by study authors were extracted by the same reviewers (Y.W., A.M.E.J.)

Table 1. Antibacterials (ABs) of study that are frequently prescribed among COPD patients.*

Category	Sub-category	ABs included
Beta-lactam	Penicillins	Amoxicillin/clavulanic acid (co-amoxiclav), Amoxicillin, Flucloxacillin, Pheneticillin, phenoxymethylpenicillin (penicillin V),
	Cephalosporins	Cefaclor, Cefuroxime, Ceftriaxone, Cephradine, Ceftazidime
Macrolides		Erythromycin, Clarithromycin, Azithromycin, Roxithromycin, Clindamycin,
Tetracycline		Tetracycline, Doxycycline, Minocycline,
Quinolones	Fluoroquinolone	Ciprofloxacin, Moxifloxacin, Levofloxacin, Ofloxacin, Norfloxacin,
	Other quinolone	Pipemidic acid
Sulfonamides		Sulfamethoxazole
Others		Nitrofurantoin, Methenamine, Trimethoprim

*based on two Cochrane reviews[4] and use within the University Groningen prescription database IADB.nl from Netherlands (http://www.iadb.nl/)

and checked by another reviewer (M.A.B.). Quality of evidence was evaluated by grade 0 to 4 based on criteria (Table 2) used by previous studies.[11,12]

The strength of the DDIs were classified into four levels (1= strong /2 = substantial /3 = moderate /4 = weak/no) according to the preset published criteria (Table 3).[12] In case

Table 2. Quality of Evidence for DDIs[11,12]

Definition	Score
Clinical researches with appropriate control group and relevant pharmacokinetics and/or pharmacodynamics parameters. The studies meet all of the criteria below: • The interacting effect of concomitant medication with investigated drugs is reported in the manuscript. • All of potential confounders are mentioned and taken into account (for example smoking behavior or renal function). • The results of interaction are built on the 'steady-state kinetics'. • - Variation in dose was adjusted.	4
Clinical researches with appropriate control group and relevant pharmacokinetics and/or pharmacodynamics parameters which do not meet one or more pre-defined criteria above.	3
Complete observational studies with clinically relevant results.	2
Incomplete observational studies. (*e.g.* without controlling confounders or presence of other explanation factors for the adverse reaction), case reports, SmPc.	1
In vitro studies, *in vivo* animal studies, prediction modelling studies.	0

Table 3. Description for level of DDIs[10]

Definition	Score*
Involving inhibitor = > 200% ↑AUC; clearance ↓ > 67%	1
Involving inducer = > 90% ↓ AUC; clearance ↑ ≥ 900%	1
For observational studies, RR/OR ≥ 10	1
Involving inhibitor = 75-200% ↑AUC; clearance ↓ ≥ 43% to < 67%	2
Involving inducer = 60-90% ↓ AUC; clearance ↑ ≥ 150% to < 900%	2
For observational studies, RR/OR = 3~9	2
Involving inhibitor = 25-75% ↑AUC; clearance ↓ ≥ 20% to < 43%	3
Involving inducer = 25-60% ↓AUC; clearance ↑ ≥ 33 % to < 150%	3
For observational studies, RR/OR = 1.5~2.9	3
<25% change in AUC; clearance ↓ < 20% or ↑ < 33 %	4
For observational studies, RR/OR < 1.5	4
a. For the Interacting drugs with narrow therapeutic index, the degree of DDIs will be improved to the one higher degree of level.	Exception
b. If the DDIs level cannot be judged by the above criteria, we assess it by discussion based on available data and evidence.	Exception

*definition: 1 = strong interaction, 2 = substantial interaction, 3 = moderate interaction, and 4 = weak/no interaction

of several studies on the same DDI combination, we categorized the DDI based on the highest level of severity. Considering that narrow therapeutic index (NTI) drugs are more vulnerable to DDIs, the strength of the DDI was upgraded one level.[12]

RESULTS

Publications identified by literature search

Our search yielded 1,412 and 1,734 studies from Pubmed and Embase, respectively (Figure 1). After removing duplicates, 2,560 articles were screened by title and abstracts, of which 630 papers were included for full-text screening, resulting in 282 eligible articles. With 36 studies identified from other resources, we got 318 studies finally for assessment in this review.

The interacting drugs, underlying mechanisms, levels and practice recommendations of the DDIs are presented in Table 4. Details on individual studies of DDIs with a potential clinical significance (level 1 to 3) were presented in Supplementary Table S1 and S2 and the data of studies with a low level (weak or no) of DDIs were presented in Table S3.

Prescribing AB in COPD: step-by-step approach
1. Check if comorbidity is present (Table 4). 2. A quick overview on AB and its interacting medication, possible interacting mechanism, level of interaction, and practical recommendations is provided in Table 4. 3. Detailed explanation about related interacting mechanism and recommendation to manage related DDIs is provided in main text.

Mechanisms of DDI

AB can act as an inhibitor/inducer and/or a substrate producing moderate to strong DDI with other co-administered medication. There are two scenarios: (1) co-administered drug alters the pharmacokinetics parameters of AB; and (2) AB influences the pharmacokinetics parameters of co-administered medication. The main mechanisms of these DDIs are complex-forming, inhibition/ induction of drug metabolizing enzymes and alteration of drug transporters (Table 4). The ability to inhibit CYP3A4 makes the ABs prone to interact with many different drugs as CYP3A4 metabolizes more than 50% of the clinically prescribed drugs.[13]

Information structured according to drugs for comorbidities

The presentation of information on potential clinically significant DDIs with moderate to strong level of interaction is according to the most frequent comorbidities that

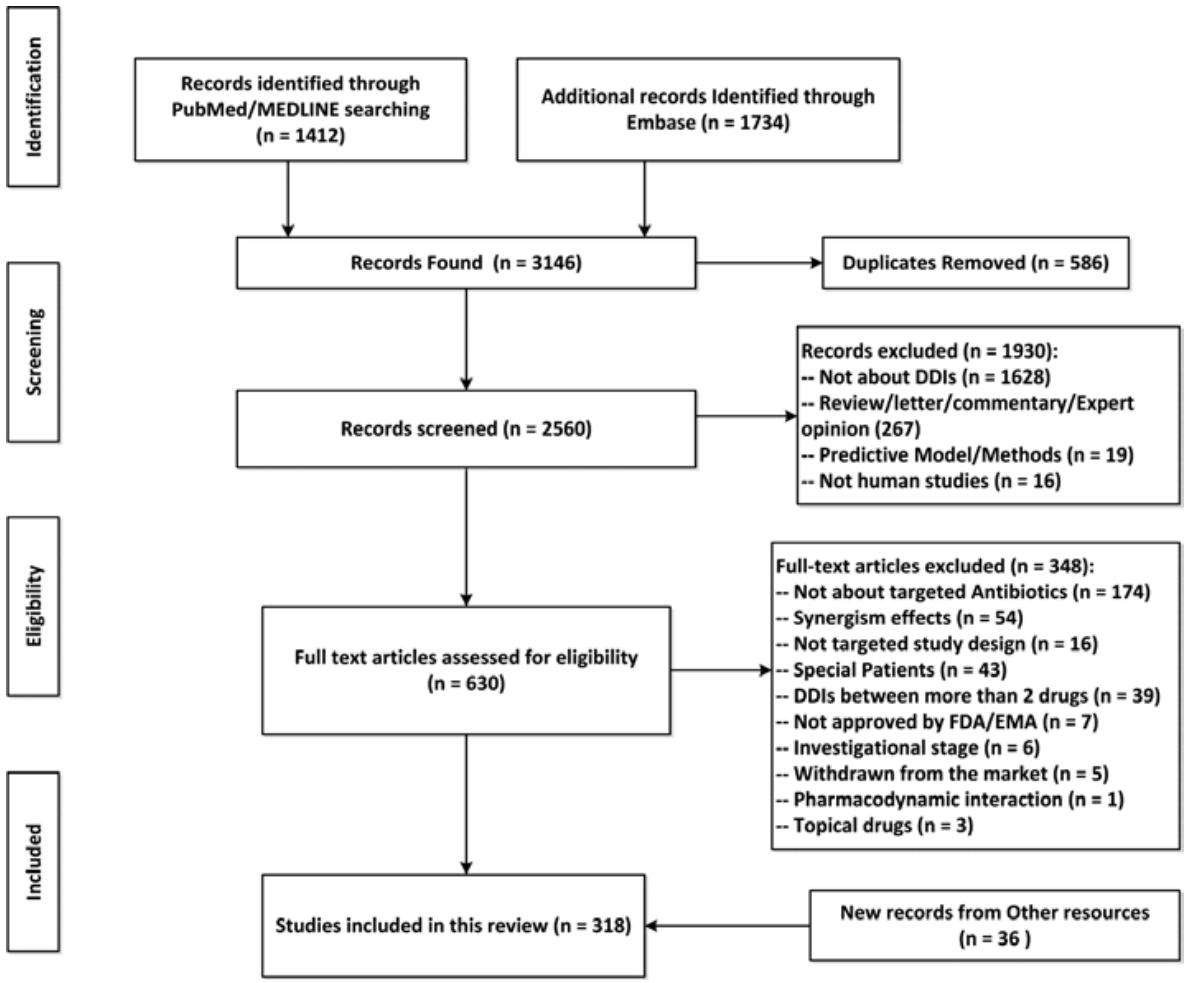


Figure 1. Flowchart of study selection.

have been reported in COPD patients.[8,14] Potential mechanisms of DDIs and actionable recommendation to manage the DDIs are provided in Table 4.

1. Diabetes

Patients with COPD have a 50% higher risk to develop diabetes than persons without COPD.[15] Some antidiabetic drugs are substrates of enzymes like CYP3A4 (glipizide, tolbutamide), CYP2C9 (glipizide, glyburide) and CYP2C8 (repaglinide); and substrates of drug transporter like P-gp transporter (glipizide, glyburide).[16-26] ABs may inhibit the function of those metabolic enzymes and transporters such as clarithromycin (CYP3A4 and P-gp inhibitor), trimethoprim–sulfamethoxazole (CYP2C8/2C9 inhibitor) and levofloxacin (P-gp inhibitor). These medicines can potentially increase the blood concentration of those antidiabetic agents.[16-26] Consequently, patients may develop hypoglycemia. Therefore, it is suggested to avoid these combinations by replacing related AB or adjusting the dose of antidiabetic agents as well as monitoring the patients' blood glucose.

2. Heart and circulatory system diseases

2.1. Antihypertensive agents

Hypertension is associated with COPD with relative risk of 1.6.[15] Antihypertensive calcium channel blocker (CCB) like diltiazem and verapamil are CYP3A4 substrates.[27-29] Therefore, macrolides (CYP3A4 inhibitors) can enhance the pharmacologic activity of CCB.[30] Avoiding the combination by substitution of macrolides or CCB to another group of drugs or adjusting the dose of CCB while monitoring the blood pressure is recommended. Erythromycin and clarithromycin are the most potent CYP3A4 inhibitors, while azithromycin and roxithromycin are weak inhibitors.[30,31] Hence, if prescribing macrolides, choosing macrolides with minimal inhibitory capacity to be co-prescribed with CCB may minimize the risk of DDI.

Spironolactone, a potassium sparing diuretic, is used to lower blood pressure. Spironolactone and trimethoprim–sulfamethoxazole combination may produce hyperkalemia because both drugs can inhibit renal excretion of potassium.[32] Therefore, avoiding combination by selecting an alternative AB or adjusting the dose of spironolactone and closely monitoring potassium plasma levels is strongly recommended.

2.2. Lipid-lowering drugs

Lipid metabolism problem is one of the most prevalent comorbidities in COPD patients.[14] The main pharmacologic approach to manage blood cholesterol levels is by statin therapy.[33] Some ABs increase the plasma concentration of statins by several mechanisms. Statins like simvastatin and atorvastatin are bio-degraded by CYP3A4.[34,35] Therefore, potent CYP3A4 inhibitors (erythromycin and clarithromycin) increase the risk for statin related side effects like rhabdomyolysis.[34,35] Other statins like rosuvastatin, pravastatin and fluvastatin are not CYP3A4 substrates.[36] Yet, the hepatic clearance of these statins are facilitated by anion–transporting polypeptides.[37] These influx transporters facilitate the transportation of statins from systemic blood to liver cells to be metabolized or subsequently delivered into the bile for elimination.[37] Clarithromycin and erythromycin have been reported to be inhibitors of these transporters.[38] Therefore, replacing erythromycin and clarithromycin with other ABs, temporarily stopping statins, or adjusting the dose of statins while monitoring statin related side effects is recommended.

2.3. Oral anticoagulants

Both coumarins and direct oral anticoagulants (DOACs) may interact with ABs. Multiple studies reported that DDIs between ABs with coumarins (warfarin, phenprocoumon, acenocoumarol) led to increased risks of hemorrhage.[39-58] Several interacting mechanisms were proposed.[59,60] One mechanism is by disruption of intestinal flora

that synthesizes vitamin K, as many ABs could alter the balance of gut flora.[59] Another mechanism is that ABs (e.g. trimethoprim–sulfamethoxazole and macrolide) alter coumarins' metabolism which mainly involves CYP2C9 and CYP3A4, respectively.[60] Therefore, to choose alternative AB or if not possible, to monitor INR values and adjust the dose of coumarins is recommended.

DOACs are regarded as a safe alternative to replace coumarins.[61] However, since some DOACs (edoxaban, rivaroxaban, dabigatran) are substrates of CYP3A4 and/or P-gp transporter, their AUC values can be increased by ABs like macrolides.[62,63] Therefore, when macrolides and DOACs are required in combination, careful monitoring the signs of bleeding is needed, and adjusting the dose of DOACs should be done if it is necessary.

2.4. Antiarrhythmic agents

Some antiarrhythmic agents like digoxin, quinidine, lignocaine, and procainamide potentially interact with ABs.[64-75] Quinidine and lignocaine are CYP3A4 substrates, and therefore, macrolides may inhibit their degradation and increase their bioavailabilities.[64,65] Meanwhile, the renal clearance of procainamide and digoxin were inhibited by trimetophrim.[66,67,72,73] Mechanism of interaction is inhibition of tubular secretion via inhibition of renal organic cation transporter because they are substrates of the transporter.[66,67,72,73] Consequently, blood concentrations of these drugs are increased.[66,67,72,73] Digoxin is a substrate of P-gp transporter.[68-71] Accordingly, AUC of digoxin is elevated by clarithromycin and therefore, may cause toxicities.[68-71] Since quinidine, lignocaine, digoxin, and procainamide are drugs with NTI, avoiding ABs that can lead to DDIs with these drugs is recommended.[76,77] However, if they are necessary to be co-prescribed, therapeutic drug monitoring (TDM) of these antiarrhythmic agents is strongly recommended.[77]

3. Respiratory diseases

3.1. Medication for obstructive airways diseases

One of the most prevalent comorbidities in COPD is asthma.[14] Some anti-asthma drugs such as methylprednisolone, montelukast, loratadine, roflumilast and theophylline were substrates of CYP3A4 and/or P-gp transporter and therefore, evidenced to interact with macrolides.[78-87] Hence, one might consider other ABs to be combined with asthma drugs, or closely monitor patients, especially in case of theophylline which is a NTI drug.[88] As theophylline is also metabolized by CYP1A2,[89] ciprofloxacin (a CYP1A2 potent inhibitor) should be avoided.[90-97]

3.2. Anti-mycobacterial agents

Tuberculosis and COPD diseases share comparable risk factors and therefore, can coincide in individuals, particularly elderly patients.[98] Rifampicin and rifabutin (anti-mycobacterial agents) work as potent inducers of hepatic and intestinal CYP enzymes.[99]

Table 4. DDI of antibacterials (ABs) for COPD exacerbation and other drugs for treating its comorbidities

Comorbidity	Medication	Interacting AB
1. Diabetes		
Antidiabetic medication	Glipizide, glyburide	TMP-SMX
	Glyburide	Clarithromycin
	Glipizide, glyburide	Levofloxacin
	Tolbutamide	Clarithromycin
		TMP-SMX
	Glipizide, repaglinide	Clarithromycin
	Repaglinide, rosiglitazone	TMP-SMX
	Metformin	TMP-SMX
2. Heart and circulatory system diseases		
2.1 Antihypertensive agents	Spironolactone	TMP-SMX
	Calcium channel blocker	Erythromycin, clarithromycin
		Azithromycin
2.2 Lipid-lowering drugs	Simvastatin	Erythromycin
	Atorvastatin	Clarithromycin
		Erythromycin
	Rosuvastatin/pravastatin/fluvastatin	Clarithromycin
2.3 Oral anticoagulants	Warfarin, phenprocoumon / acenocoumarol	TMP-SMX
		Amoxicillin/co-amoxiclav, ceftriaxone
		Clarithromycin, azithromycin, ciprofloxacin, levofloxacin, ofloxacin, doxycycline
	Edoxaban, dabigatran, rivaroxaban	Erythromycin, clarithromycin
	Warfarin	Moxifloxacin

Mechanism	Management suggestion	Level of interaction	Ref.
Inhibition of CYP2C9 Inhibition of P-gp	Consider alternative, adjusted dose of substrate or used cautiously by monitoring patients' blood glucose.	2	16-19
Inhibition of P-gp Inhibition of CYP3A4 & P-gp Inhibition of CYP2C9 Inhibition of CYP3A4 Inhibition of CYP2C8 Inhibition of OCT2 & MATE1	Monitor patients' blood glucose and if necessary, adjusted dose of substrate.	3	16, 20-26
Inhibition of potassium secretion	Avoid combination or adjusted dose of substrates & closely monitoring potassium plasma levels.	1	32
Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	27-29
Inhibition of CYP3A4	Monitor side effects and if necessary, adjusted dose of substrate.	3	27
Inhibition of CYP3A4	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	34
Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	35
Inhibition of CYP3A4 Inhibition of OAT	Monitor side effects and if necessary, adjusted the dose of substrate.	3	36, 204
Inhibition of CYP2C9	Avoid combination or closely monitor the change of INR routinely and adjusted the dose if needed.	1	39-58
Alterations in normal gut flora Inhibition of CYP3A4 or alterations in normal gut flora	Choose alternative AB or if not possible, monitor the change of INR routinely.	2	
Inhibition of CYP3A4 &/or P-gp	Consider alternative/adjusted dose of substrate or monitor the signs of excessive anticoagulant effect.	2	62, 63
Inhibition of CYP3A4 or alterations in normal gut flora	Monitor the change of INR routinely	3	41

Table 4. (continued)

Comorbidity	Medication	Interacting AB
2.4 Antiarrhythmic agent	Digoxin	Clarithromycin
	Quinidine, lignocaine	Erythromycin
	Procainamide	TMP
	Pindolol, digoxin	TMP-SMX
	Procainamide	Levofloxacin, ofloxacin
3. Respiratory diseases		
3.1. Medication for obstructive airways diseases	Methylprednisolone, montelukast	Clarithromycin
	Theophylline	Erythromycin
		Ciprofloxacin
	Loratadine	Erythromycin, clarithromycin
	Roflumilast	Erythromycin
3.2. Anti-TB drugs	Rifabutin	Clarithromycin
	Rifampicin, rifabutin	Clarithromycin
	Rifampicin, rifabutin	TMP-SMX, doxycycline
	Rifampicin	TMP-SMX
		Moxifloxacin
4. Neurological disorders		
4.1. Antiparkinson Agents	Bromocriptine	Erythromycin
	Cabergoline	Clarithromycin
4.2. Antiepileptic drugs	Carbamazepine, phenytoin	Doxycycline
	Carbamazepine	Ciprofloxacin
	Phenytoin	TMP-SMX
	Phenobarbital	Doxycycline
5. Depression and psychiatric disorders		
Antidepressant, Anxiolytic, & Antipsychotic agents	Buspirone	Erythromycin
	Quetiapine	Erythromycin
	Pimozide, trazodone	Clarithromycin
	Clozapine	Ciprofloxacin
	Diazepam	Ciprofloxacin

Mechanism	Management suggestion	Level of interaction	Ref.
Inhibition of P-gp	Avoid combination or perform TDM and if necessary, adjusted dose of substrate.	1	68-71
Inhibition of CYP3A4 Inhibition of tubular secretion	Consider alternative or perform TDM and if necessary, adjusted dose of substrate.	2	64-67
Inhibition of tubular secretion Inhibition of OCT	Perform TDM and if necessary, adjusted dose of substrate.	3	72-75
Inhibition of CYP3A4 & P-gp Inhibition of CYP3A4 Inhibition of CYP1A2	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects. For theophylline, perform TDM.	2	78-85, 90-97
Inhibition of CYP3A4 Inhibition of CYP3A4	Monitor side effects and if necessary, adjusted dose of substrate.	3	86, 87
Inhibition of CYP3A4	Avoid combination	1	101, 110, 111
Induction of CYP3A4	Consider alternative AB for COPD	2	100, 101
Induction of CYP3A4/ CYP2C9 Inhibition of mixed oxidases Inducing phase II enzymes	Consider alternative AB for COPD or monitor the effectiveness of AB and if necessary, adjusted dose of AB.	3	102-104, 106-109
Inhibition of CYP3A4	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	112
Inhibition of CYP3A4 & P-gp	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	113
Induction of CYP3A4	Consider alternative or perform TDM	2	117, 116
Inhibition of CYP3A4/1A2	Consider alternative or perform TDM	2	118
Inhibition of CYP2C8	Consider alternative or perform TDM	2	116, 119
Induction of CYP3A4	Monitor side effects and if necessary, adjusted dose of substrate.	3	115
Inhibition of CYP3A4	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	125
Inhibition of CYP3A4 Inhibition of CYP3A4 Inhibition of CYP1A2	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects. For clozapine, perform TDM.	2	122-124, 129
Inhibition of CYP3A4	Monitor side effects and if necessary, adjusted the dose of substrate.	3	127

Table 4. (continued)

Comorbidity	Medication	Interacting AB
6. Dyspepsia		
Antidyspepsia medications	Aluminum hydroxide, sucralfat	Quinolone, tetracyclines
	Lansoprazole	Clarithromycin
	Calcium carbonate	Quinolone, tetracyclines
	Bismuth subsalicylate	Quinolone, tetracyclines
7. HIV		
Anti-HIV drugs	Didanosine	Ciprofloxacin
	Saquinavir	Erythromycin
	Lamivudine, didanosine	TMP-SMX
8. Other		
Pulmonary arterial hypertension medications	Bosentan	Clarithromycin
	Ambrisentan	Clarithromycin
Insomnia medications	Brotizolam, triazolam, zopiclone	Erythromycin
	Zolpidem	Ciprofloxacin
Antifungal agents	Voriconazole Itraconazole	Erythromycin Ciprofloxacin
Antineoplastic drugs	Vinorelbine	Clarithromycin
Anti-gout drugs	Colchicine	Clarithromycin
		Azithromycin
	Probenecid	Ciprofloxacin
Anesthesia drugs	Midazolam	Clarithromycin, erythromycin
	Ketamine	Clarithromycin

Mechanism	Management suggestion	Level of interaction	Ref.
Complex-forming	Avoid combination or administer quinolone at least 2 hours before or 6 hours after co-agents.	1	131-142
Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	147
Complex-forming	Avoid co-administration or administration interval of at least 2 h or more	2	131, 139
Complex-forming	Administration interval of at least 2 h or more	3	143, 205
Complex-forming	Avoid combination or administer quinolone at least 2 hours before or 6 hours after the co-agents.	1	149, 150
Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	151
Inhibition of tubular secretion	Monitor side effects and if necessary, adjusted dose of substrate.	3	152, 153
Inhibition of CYP3A4 & P-gp	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	206
Inhibition of CYP3A4 & P-gp	Monitor side effects and if necessary, adjusted the dose of substrate.	3	207
Inhibition of CYP3A4	Consider an alternative AB or other hypnotic drugs (not a CYP3A4 substrate)	2	208-210
Inhibition of CYP3A4	Monitor side effects and if necessary, choose alternative AB or other hypnotic drugs (not a CYP3A4 substrate)	3	211
Inhibition of CYP3A4 Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects. For voriconazole, perform TDM and adjust the dose if needed.	2	154, 155
Inhibition of CYP3A4 & P-gp	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	179
Inhibition of CYP3A4	Avoid combination or perform TDM and adjust the dose if needed.	1	180
Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	180
Inhibition of OAT	Monitor side effects and if necessary, adjusted dose of substrate.	3	194, 195
Inhibition of CYP3A4	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	156-160
Inhibition of CYP3A4	Consider alternative or perform TDM and adjust the dose if needed.	2	161

Table 4. (continued)

Comorbidity	Medication	Interacting AB
	Alfentanil	Erythromycin
	Ropivacaine	Clarithromycin Ciprofloxacin
	Midazolam	Roxithromycin
Analgesics	Oxycodone	Clarithromycin
Immunosuppressant drugs	Cyclosporine	Erythromycin
	Everolimus	Erythromycin
	Tacrolimus	Levofloxacin
	Cyclosporine	Ciprofloxacin
Vasoactive agent	Sildenafil	Clarithromycin, erythromycin, ciprofloxacin
Appetite suppressant	Sibutramine	Clarithromycin
Emergency birth control	Ulipristal acetate	Erythromycin
Antimalarial agent	Halofantrine	Tetracycline
Muscle relaxant	Tizanidine	Ciprofloxacin
Anti-diarrheal	Loperamid	TMP-SMX
Anemia medications	Iron supplements	Quinolone, tetracyclines
Other metal cations	Zinc sulfate	Quinolone, tetracyclines
	Calcium acetate, calcium carbonate, calcium polycarbophil, patiromer, lanthanum carbonate, sevelamer	Quinolone, tetracyclines
Other ABs	Linezolid	Clarithromycin
	Dapson	Trimethoprim
	Neomycin	Penicillin V

Definition of level of interaction: 1 = strong interaction, 2 = substantial interaction, 3 = moderate interaction, and 4 = weak/no interaction; Ref. = reference; h = hour; OCT= organic cation transporter; OAT= Organic anion transporter; MATE=

Mechanism	Management suggestion	Level of interaction	Ref.
Inhibition of CYP3A4 Inhibition of CYP3A4 Inhibition of CYP1A2 Inhibition of CYP3A4	Monitor side effects and if necessary, adjusted the dose of substrate.	3	162-166
Inhibition of CYP3A4	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	167
Inhibition of CYP3A4 Inhibition of CYP3A4 and/ P-gp	Avoid combination or adjusted dose of substrates & perform TDM.	1	168, 169, 181, 182
Inhibition of CYP3A4 or P-gp	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	170
Inhibition of CYP3A4	Monitor side effects and if necessary, adjusted the dose of substrate.	3	171, 172
Inhibition of CYP3A4	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	173, 174
Inhibition of CYP3A4 & P-gp	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	175, 176
Inhibition of CYP3A4	Avoid combination or adjusted dose of substrates & closely monitoring side effects.	1	178
Probably by CYP3A4 inhibition	Avoid combination or perform TDM and adjust the dose if needed.	1	177
Inhibition of CYP1A2	Avoid combination or perform TDM and adjust the dose if needed.	1	183
Inhibition of CYP2C8	Consider alternative/adjusted dose of substrate or used cautiously by monitoring side effects.	2	186
Complex-forming	Avoid co-administration or administration interval of at least 2 hours or more	2	212-220
Complex-forming	Avoid co-administration or administration interval of at least 2 h or more	2	144, 188, 189
Complex-forming	Administration interval of at least 2 h or more	3	139, 190-193
Inhibition of P-gp	Consider alternative or perform TDM and adjust the dose if needed.	2	196
Inhibition of CYP2C8	Monitor side effects and if necessary, adjusted the dose of substrate.	3	187
NA	Consider alternative or adjusted the dose of penicillin.	3	221

multidrug and toxin extrusion 1; P-gp: P-glycoprotein; TMP-SMX= Trimethoprim and Sulfonamides; TDM = therapeutic drug monitoring; NA = not available yet. All detailed supported information about each DDI were available in Table S1 and S2.

They could markedly reduce the ABs activities of clarithromycin, doxycycline, and trimethoprim–sulfamethoxazole by rapidly elimination.[100-104] Since, rifampicin also exhibits other ABs activities such as treating methicillin-resistant staphylococcus aureus (MRSA) in combination with other drugs, rationalizing antimicrobial therapy should be considered accordingly.[105] Alternative AB for treating COPD is also recommended to reduce the risk of treatment failures.

Moxifloxacin might be an alternative AB as the evidence of moxifloxacin interaction with rifampicin was not consistent with moderate or weak interactions.[106-109] Moxifloxacin is not metabolized by CYP450 and its interacting mechanisms with rifampicin might be facilitated by induction of other enzymes like uridine diphosphate-glucuronosyltransferases and sulfotransferases.[106-109]

Rifabutin and rifampicin are CYP substrates. Rifabutin is a CYP3A4 substrate, and therefore, macrolides may increase its serum concentration and enhance the risk of related ADR.[101,110,111] Another study reported rifampicin concentration in blood is moderately elevated by co-trimoxazole.[104] It was assumed that the interaction was facilitated by inhibition of the mixed function oxidases, which is responsible for metabolizing rifampicin.[104] Thus, considering alternative AB or monitoring the clinical and biochemical parameters for rifampicin related hepatotoxicity is suggested when rifampicin and co-trimoxazole are combined.

What need to be mentioned is that not all the drugs for atypical mycobacterium spp were included in this review due to the selection limitation of ABs that used frequently among COPD patients. For drugs outside the scope of this review, other references (*e.g.* SPCs) need to be considered.

4. Neurological disorders

4.1. Anti-Parkinson drugs

Bromocriptine and cabergoline (dopamine agonists) are substrates of CYP3A4 and/or P-gp transporter.[112,113] Co-prescription of these drugs with clarithromycin and erythromycin may produce major interactions and therefore, might lead to toxicities.[112,113] Thus, avoiding combination is recommended. However, if it is not possible, adjusting the dose of those Parkinson medication and closely monitoring side effects are needed.

4.2. Antiepileptic drugs

Carbamazepine, phenytoin, and phenobarbital could stimulate the activity of a variety of CYP (CYP1A2/2C9/3A4) and glucuronyl transferase enzymes, which results in multiple DDIs with other substrates for these enzymes.[114-116] Carbamazepine and phenytoin were reported to reduce $t_{1/2}$ of doxycycline by stimulating the hepatic metabolism of

doxycycline.[117] It is suggested to consider an alternative AB or to adjust the dose of antiepileptic drugs while monitoring the AB activity of doxycycline.

Moreover, carbamazepine and phenytoin are substrates of CYP1A2/3A4 and CYP2C8, respectively. A CYP1A2/3A4 inhibitor (ciprofloxacin) and a CYP2C8 inhibitor (trimethoprim) were reported to increase the bioavailability of carbamazepine and phenytoin, respectively.[116-119] Moreover, phenytoin is a NTI drug and therefore, avoiding using trimethoprim concomitantly or performing TDM of phenytoin is recommended when this DDI is not avoidable.[120]

Meanwhile, ciprofloxacin was reported to increase AUC of carbamazepine by more than 50%.[118] Although it is not clear whether carbamazepine can be included as a NTI drug, the rise of carbamazepine plasma concentration because of this DDI needs special caution.[121] Dose adjustment and TDM of carbamazepine are suggested to diminish potential toxicities.

5. Depression and psychiatric disorders

Depression and psychiatric disorders are common among COPD patients.[14] Some antidepressant (trazodone), anxiolytic (buspirone), and antipsychotic (quetiapine, and pimozide) drugs are CYP3A4 substrates and therefore, might trigger clinically relevant DDIs with ABs.[122-125] Erythromycin and clarithromycin increased AUCs of these drugs substantially.[122-125] Considering alternative AB or adjusting the dose of substrates and monitoring related side effects is the way to control potential ADR.

CYP3A4 is also responsible for metabolizing diazepam, in addition to CYP2C19.[126] Ciprofloxacin was reported to decrease diazepam clearance moderately by inhibiting CYP3A4 activity.[127] Monitoring diazepam-related side effects can therefore be considered when this combination is prescribed.

Ciprofloxacin is also a potent CYP1A2 inhibitor.[128] Therefore, metabolism of an atypical antipsychotic clozapine, a CYP1A2 substrate with NTI, can be relevantly altered by ciprofloxacin which produces a significant increase of clozapine serum concentration.[129,130] Replacing ciprofloxacin or TDM of clozapine is option that can be chosen in managing this DDI.

6. Dyspepsia

Drugs containing metal cations (*e.g.* antacids, sucralfate and bismuth salts) produced chemical interactions with some ABs like oral tetracyclines (*e.g.* tetracycline, doxycycline) and fluoroquinolones (*e.g.* ciprofloxacin, moxifloxacin).[131-144] Tetracyclines have a high affinity to form chelates due to their structural features with lots of chelation sites.[145]

Meanwhile, fluoroquinolones have two main sites of metal chelation: 4-keto oxygen and 3-carboxylic acid groups.[146]

The formation of metal ion chelation complexes decreased absorption of tetracycline and fluoroquinolones, the reduced bioavailability may lead to ineffectiveness of these ABs.[131-144] Therefore, it is recommended to avoid combination by replacing tetracyclines and fluoroquinolones with another AB, *e.g.* amoxicillin or amoxicillin/clavulanic acid. It was reported that antacids did not affect the bioavailability of amoxicillin and amoxicillin/clavulanic acid when they were co-administered.[136] If replacement of the AB is not possible, substitution of antacids, sucralfate or bismuth salts to PPI is also favored. Another alternative is to separate administration by using quinolone or tetracycline at least 2 hours before and 6 hours after the dyspepsia drugs.

When considering a PPI, lansoprazole may not be the best alternative as it is partly metabolized by CYP3A4 and found to interact with clarithromycin.[147]

7. HIV

HIV-positive patients have about 50% higher risk to develop COPD than HIV-negative patients.[148] Then, the risk of co-prescriptions for treating those chronic conditions is also possibly high. A protease inhibitor (saquinavir) and nucleoside reverse transcriptase inhibitors (didanosine and lamivudine) were found to clinically interact with ABs.[149-153]

Didanosine is very acid sensitive, and therefore, the didanosine formulations are supplemented by buffering mixtures containing magnesium hydroxide, dihydroxyaluminum sodium carbonate, and sodium citrate to prevent hydrolysis by gastric acid.[149] These metal ions may form chelation complexes with quinolones and reduce their serum concentration.[149,150] Two studies confirmed the didanosine and ciprofloxacin interaction, and recommended that when co-administration cannot be avoided, ciprofloxacin must be given at least 2 hours before didanosine.[149,150]

Trimethoprim–sulfamethoxazole may inhibit clearances of didanosine and lamivudine by competitively hinder their renal secretion.[152,153] Consequently, AUCs of didanosine and lamivudine elevate moderately.[152,153] Monitoring of the presumed side effects should be performed.

Saquinafir is metabolized by CYP3A4 and the presence of erythromycin increased its AUC by almost 100%.[151] Choosing an alternative AB or adjusting the dose of saquinafir while monitoring toxicities can be considered to manage this DDI.

8. Other potential clinically significant DDI

Some other drugs that have indications for comorbidities in COPD patients were found to interact with ABs. Some individual drugs of different classes (*e.g.* voriconazole and

vinorelbine) are metabolized by CYP3A4.[154-182] Therefore, their metabolism is interfered by CYP3A4 inhibitors (macrolides).[154-182] Other drugs are CYP1A2 substrates (*e.g.* ropivacaine and tizanidine) and therefore, CYP1A2 potent inhibitors like quinolones significantly alter their metabolism and elevate their bioavailabilities.[164,183-185] Others are CYP2C8 substrates (e.g. loperamid for diarrhea) and therefore, trimethoprim (a CYP2C8 potent inhibitor) inhibits their clearance and increases their AUC values.[186,187] Some drugs containing metal cations (*e.g.* Fe, Zn, Ca) should be avoided or administered separately at least 2 hours or more with quinolones and tetracyclines.[139,144,188-193] Other interactions were facilitated by drug transporters. An uricosuric agent (probenecid) interacts moderately with ciprofloxacin via competitive inhibition of organic anion transporters in renal tubules.[194,195] Meanwhile, linezolid (other AB), which is a substrate of P-gp transporter, can potentially produce clinically significant interaction with P-gp inhibitors (macrolides).[196]

DDI related to NTIs

Some ABs may interact with NTI drugs and therefore, can produce serious ADRs. The NTI drugs in this review includes CYP3A4 substrates (theophylline, ketamine, everolimus, tacrolimus, halofantrine, lignocaine, quinidine, voriconazole, carbamazepine, warfarin, cyclosporine, colchicine, phenprocoumon/acenocoumarol); CYP1A2 substrates (theophylline, carbamazepine, clozapine, tizanidine); CYP2C9 substrates and sensitive to alterations in normal gut flora (warfarin, phenprocoumon/acenocoumarol); a CYP2C8 substrate (phenytoin); substrates of P-gp transporter (digoxin, linezolid); and a substrate of organic cation transporter (procainamide).[76,77,88,120,197]

DISCUSSION

Included articles

This study outlined the possible DDIs related to frequently prescribed ABs in COPD patients from clinical and observational studies. We only included well-designed studies (2 points or higher) since they provide more valid evidence than studies without a control or comparison group (0 or 1 point). DDIs based on case-reports or hypotheses may lead to unnecessary warnings if these are not confirmed by well-designed studies. One classic example at this point is ABs and oral contraceptive interactions; lots of cases reported unintended pregnancies after ABs were prescribed to women on oral contraceptives, which attracted much attention from health practitioners.[198,199] After scientific evidence from clinical and pharmacokinetic studies has consistently and repeatedly failed to support such interaction, the warning about DDIs between hormonal contraception and non-rifampicin ABs were finally canceled by related guidelines.[199]

Mechanisms of DDI

The DDI of potential clinical significance between AB and co-administered medication may occur in two situations: (1) co-administered drug influences the absorption, distribution, metabolism, and elimination (ADME) of AB; and (2) AB influences the ADME of co-administered medication. When AB acted as substrates, some co-administered drugs reduced the blood concentration of AB and led to treatment failure of AB in reducing exacerbations. Other co-administered drugs increased the blood concentration of AB, which could result in the termination of AB use because of an ADR, and therefore acted against the control of infections. As inhibitors, the blood concentrations of co-administered drugs were increased by AB which may also produce an ADR and lead to termination of co-administered drugs, and therefore, may produce a treatment failure of comorbidities. In all, DDIs related to ABs may hinder effective infection control and exacerbation management among COPD patients as well as treatment of comorbidities in COPD.

Comorbidities among COPD patients

The impact of comorbidities on quality of life in COPD patients are well reported, however, potential drug interactions between drugs for these comorbidities and ABs used for COPD has received little specific attention. From this review, we found that many drugs (*e.g.* those used for heart and circulatory system disease) should not be co-administered with related AB and other actions such as dose adjustment, choosing an alternative drug and monitoring ADRs are necessary. These drug interactions could not only influence treatment options of clinical practitioner but also influence treatment effects for both COPD and comorbidities.

Information collected from this review can be used as input to improve the sensitivity and specificity of drug-drug interaction alert systems. Moreover, this study may also be attractive for researchers in this field who may take into account the availability of high-quality studies when evaluating the evidence for many potential interactions.

Special warning for NTI drugs

We found that some NTI drugs might potentially interact with ABs. Because of the narrow separation between effective and toxic dosing of these drugs, small alteration on their pharmacokinetics parameters can produce fatal consequences.[88,120] Therefore, combination of particular AB which have an ability to inhibit their clearance pathways should be avoided if it is possible. However, if the benefits of combination outweigh the potential side effects, dose adjustment and performing TDM of the NTI drugs are strongly recommended.

Limitations

Some limitations to this review are worth to be mentioned. First, although we reviewed a significant part of the literature, we did not include all sources that might indicate relevant DDIs such as case reports, summary of product characteristics or theoretical hypotheses. As a result, we did not find some DDIs that are considered serious and clinically highly relevant, such as QT-interval prolonging interactions for combinations of macrolides with other QT-prolonging drugs or the risk for pseudotumor cerebri in case of combination of doxycycline with vitamin-A analogs.[200,201] Such interactions are commonly found as case reports, as it is unethical to design studies to confirm these serious risks in clinical studies. However for some DDIs, it is possible to study the clinical manifestation of a potential DDI in an observational study using a real world drug utilization data.[202] Secondly, selection of ABs included in this review was based on their frequent use in COPD and therefore, information for other ABs used for COPD comorbidities such as atypical *Mycobacterium spp* is limited and therefore, may restrict the application scope of this review. Thirdly, due to limited comparative analyses for several specific DDIs included in this review, it may be difficult to make recommendations for a specific situation. Our classification of DDIs levels just offers a general consideration. The specific impact of a DDI is decided by many variables like different doses and formulations, the comorbidities of patients, *etc*. Therefore, case-by-case analysis is important in clinical practice and a drug interaction handbook like Stockley's Drug Interactions further expands on these issues.[203]

CONCLUSION

Clinically significant DDIs related to ABs may involve a wide range of indicated drugs to treat comorbidities in COPD. Clinicians should pay attention to these drug interactions when prescribing AB to reduce the frequency and severity of exacerbations in COPD patients and take necessary actions to ensure therapeutic effect and safety of patients. This study may contribute to better prescribing of ABs to COPD patients with comorbidities using potentially interacting combination. Furthermore, the information may be used to point at gaps in scientific knowledge about potential adverse effects from DDIs.

SUPPLEMENTARY DATA

Table S1 to S3 are available as Supplementary data at JAC Online (https://doi.org/10.1093/jac/dkz221)

REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017; 195: 557-82.
2. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012; 379: 1341-51.
3. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355-65.
4. Vollenweider DJ, Jarrett H, Steurer-Stey CA et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 12: CD010257.
5. Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2013; CD009764.
6. Wang Y, Zijp TR, Bahar MA et al. Effects of prophylactic antibiotics on patients with stable COPD: A systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2018; 73: 3231-43.
7. Wedzicha JA, Calverley PMA, Albert RK et al. Prevention of COPD exacerbations: A european respiratory Society/American thoracic society guideline. *Eur Respir J* 2017; 50: 10.1183/13993003.02265,2016. Print 2017 Sep.
8. Chetty U, McLean G, Morrison D et al. Chronic obstructive pulmonary disease and comorbidities: A large cross-sectional study in primary care. *Br J Gen Pract* 2017; 67: e321-8.
9. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *Br J Clin Pharmacol* 2004; 57: 6-14.
10. Bahar MA, Hak E, Bos JH et al. The burden and management of cytochrome P450 2D6 (CYP2D6)-mediated drug–drug interaction (DDI): Co-medication of metoprolol and paroxetine or fluoxetine in the elderly. *Pharmacoepidemiol Drug Saf* 2017; 26: 752-65.
11. van Roon EN, Flikweert S, le Comte M et al. Clinical relevance of drug-drug interactions : A structured assessment procedure. *Drug Saf* 2005; 28: 1131-9.
12. Bahar MA, Setiawan D, Hak E et al. Pharmacogenetics of drug-drug interaction and drug-drug-gene interaction: A systematic review on CYP2C9, CYP2C19 and CYP2D6. *Pharmacogenomics* 2017; 18: 701-39.
13. Zhou S, Chan E, Li X et al. Clinical outcomes and management of mechanism-based inhibition of cytochrome P450 3A4. *Ther Clin Risk Manag* 2005; 1: 3-13.
14. Divo M, Cote C, de Torres JP et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155-61.
15. Mannino DM, Thorn D, Swensen A et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962-9.
16. Schelleman H, Bilker WB, Brensinger CM et al. Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010; 88: 214-22.
17. Lilja JJ, Niemi M, Fredrikson H et al. Effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. *Br J Clin Pharmacol* 2007; 63: 732-40.
18. Tan A, Holmes HM, Kuo YF et al. Coadministration of co-trimoxazole with sulfonylureas: Hypoglycemia events and pattern of use. *J Gerontol A Biol Sci Med Sci* 2015; 70: 247-54.
19. Kradjan WA, Witt DM, Opheim KE et al. Lack of interaction between glipizide and co-trimoxazole. *J Clin Pharmacol* 1994; 34: 997-1002.
20. Jayasagar G, Dixit AA, Kishan V et al. Effect of clarithromycin on the pharmacokinetics of tolbutamide. *Drug Metabol Drug Interact* 2000; 16: 207-15.
21. Wing LM, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: Effects

of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985; 20: 482-5.

22. Niemi M, Neuvonen PJ, Kivisto KT. The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2001; 70: 58-65.
23. Niemi M, Kajosaari LI, Neuvonen M et al. The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004; 57: 441-7.
24. Hruska MW, Amico JA, Langaee TY et al. The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. *Br J Clin Pharmacol* 2005; 59: 70-9.
25. Grun B, Kiessling MK, Burhenne J et al. Trimethoprim-metformin interaction and its genetic modulation by OCT2 and MATE1 transporters. *Br J Clin Pharmacol* 2013; 76: 787-96.
26. Muller F, Pontones CA, Renner B et al. N(1)-methylnicotinamide as an endogenous probe for drug interactions by renal cation transporters: Studies on the metformin-trimethoprim interaction. *Eur J Clin Pharmacol* 2015; 71: 85-94.
27. Wright AJ, Gomes T, Mamdani MM et al. The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ* 2011; 183: 303-7.
28. Gandhi S, Fleet JL, Bailey DG et al. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. *JAMA* 2013; 310: 2544-53.
29. Fraser LA, Shariff SZ, McArthur E et al. Calcium channel blocker-clarithromycin drug interaction did not increase the risk of nonvertebral fracture: A population-based study. *Ann Pharmacother* 2015; 49: 185-8.
30. Westphal JF. Macrolide–induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: An update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; 50: 285-95.
31. Yamazaki H, Shimada T. Comparative studies of in vitro inhibition of cytochrome P450 3A4-dependent testosterone 6beta-hydroxylation by roxithromycin and its metabolites, troleandomycin, and erythromycin. *Drug Metab Dispos* 1998; 26: 1053-7.
32. Antoniou T, Hollands S, Macdonald EM et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. *CMAJ* 2015; 187: E138-43.
33. Parhofer KG. The treatment of disorders of lipid metabolism. *Dtsch Arztebl Int* 2016; 113: 261-8.
34. Kantola T, Kivisto KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; 64: 177-82.
35. Amsden GW, Kuye O, Wei GC. A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002; 42: 444-9.
36. Li DQ, Kim R, McArthur E et al. Risk of adverse events among older adults following co-prescription of clarithromycin and statins not metabolized by cytochrome P450 3A4. *CMAJ* 2015; 187: 174-80.
37. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol* 2009; 158: 693-705.
38. Seithel A, Eberl S, Singer K et al. The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. *Drug Metab Dispos* 2007; 35: 779-86.
39. Glasheen JJ, Fugit RV, Prochazka AV. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. *J Gen Intern Med* 2005; 20: 653-6.
40. Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. *Am J Med* 2014; 127: 657.
41. Ghaswalla PK, Harpe SE, Tassone D et al. Warfarin-antibiotic interactions in older adults of an outpatient anticoagulation clinic. *Am J Geriatr Pharmacother* 2012; 10: 352-60.

42. Mergenhagen KA, Olbrych PM, Mattappallil A et al. Effect of azithromycin on anticoagulation-related outcomes in geriatric patients receiving warfarin. *Clin Ther* 2013; 35: 425-30.

43. McCall KL, Anderson HG,Jr., Jones AD. Determination of the lack of a drug interaction between azithromycin and warfarin. *Pharmacotherapy* 2004; 24: 188-94.

44. Fischer HD, Juurlink DN, Mamdani MM et al. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: A population-based study. *Arch Intern Med* 2010; 170: 617-21.

45. Washington C, Hou SY, Hughes NC et al. Ciprofloxacin prolonged-release tablets do not affect warfarin pharmacokinetics and pharmacodynamics. *J Clin Pharmacol* 2007; 47: 1320-6.

46. Israel DS, Stotka J, Rock W et al. Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. *Clin Infect Dis* 1996; 22: 251-6.

47. Bianco TM, Bussey HI, Farnett LE et al. Potential warfarin-ciprofloxacin interaction in patients receiving long-term anticoagulation. *Pharmacotherapy* 1992; 12: 435-9.

48. Abdel-Aziz MI, Ali MA, Hassan AK et al. Warfarin-drug interactions: An emphasis on influence of polypharmacy and high doses of amoxicillin/clavulanate. *J Clin Pharmacol* 2016; 56: 39-46.

49. Schelleman H, Bilker WB, Brensinger CM et al. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: Interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther* 2008; 84: 581-8.

50. Baillargeon J, Holmes HM, Lin YL et al. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* 2012; 125: 183-9.

51. O'Reilly RA, Motley CH. Racemic warfarin and trimethoprim-sulfamethoxazole interaction in humans. *Ann Intern Med* 1979; 91: 34-6.

52. Mercadal Orfila G, Gracia Garcia B, Leiva Badosa E et al. Retrospective assessment of potential interaction between levofloxacin and warfarin. *Pharm World Sci* 2009; 31: 224-9.

53. Liao S, Palmer M, Fowler C et al. Absence of an effect of levofloxacin on warfarin pharmacokinetics and anticoagulation in male volunteers. *J Clin Pharmacol* 1996; 36: 1072-7.

54. Stroud LF, Mamdami MM, Kopp A et al. The safety of levofloxacin in elderly patients on warfarin. *Am J Med* 2005; 118: 1417.

55. Penning-van Beest, van Meegen E, Rosendaal FR et al. Drug interactions as a cause of overanticoagulation on phenprocoumon or acenocoumarol predominantly concern antibacterial drugs. *Clin Pharmacol Ther* 2001; 69: 451-7.

56. Jobski K, Behr S, Garbe E. Drug interactions with phenprocoumon and the risk of serious haemorrhage: A nested case-control study in a large population-based german database. *Eur J Clin Pharmacol* 2011; 67: 941-51.

57. Abbas S, Ihle P, Harder S et al. Risk of bleeding and antibiotic use in patients receiving continuous phenprocoumon therapy. A case-control study nested in a large insurance- and population-based german cohort. *Thromb Haemost* 2014; 111: 912-22.

58. Penning-van Beest, Koerselman J, Herings RM. Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants. *J Thromb Haemost* 2008; 6: 284-90.

59. Juurlink DN. Drug interactions with warfarin: What clinicians need to know. *CMAJ* 2007; 177: 369-71.

60. Ufer M. Comparative pharmacokinetics of vitamin K antagonists - warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; 44: 1227-46.

61. Thachil J. The newer direct oral anticoagulants: A practical guide. *Clin Med (Lond)* 2014; 14: 165-75.

62. Parasrampuria DA, Mendell J, Shi M et al. Edoxaban drug-drug interactions with ketoconazole, erythromycin, and cyclosporine. *Br J Clin Pharmacol* 2016; 82: 1591-600.

63. Gouin-Thibault I, Delavenne X, Blanchard A et al. Interindividual variability in dabigatran

and rivaroxaban exposure: Contribution of ABCB1 genetic polymorphisms and interaction with clarithromycin. *J Thromb Haemost* 2017; 15: 273-83.

64. Damkier P, Hansen LL, Brosen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999; 48: 829-38.
65. Isohanni MH, Neuvonen PJ, Olkkola KT. Effect of erythromycin and itraconazole on the pharmacokinetics of oral lignocaine. *Pharmacol Toxicol* 1999; 84: 143-6.
66. Kosoglou T, Rocci ML,Jr., Vlasses PH. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988; 44: 467-77.
67. Vlasses PH, Kosoglou T, Chase SL et al. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* 1989; 149: 1350-3.
68. Zapater P, Reus S, Tello A et al. A prospective study of the clarithromycin-digoxin interaction in elderly patients. *J Antimicrob Chemother* 2002; 50: 601-6.
69. Chan AL, Wang MT, Su CY et al. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: A population-based study. *Eur J Clin Pharmacol* 2009; 65: 1237-43.
70. Tanaka H, Matsumoto K, Ueno K et al. Effect of clarithromycin on steady-state digoxin concentrations. *Ann Pharmacother* 2003; 37: 178-81.
71. Rengelshausen J, Goggelmann C, Burhenne J et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. *Br J Clin Pharmacol* 2003; 56: 32-8.
72. Petersen P, Kastrup J, Bartram R et al. Digoxin-trimethoprim interaction. *Acta Med Scand* 1985; 217: 423-7.
73. Bauer LA, Black DJ, Lill JS et al. Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* 2005; 49: 1649-51.
74. Martin DE, Shen J, Griener J et al. Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* 1996; 36: 85-91.
75. Ujhelyi MR, Bottorff MB, Schur M et al. Aging effects on the organic base transporter and stereoselective renal clearance. *Clin Pharmacol Ther* 1997; 62: 117-28.
76. Raebel MA, Carroll NM, Andrade SE et al. Monitoring of drugs with a narrow therapeutic range in ambulatory care. *Am J Manag Care* 2006; 12: 268-75.
77. Campbell T, Williams K. Therapeutic drug monitoring: Antiarrhythmic drugs. *Br J Clin Pharmacol* 2001; 52: 21-33.
78. Fost DA, Leung DY, Martin RJ et al. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol* 1999; 103: 1031-5.
79. Hegazy SK, Mabrouk MM, Elsisi AE et al. Effect of clarithromycin and fluconazole on the pharmacokinetics of montelukast in human volunteers. *Eur J Clin Pharmacol* 2012; 68: 1275-80.
80. Branigan TA, Robbins RA, Cady WJ et al. The effects of erythromycin on the absorption and disposition of kinetics of theophylline. *Eur J Clin Pharmacol* 1981; 21: 115-20.
81. Reisz G, Pingleton SK, Melethil S et al. The effect of erythromycin on theophylline pharmacokinetics in chronic bronchitis. *Am Rev Respir Dis* 1983; 127: 581-4.
82. Prince RA, Wing DS, Weinberger MM et al. Effect of erythromycin on theophylline kinetics. *J Allergy Clin Immunol* 1981; 68: 427-31.
83. May DC, Jarboe CH, Ellenburg DT et al. The effects of erythromycin on theophylline elimination in normal males. *J Clin Pharmacol* 1982; 22: 125-30.
84. Maddux MS, Leeds NH, Organek HW et al. The effect of erythromycin on theophylline pharmacokinetics at steady state. *Chest* 1982; 81: 563-5.
85. Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. *Clin Pharmacol Ther* 1979; 26: 36-40.

86. Carr RA, Edmonds A, Shi H et al. Steady-state pharmacokinetics and electrocardiographic pharmacodynamics of clarithromycin and loratadine after individual or concomitant administration. *Antimicrob Agents Chemother* 1998; 42: 1176-80.

87. Brannan MD, Reidenberg P, Radwanski E et al. Loratadine administered concomitantly with erythromycin: Pharmacokinetic and electrocardiographic evaluations. *Clin Pharmacol Ther* 1995; 58: 269-78.

88. Blix HS, Viktil KK, Moger TA et al. Drugs with narrow therapeutic index as indicators in the risk management of hospitalised patients. *Pharm Pract (Granada)* 2010; 8: 50-5.

89. Ha HR, Chen J, Freiburghaus A et al. Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; 39: 321-6.

90. Nix DE, DeVito JM, Whitbread MA et al. Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. *J Antimicrob Chemother* 1987; 19: 263-9.

91. Wijnands WJ, Vree TB, van Herwaarden CL. The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986; 22: 677-83.

92. Loi CM, Parker BM, Cusack BJ et al. Individual and combined effects of cimetidine and ciprofloxacin on theophylline metabolism in male nonsmokers. *Br J Clin Pharmacol* 1993; 36: 195-200.

93. Robson RA, Begg EJ, Atkinson HC et al. Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. *Br J Clin Pharmacol* 1990; 29: 491-3.

94. Prince RA, Casabar E, Adair CG et al. Effect of quinolone antimicrobials on theophylline pharmacokinetics. *J Clin Pharmacol* 1989; 29: 650-4.

95. Raoof S, Wollschlager C, Khan FA. Ciprofloxacin increases serum levels of theophylline. *Am J Med* 1987; 82: 115-8.

96. Antoniou T, Gomes T, Mamdani MM et al. Ciprofloxacin-induced theophylline toxicity: A population-based study. *Eur J Clin Pharmacol* 2011; 67: 521-6.

97. Batty KT, Davis TM, Ilett KF et al. The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 1995; 39: 305-11.

98. Inghammar M, Ekbom A, Engström G et al. COPD and the risk of tuberculosis-a population-based cohort study. *PloS One* 2010; 5: e10138.

99. Baciewicz AM, Chrisman CR, Finch CK et al. Update on rifampin, rifabutin, and rifapentine drug interactions. *Curr Med Res Opin* 2013; 29: 1-12.

100. Wallace Jr RJ, Brown BA, Griffith DE et al. Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for mycobacterium avium-M. intracellulare infection. *J Infect Dis* 1995; 171: 747-50.

101. Hafner R, Bethel J, Power M et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998; 42: 631-9.

102. Colmenero JD, Fernandez-Gallardo LC, Agundez JA et al. Possible implications of doxycycline-rifampin interaction for treatment of brucellosis. *Antimicrob Agents Chemother* 1994; 38: 2798-802.

103. Winter HR, Trapnell CB, Slattery JT et al. The effect of clarithromycin, fluconazole, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). *Clin Pharmacol Ther* 2004; 76: 313-22.

104. Bhatia RS, Uppal R, Malhi R et al. Drug-interaction between rifampicin and cotrimoxazole in patients with tuberculosis. *Hum Exp Toxicol* 1991; 10: 419-21.

105. Garske L, Kidd T, Gan R et al. Rifampicin and sodium fusidate reduces the frequency of methicillin-resistant staphylococcus aureus (MRSA) isolation in adults with cystic fibrosis and chronic MRSA infection. *J Hosp Infect* 2004; 56: 208-14.

106. Weiner M, Burman W, Luo CC et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother* 2007; 51: 2861-6.

107. Nijland HM, Ruslami R, Suroto AJ et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007; 45: 1001-7.

108. Manika K, Chatzika K, Papaioannou M et al. Rifampicin-moxifloxacin interaction in tuberculosis treatment: A real-life study. *Int J Tuberc Lung Dis* 2015; 19: 1383-7.

109. Naidoo A, Chirehwa M, McIlleron H et al. Effect of rifampicin and efavirenz on moxifloxacin concentrations when co-administered in patients with drug-susceptible TB. *Antimicrob Chemother* 2017; 72: 1441-9.

110. Apseloff G, Foulds G, LaBoy-Goral L et al. Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *Eur Respir J* 1998; 38: 830-5.

111. Jordan MK, Polis MA, Kelly G et al. Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *J Clin Pharmacol* 2000; 44: 2170-2.

112. Nelson MV, Berchou RC, Kareti D et al. Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* 1990; 47: 694-7.

113. Nakatsuka A, Nagai M, Yabe H et al. Effect of clarithromycin on the pharmacokinetics of cabergoline in healthy controls and in patients with parkinson's disease. *J Pharmacol Sci* 2006; 100: 59-64.

114. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol* 2006; 61: 246-55.

115. Neuvonen PJ, Penttila O. Interaction between doxycycline and barbiturates. *Br Med J* 1974; 1: 535-6.

116. Hansen JM, Kampmann JP, Siersbaek-Nielsen K et al. The effect of different sulfonamides on phenytoin metabolism in man. *Acta Med Scand Suppl* 1979; 624: 106-10.

117. Penttila O, Neuvonen PJ, Aho K et al. Interaction between doxycycline and some antiepileptic drugs. *Br Med J* 1974; 2: 470-2.

118. Shahzadi A, Javed I, Aslam B et al. Therapeutic effects of ciprofloxacin on the pharmacokinetics of carbamazepine in healthy adult male volunteers. *Pak J Pharm Sci* 2011; 24: 63-8.

119. Antoniou T, Gomes T, Mamdani MM et al. Trimethoprim/sulfamethoxazole-induced phenytoin toxicity in the elderly: A population-based study. *Br J Clin Pharmacol* 2011; 71: 544-9.

120. Greenberg RG, Melloni C, Wu H et al. Therapeutic index estimation of antiepileptic drugs: A systematic literature review approach. *Clin Neuropharmacol* 2016; 39: 232-40.

121. Bialer M, Rene'H L, Perucca E. Does carbamazepine have a narrow therapeutic plasma concentration range? *Ther Drug Monit* 1998; 20: 56-9.

122. Li KY, Li X, Cheng ZN et al. Effect of erythromycin on metabolism of quetiapine in chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005; 60: 791-5.

123. Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; 65: 10-20.

124. Farkas D, Volak LP, Harmatz JS et al. Short-term clarithromycin administration impairs clearance and enhances pharmacodynamic effects of trazodone but not of zolpidem. *Clin Pharmacol Ther* 2009; 85: 644-50.

125. Kivisto KT, Lamberg TS, Kantola T et al. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; 62: 348-54.

126. Dean L. Diazepam therapy and CYP2C19 genotype. In: Pratt V, McLeod H, Rubinstein W *et al* eds. *Medical Genetics Summaries*. US: National Center for biotechnology information, 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK379740/.

127. Kamali F, Thomas SH, Edwards C. The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* 1993; 44: 365-7.

128. Fuhr U, Anders EM, Mahr G et al. Inhibitory potency of quinolone antibacterial agents against cytochrome P450IA2 activity in vivo and in vitro. *Antimicrob Agents Chemother* 1992; 36: 942-8.

129. Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: A study in patients with schizophrenia. *Eur J Clin Pharmacol* 2000; 56: 585-9.

130. Meyer JM, Proctor G, Cummings MA et al. Ciprofloxacin and clozapine: A potentially fatal but underappreciated interaction. *Case Rep Psychiatry* 2016; 2016: .

131. Nix DE, Wilton JH, Ronald B et al. Inhibition of norfloxacin absorption by antacids. *Antimicrob Agents Chemother* 1990; 34: 432-5.

132. Garty M, Hurwitz A. Effect of cimetidine and antacids on gastrointestinal absorption of tetracycline. *Clin Pharmacol Ther* 1980; 28: 203-7.

133. Van Slooten AD, Nix DE, Wilton JH et al. Combined use of ciprofloxacin and sucralfate. *DICP* 1991; 25: 578-82.

134. Parpia SH, Nix DE, Hejmanowski LG et al. Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob Agents Chemother* 1989; 33: 99-102.

135. Lehto P, Kivisto KT. Effect of sucralfate on absorption of norfloxacin and ofloxacin. *Antimicrob Agents Chemother* 1994; 38: 248-51.

136. Deppermann KM, Lode H, Hoffken G et al. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* 1989; 33: 1901-7.

137. Nix DE, Watson WA, Lener ME et al. Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. *Clin Pharmacol Ther* 1989; 46: 700-5.

138. Stass H, Bottcher MF, Ochmann K. Evaluation of the influence of antacids and H2 antagonists on the absorption of moxifloxacin after oral administration of a 400mg dose to healthy volunteers. *Clin Pharmacokinet* 2001; 40 Suppl 1: 39-48.

139. Frost RW, Lasseter KC, Noe AJ et al. Effects of aluminum hydroxide and calcium carbonate antacids on the bioavailability of ciprofloxacin. *Antimicrob Agents Chemother* 1992; 36: 830-2.

140. Motoya T, Shimozono T, Yamaguchi T et al. Effects of milk and aluminum hydroxide on the absorption of norfloxacin, ciprofloxacin and tosufloxacin in healthy volunteers. *J Appl Ther* 1997; 1: 213-7.

141. Nguyen VX, Nix DE, Gillikin S et al. Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. *Antimicrob Agents Chemother* 1989; 33: 434-6.

142. Nix DE, Watson WA, Handy L et al. The effect of sucralfate pretreatment on the pharmacokinetics of ciprofloxacin. *Pharmacotherapy* 1989; 9: 377-80.

143. Albert KS, Welch RD, DeSante KA et al. Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrheal mixture. *J Pharm Sci* 1979; 68: 586-8.

144. Mapp RK, McCarthy TJ. The effect of zinc sulphate and of bicitropeptide on tetracycline absorption. *S Afr Med J* 1976; 50: 1829-30.

145. Chopra I, Roberts M. Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol Mol Biol Rev* 2001; 65: 232,60 ; second page, table of contents.

146. Kamberi M, Nakashima H, Ogawa K et al. The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. *Br J Clin Pharmacol* 2000; 49: 98-103.

147. Miura M, Tada H, Yasui-Furukori N et al. Effect of clarithromycin on the enantioselective disposition of lansoprazole in relation to CYP2C19 genotypes. *Chirality* 2005; 17: 338-44.

148. Crothers K, Butt AA, Gibert CL et al. Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* 2006; 130: 1326-33.

149. Sahai J, Gallicano K, Oliveras L et al. Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* 1993; 53: 292-7.

150. Knupp CA, Barbhaiya RH. A multiple-dose pharmacokinetic interaction study between didanosine (videx) and ciprofloxacin (cipro) in male subjects seropositive for HIV but asymptomatic. *Biopharm Drug Dispos* 1997; 18: 65-77.

151. Grub S, Bryson H, Goggin T et al. The interaction of saquinavir (soft gelatin capsule) with ketoconazole, erythromycin and rifampicin: Comparison of the effect in healthy volunteers and in HIV-infected patients. *Eur J Clin Pharmacol* 2001; 57: 115-21.

152. Srinivas NR, Knupp CA, Batteiger B et al. A pharmacokinetic interaction study of didanosine coadministered with trimethoprim and/or sulphamethoxazole in HIV seropositive asymptomatic male patients. *Br J Clin Pharmacol* 1996; 41: 207-15.

153. Moore KH, Yuen GJ, Raasch RH et al. Pharmacokinetics of lamivudine administered alone and with trimethoprim-sulfamethoxazole. *Clin Pharmacol Ther* 1996; 59: 550-8.

154. Shi HY, Yan J, Zhu WH et al. Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. *Eur J Clin Pharmacol* 2010; 66: 1131-6.

155. Sriwiriyajan S, Samaeng M, Ridtitid W et al. Pharmacokinetic interactions between ciprofloxacin and itraconazole in healthy male volunteers. *Biopharm Drug Dispos* 2011; 32: 168-74.

156. Olkkola KT, Aranko K, Luurila H et al. A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; 53: 298-305.

157. Yeates RA, Laufen H, Zimmermann T. Interaction between midazolam and clarithromycin: Comparison with azithromycin. *Int J Clin Pharmacol Ther* 1996; 34: 400-5.

158. Quinney SK, Haehner BD, Rhoades MB et al. Interaction between midazolam and clarithromycin in the elderly. *Br J Clin Pharmacol* 2008; 65: 98-109.

159. Zimmermann T, Yeates RA, Laufen H et al. Influence of the antibiotics erythromycin and azithromycin on the pharmacokinetics and pharmacodynamics of midazolam. *Arzneimittelforschung* 1996; 46: 213-7.

160. Mattila MJ, Vanakoski J, Idanpaan-Heikkila JJ. Azithromycin does not alter the effects of oral midazolam on human performance. *Eur J Clin Pharmacol* 1994; 47: 49-52.

161. Hagelberg NM, Peltoniemi MA, Saari TI et al. Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral S-ketamine. *Eur J Pain* 2010; 14: 625-9.

162. Backman JT, Aranko K, Himberg JJ et al. A pharmacokinetic interaction between roxithromycin and midazolam. *Eur J Clin Pharmacol* 1994; 46: 551-5.

163. Bartkowski RR, Goldberg ME, Larijani GE et al. Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; 46: 99-102.

164. Jokinen MJ, Olkkola KT, Ahonen J et al. Effect of ciprofloxacin on the pharmacokinetics of ropivacaine. *Eur J Clin Pharmacol* 2003; 58: 653-7.

165. Jokinen MJ, Ahonen J, Neuvonen PJ et al. Effect of clarithromycin and itraconazole on the pharmacokinetics of ropivacaine. *Pharmacol Toxicol* 2001; 88: 187-91.

166. Jokinen MJ, Ahonen J, Neuvonen PJ et al. The effect of erythromycin, fluvoxamine, and their combination on the pharmacokinetics of ropivacaine. *Anesth Analg* 2000; 91: 1207-12.

167. Liukas A, Hagelberg NM, Kuusniemi K et al. Inhibition of cytochrome P450 3A by clarithromycin uniformly affects the pharmacokinetics and pharmacodynamics of oxycodone in young and elderly volunteers. *J Clin Psychopharmacol* 2011; 31: 302-8.

168. Gupta SK, Bakran A, Johnson RW et al. Cyclosporin-erythromycin interaction in renal transplant patients. *Br J Clin Pharmacol* 1989; 27: 475-81.

169. Freeman DJ, Martell R, Carruthers SG et al. Cyclosporin-erythromycin interaction in normal subjects. *Br J Clin Pharmacol* 1987; 23: 776-8.

170. Federico S, Carrano R, Capone D et al. Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients - ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; 45: 169-75.

171. Wrishko RE, Levine M, Primmett DR et al. Investigation of a possible interaction between ciprofloxacin and cyclosporine in renal transplant patients. *Transplantation* 1997; 64: 996-9.

172. Tan KK, Trull AK, Shawket S. Co-administration of ciprofloxacin and cyclosporin: Lack of evidence for a pharmacokinetic interaction. *Br J Clin Pharmacol* 1989; 28: 185-7.

173. Hedaya MA, El-Afify DR, El-Maghraby GM. The effect of ciprofloxacin and clarithromycin on sildenafil oral bioavailability in human volunteers. *Biopharm Drug Dispos* 2006; 27: 103-10.

174. Muirhead GJ, Faulkner S, Harness JA et al. The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. *Br J Clin Pharmacol* 2002; 53 Suppl 1: 37S-43S.

175. Shinde DD, Kim HS, Choi JS et al. Different effects of clopidogrel and clarithromycin on the enantioselective pharmacokinetics of sibutramine and its active metabolites in healthy subjects. *J Clin Pharmacol* 2013; 53: 550-8.

176. Pan W, Bae SK, Shim EJ et al. Effects of clopidogrel and clarithromycin on the disposition of sibutramine and its active metabolites M1 and M2 in relation to CYP2B6*6 polymorphism. *Xenobiotica* 2013; 43: 211-8.

177. Bassi PU, Onyeji CO, Ukponmwan OE. Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers. *Br J Clin Pharmacol* 2004; 58: 52-5.

178. Pohl O, Osterloh I, Gotteland JP. Effects of erythromycin at steady-state concentrations on the pharmacokinetics of ulipristal acetate. *J Clin Pharm Ther* 2013; 38: 512-7.

179. Yano R, Tani D, Watanabe K et al. Evaluation of potential interaction between vinorelbine and clarithromycin. *Ann Pharmacother* 2009; 43: 453-8.

180. Terkeltaub RA, Furst DE, Digiacinto JL et al. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum* 2011; 63: 2226-37.

181. Kovarik JM, Beyer D, Bizot MN et al. Effect of multiple-dose erythromycin on everolimus pharmacokinetics. *Eur J Clin Pharmacol* 2005; 61: 35-8.

182. Kovarik JM, Hsu CH, McMahon L et al. Population pharmacokinetics of everolimus in de novo renal transplant patients: Impact of ethnicity and comedications. *Clin Pharmacol Ther* 2001; 70: 247-54.

183. Granfors MT, Backman JT, Neuvonen M et al. Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* 2004; 76: 598-606.

184. Tan KK, Allwood MC, Shawket S. Effect of ciprofloxacin on the pharmacokinetics of antipyrine in healthy volunteers. *J Clin Pharm Ther* 1990; 15: 151-4.

185. Ludwig E, Szekely E, Csiba A et al. The effect of ciprofloxacin on antipyrine metabolism. *J Antimicrob Chemother* 1988; 22: 61-7.

186. Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* 1996; 41: 125-8.

187. Lee BL, Medina I, Benowitz NL et al. Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). evidence of drug interactions. *Ann Intern Med* 1989; 110: 606-11.

188. Piccolo ML, Toossi Z, Goldman M. Effect of coadministration of a nutritional

supplement on ciprofloxacin absorption. *Am J Hosp Pharm* 1994; 51: 2697-9.

189. Penttila O, Hurme H, Neuvonen PJ. Effect of zinc sulphate on the absorption of tetracycline and doxycycline in man. *Eur J Clin Pharmacol* 1975; 9: 131-4.
190. Kays MB, Overholser BR, Mueller BA et al. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis* 2003; 42: 1253-9.
191. Kato R, Ueno K, Imano H et al. Impairment of ciprofloxacin absorption by calcium polycarbophil. *J Clin Pharmacol* 2002; 42: 806-11.
192. Lesko LJ, Offman E, Brew CT et al. Evaluation of the potential for drug interactions with patiromer in healthy volunteers. *J Cardiovasc Pharmacol Ther* 2017; 22: 434-46.
193. How PP, Fischer JH, Arruda JA et al. Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clin J Am Soc Nephrol* 2007; 2: 1235-40.
194. Landersdorfer CB, Kirkpatrick CM, Kinzig M et al. Competitive inhibition of renal tubular secretion of ciprofloxacin and metabolite by probenecid. *Br J Clin Pharmacol* 2010; 69: 167-78.
195. Jaehde U, Sorgel F, Reiter A et al. Effect of probenecid on the distribution and elimination of ciprofloxacin in humans. *Clin Pharmacol Ther* 1995; 58: 532-41.
196. Bolhuis MS, van Altena R, van Soolingen D et al. Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients. *Eur Respir J* 2013; 42: 1614-21.
197. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol* 2000; 49: 303-12.
198. Dickinson BD, Altman RD, Nielsen NH et al. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; 98: 853-60.
199. Taylor J, Pemberton MN. Antibiotics and oral contraceptives: New considerations for dental practice. *Br Dent J* 2012; 212: 481-3.
200. Albert RK, Schuller JL, Network CCR. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit* 2014; 189: 1173-80.
201. Tabibian JH, Gutierrez MA. Doxycycline-induced pseudotumor cerebri. *South Med J* 2009; 102: 310-1.
202. Berger FA, Monadian N, Groot N et al. QTc prolongation during ciprofloxacin and fluconazole combination therapy: Prevalence and associated risk factors. *Br J Clin Pharmacol* 2018; 84: 369-78.
203. Baxter K, Preston C. *Stockley's Drug Interactions*. London: Pharmaceutical Press, 2010.
204. Siedlik PH, Olson SC, Yang BB et al. Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol* 1999; 39: 501-4.
205. Ericsson CD, Feldman S, Pickering LK et al. Influence of subsalicylate bismuth on absorption of doxycycline. *JAMA* 1982; 247: 2266-7.
206. Markert C, Schweizer Y, Hellwig R et al. Clarithromycin substantially increases steady-state bosentan exposure in healthy volunteers. *Br J Clin Pharmacol* 2014; 77: 141-8.
207. Markert C, Hellwig R, Burhenne J et al. Interaction of ambrisentan with clarithromycin and its modulation by polymorphic SLCO1B1. *Eur J Clin Pharmacol* 2013; 69: 1785-93.
208. Tokairin T, Fukasawa T, Yasui-Furukori N et al. Inhibition of the metabolism of brotizolam by erythromycin in humans: In vivo evidence for the involvement of CYP3A4 in brotizolam metabolism. *Br J Clin Pharmacol* 2005; 60: 172-5.
209. Phillips JP, Antal EJ, Smith RB. A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol* 1986; 6: 297-9.
210. Aranko K, Luurila H, Backman JT et al. The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; 38: 363-7.
211. Vlase L, Popa A, Neag M et al. Pharmacokinetic interaction between zolpidem and ciprofloxacin in healthy volunteers. *Eur J Drug Metab Pharmacokinet* 2011; 35: 83-7.

212. Polk RE, Healy DP, Sahai J et al. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. *Respir Care* 1989; 33: 1841-4.

213. Kara M, Hasinoff BB, McKay DW et al. Clinical and chemical interactions between iron preparations and ciprofloxacin. *Br J Clin Pharmacol* 1991; 31: 257-61.

214. Lehto P, Kivisto KT, Neuvonen PJ. The effect of ferrous sulphate on the absorption of norfloxacin, ciprofloxacin and ofloxacin. *Br J Clin Pharmacol* 1994; 37: 82-5.

215. Gothoni G, Neuvonen PJ, Mattila M et al. Iron-tetracycline interaction: Effect of time interval between the drugs. *Acta Med Scand* 1972; 191: 409-11.

216. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. effect of food, milk, and iron. *J Am Acad Dermatol* 1985; 12: 308-12.

217. Neuvonen PJ, Penttila O. Effect of oral ferrous sulphate on the half-life of doxycycline in man. *Eur J Clin Pharmacol* 1974; 7: 361-3.

218. Neuvonen PJ, Turakka H. Inhibitory effect of various iron salts on the absorption of tetracycline in man. *Eur J Clin Pharmacol* 1974; 7: 357-60.

219. Venho VM, Salonen RO, Mattila MJ. Modification of the pharmacokinetics of doxycycline in man by ferrous sulphate or charcoal. *Eur J Clin Pharmacol* 1978; 14: 277-80.

220. Stass H, Kubitza D. Effects of iron supplements on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone, in humans. *Clin Pharmacokinet* 2001; 40 Suppl 1: 57-62.

221. Cheng SH, White A. Effect of orally administered neomycin on the absorption of penicillin V. *N Engl J Med* 1962; 267: 1296-7.

PART II

Neuropsychiatric safety of varenicline use for smoking cessation and the application of prescription sequence symmetry analysis in drug safety evaluation