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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

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

Objectives: (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 8 February 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 levels 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: (i) co-administered drugs altering the pharmacokinetics of ABs; and (ii) ABs interfering with the pharmacokinetics of co-administered drugs. The DDIs could lead to therapeutic failures or toxicities.

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

Introduction

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, such as increased cough, dyspnoea and production of sputum.[2] Exacerbations of COPD can be triggered by respiratory tract infections; 40%–60% of exacerbations are caused by bacteria, especially *Haemophilus influenzae, Streptococcus pneumoniae* and

Moraxella catarrhalis.[3] Evidence from randomized controlled trials 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 interactions between ABs and co-administered drugs. In addition, COPD is an age-related disease and the elderly are more susceptible to the effect of DDIs because of gradual physiological changes affecting pharmacokinetics and pharmacodynamics.[9]

The objectives of this study were to: (i) systematically review DDIs related to frequently prescribed ABs among COPD patients from observational and clinical studies; and (ii) improve AB prescribing safety in clinical practice by structuring DDIs according to comorbidities of COPD. Studies without comparison groups, and therefore with low quality of the causal evidence, such as case reports about QT-interval prolonging interactions, are not included in this review. A DDI handbook such as *Stockley's Drug Interactions* and the official product information should be referred to for the clinical impact of these kinds of interaction.

Methods

Search strategy

We conducted a systematic review following the PRISMA guideline. PubMed and Embase databases were searched for related articles published in English up to 8 February 2018 using key terms 'drug interactions', 'pharmacokinetics' and 'pharmacodynamics', and a list of most frequently used ABs for COPD (Table 1). The ABs were selected based on two related Cochrane reviews and their prescription frequency in the University of Groningen prescription database IADB.nl (http://www.iadb.nl/) covering drug prescriptions for ~700000 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. Full search details are provided in the Supplementary data, available at *JAC* Online.

Study selection criteria

Eligible studies met the following criteria: (i) DDIs in humans; (ii) involving the targeted ABs; and (iii) being clinical trials, randomized controlled trials or cohort or case–control studies. We excluded case reports and other descriptive studies. We further excluded studies with subjects whose pharmacokinetics and pharmacodynamics were not comparable to those of general COPD patients, e.g. newborn babies, pregnant women and patients with severe renal/hepatic impairment. Other exclusion criteria were: (i) unregistered drugs (by FDA or EMA); (ii) involving three or more drug interactions; and (iii) not DDIs (food–drug or gene–drug interactions); (iv) not original studies (reviews, letters and editorials). Pharmacodynamic interactions were beyond the scope of this review and were excluded.

Data extraction and quality assessment

All records were exported to Refworks; titles 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 names of ABs and related interacting drugs, study design, study subjects, sample size, interacting mechanism, effects of interaction and recommendation by study authors were extracted by the same reviewers (Y. W. and A. M. E. J.) and checked by another reviewer (M. A. B.). Quality of evidence was evaluated by grading 0–4 based on criteria (Table 2) used by previous studies.[11,12]

The strengths of the DDIs were classified into four levels (1, strong; 2, substantial; 3, moderate; 4, weak/no) according to preset published criteria (Table 3).[12] In the cases of several studies on the same DDI combination, we categorized the DDI based on the highest level of severity. Considering that drugs with a narrow therapeutic index (NTI) are more vulnerable to DDIs, the strength of the DDI for such drugs was upgraded one level.[12]

Results

Publications identified by literature search

Our search yielded 1412 and 1734 studies from PubMed and Embase, respectively (Figure 1). After removing duplicates, 2560 articles were screened by title and abstract, of which 630 papers were included for full-text screening, resulting in 282 eligible articles. With 36 studies identified from other resources, we finally obtained 318 studies for assessment in this review.

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

Table 1. ABs included in the study that are frequently prescribed among COPD patients[a]

Category	Sub-category	ABs included
β-Lactam	penicillin	amoxicillin/clavulanic acid (co-amoxiclav), amoxicillin, flucloxacillin, pheneticillin, phenoxymethylpenicillin (penicillin V)
	cephalosporin	cefaclor, cefuroxime, ceftriaxone, cefradine, ceftazidime
Macrolide		erythromycin, clarithromycin, azithromycin, roxithromycin, clindamycin
Tetracycline		tetracycline, doxycycline, minocycline
Quinolone	fluoroquinolone	ciprofloxacin, moxifloxacin, levofloxacin, ofloxacin, norfloxacin
	other quinolone	pipemidic acid
Sulphonamide		sulfamethoxazole
Others		nitrofurantoin, methenamine, trimethoprim

[a]Based on two Cochrane reviews[4,5] and use within the University of Groningen (the Netherlands) prescription database, IADB.nl (http://www.iadb.nl/).

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

Definition	Score
Clinical research with appropriate control group and relevant pharmacokinetics and/or pharmacodynamic parameters. The studies meet all of the criteria below: • The interacting effect of concomitant medication with investigated drugs is reported in the manuscript. • All potential confounders are mentioned and taken into account (for example smoking behaviour or renal function). • The results of interaction are based on the steady-state kinetics. • Variation in dose was adjusted.	4
Clinical research with appropriate control group and relevant pharmacokinetics and/or pharmacodynamic parameters that does not meet one or more of the 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 explanatory factors for the adverse reaction), case reports, summary of product characteristics.	1
In vitro studies, *in vivo* animal studies, prediction modelling studies.	0

Table 3. Description of level of DDIs[10]

Definition	AUC	Clearance	Score[a]
Involved inhibitor	>200% ↑	↓ >67%	1
Involved inducer	>90% ↓	↑ ≥900%	1
For observational studies, RR/OR ≥10			1
Involved inhibitor	75%–200% ↑	↓ ≥43% to <67%	2
Involved inducer	60%–90% ↓	↑ ≥150% to <900%	2
For observational studies, RR/OR 3–9			2
Involved inhibitor	25%–75% ↑	↓ ≥20% to <43%	3
Involved inducer	25%–60% ↓	↑ ≥33% to <150%	3
For observational studies, RR/OR 1.5–2.9			3
Involved inducer/inhibitor	<25% change	↓ <20% or ↑ <33%	4
For observational studies, RR/OR <1.5			4
(a) For interacting drugs with an NTI, the degree of DDIs will be improved to the level one higher			exception
(b) If the DDI level cannot be judged by the above criteria, we assessed it by discussion based on available data and evidence			exception

RR, relative risk; OR, odds ratio; ↑, increase; ↓, decrease.
[a]1, strong interaction; 2, substantial interaction; 3, moderate interaction; and 4, weak/no interaction.

We present a step-by-step approach to AB prescribing in COPD: (i) check whether co-morbidity is present; (ii) a quick overview of the AB and its interacting medication, possible interaction mechanism, level of interaction, and practical recommendations is provided in Table 4; and (iii) detailed explanation about related interacting mechanisms and recommendations for the management of related DDIs are provided in the main text.

Mechanisms of DDI

An 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: (i) the co-administered drug alters the pharmacokinetic parameters of the AB; and (ii) the AB influences the pharmacokinetic parameters of the co-administered medication. The main mechanisms of these DDIs are complex formation, inhibition/induction of drug-metabolizing enzymes and alteration of drug transporters (Table 4). The ability to inhibit CYP3A4 makes ABs prone to interaction with many different drugs as CYP3A4 metabolizes >50% of clinically prescribed drugs.[13]

Information structured according to drugs for comorbidities

The presentation of information on potential clinically significant DDIs with a moderate to strong level of interaction is according to the most frequent comorbidities that have been reported in COPD patients.[8,14] Potential mechanisms of DDIs and actionable recommendations to manage the DDIs are provided in Table 4.

Diabetes

Patients with COPD have a 50% higher risk of developing diabetes than persons without COPD.[15] Some antidiabetic drugs are

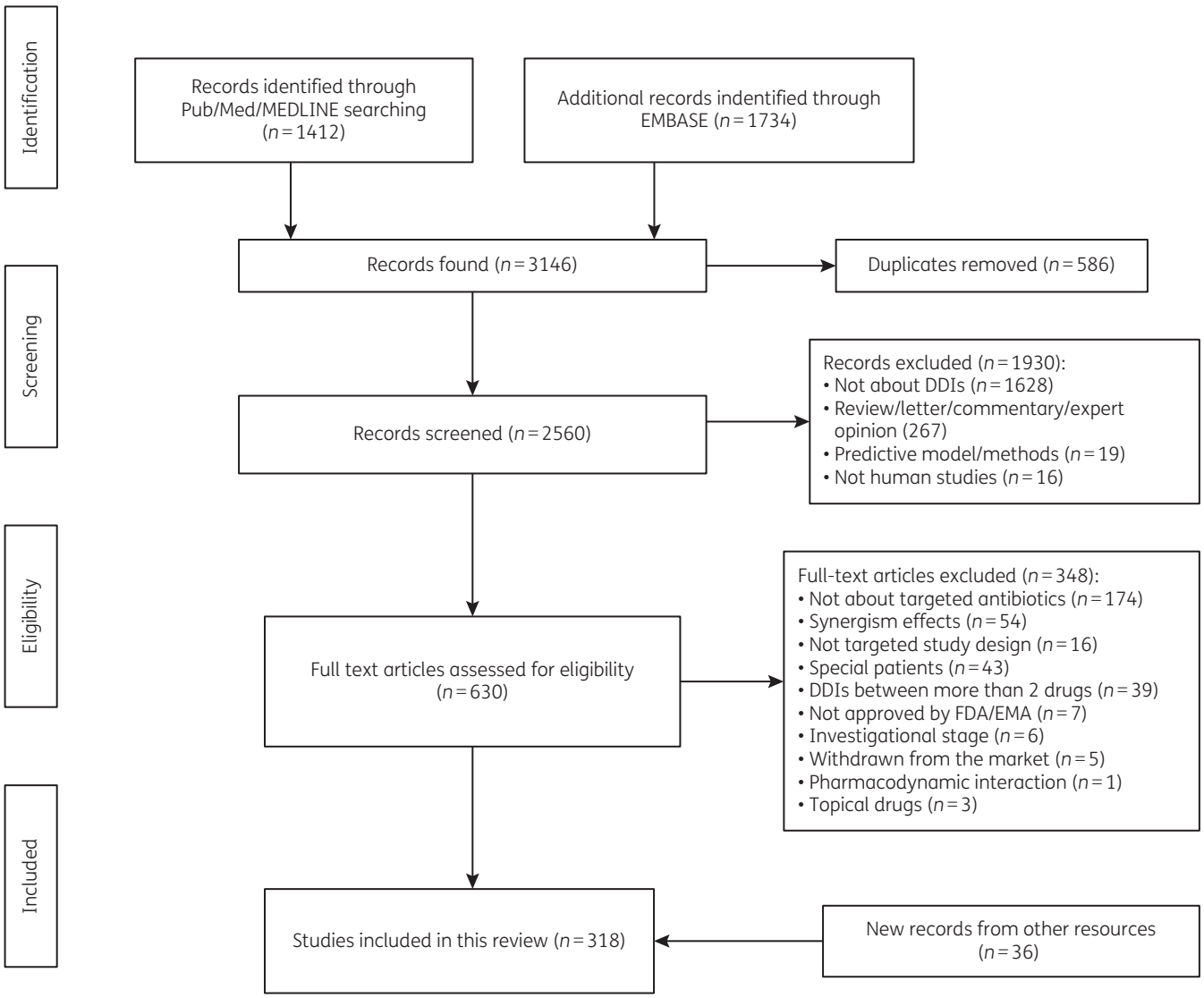

Figure 1. Flow chart of study selection.

substrates of enzymes such as CYP3A4 (glipizide, tolbutamide), CYP2C9 (glipizide, glyburide) and CYP2C8 (repaglinide), and substrates of drug transporter-like P-glycoprotein (P-gp) transporter (glipizide, glyburide).[16–26] ABs such as clarithromycin (CYP3A4 and P-gp inhibitor), trimethoprim/sulfamethoxazole (CYP2C8/2C9 inhibitor) and levofloxacin (P-gp inhibitor) may inhibit the function of these metabolic enzymes and transporters. These ABs can potentially increase the blood concentration of the antidiabetic agents mentioned above.[16–26] Consequently, patients may develop hypoglycaemia. Therefore, it is suggested that these combinations should be avoided by substituting a related AB or adjusting the dose of antidiabetic agents as well as monitoring the patients' blood glucose.

Heart and circulatory system diseases

Antihypertensive agents. Hypertension is associated with COPD with a relative risk of 1.6.[15] Antihypertensive calcium channel blockers (CCBs) such as diltiazem and verapamil are CYP3A4 substrates.[27–29] Therefore, macrolides (CYP3A4 inhibitors) can enhance the pharmacological activity of CCBs.[30] Avoiding the combination by replacement of macrolides or CCBs with another group of drugs or adjusting the dose of CCBs while monitoring 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 CCBs may minimize the risk of DDI.

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

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

Comorbidity	Medication	Interacting AB	Mechanism	Management suggestions	Level of interaction[a]	Reference
Diabetes	glipizide, glyburide	TMP/SMX	Inhibition of CYP2C9.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring patient's blood glucose.	2	16–19
Antidiabetic medication	glyburide	clarithromycin	Inhibition of P-gp.			
	glipizide, glyburide	levofloxacin	Inhibition of P-gp.	Monitor patient's blood glucose and if necessary adjust dose of substrate.	3	16,20–26
	tolbutamide	clarithromycin	Inhibition of CYP3A4 and P-gp.			
		TMP/SMX	Inhibition of CYP2C9.			
	glipizide, repaglinide	clarithromycin	Inhibition of CYP3A4.			
	repaglinide, rosiglitazone	TMP/SMX	Inhibition of CYP2C8.			
	metformin	TMP/SMX	Inhibition of OCT2 and MATE1.			
Heart and circulatory system diseases						
Antihypertensive agents	spironolactone	TMP/SMX	Inhibition of potassium secretion.	Avoid combination or adjust dose of substrates and closely monitor potassium plasma levels.	1	32
	calcium channel blocker	erythromycin, clarithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	27–29
		azithromycin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	27
Lipid-lowering drugs	simvastatin	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	34
	atorvastatin	clarithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	35
		erythromycin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	36,204
	rosuvastatin/pravastatin/fluvastatin	clarithromycin	Inhibition of OAT.			
Oral anticoagulants	warfarin, phenprocoumon/acenocoumarol	TMP/SMX	Inhibition of CYP2C9.	Avoid combination or closely monitor the change of INR routinely and adjust dose if needed.	1	39–58
		amoxicillin/co-amoxiclav, ceftriaxone	Alterations in normal gut flora.	Choose alternative AB or, if not possible, monitor the change of INR routinely.	2	
		clarithromycin, azithromycin, ciprofloxacin, levofloxacin, ofloxacin, doxycycline	Inhibition of CYP3A4 or alterations in normal gut flora.			
	edoxaban, dabigatran, rivaroxaban	erythromycin, clarithromycin	Inhibition of CYP3A4 and/or P-gp.	Consider alternative or adjusted dose of substrate or monitor signs of excessive anticoagulant effect.	2	62,63
	warfarin	moxifloxacin	Inhibition of CYP3A4 or alterations in normal gut flora.	Monitor the change of INR routinely.	3	41

Antiarrhythmic agents	digoxin	clarithromycin	Inhibition of P-gp.	Avoid combination or perform TDM and if necessary adjust dose of substrate.	1	68–71
	quinidine, lignocaine	erythromycin	Inhibition of CYP3A4.	Consider alternative or perform TDM and if necessary adjust dose of substrate.	2	64–67
	procainamide	TMP	Inhibition of tubular secretion.			
	pindolol, digoxin	TMP/SMX	Inhibition of tubular secretion.	Perform TDM and if necessary adjust dose of substrate.	3	72–75
	procainamide	levofloxacin, ofloxacin	Inhibition of OCT.			
Respiratory diseases						
Medication for obstructive airways diseases	methylprednisolone, montelukast	clarithromycin	Inhibition of CYP3A4 and P-gp.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects. For theophylline, perform TDM.	2	78–85,90–97
	theophylline	erythromycin	Inhibition of CYP3A4.			
		ciprofloxacin	Inhibition of CYP1A2.			
	loratadine	erythromycin, clarithromycin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	86,87
	roflumilast	erythromycin	Inhibition of CYP3A4.			
Anti-TB drugs	rifabutin	clarithromycin	Inhibition of CYP3A4.	Avoid combination.	1	101,110,111
	rifampicin, rifabutin	clarithromycin	Induction of CYP3A4.	Consider alternative AB for COPD	2	100,101
	rifampicin, rifabutin	TMP/SMX, doxycycline	Induction of CYP3A4/CYP2C9.	Consider alternative AB for COPD or monitor the effectiveness of AB and if necessary adjust dose of AB.	3	102–104,106–109
	rifampicin	TMP/SMX	Inhibition of mixed oxidases.			
		moxifloxacin	Induction of phase II enzymes.			
Neurological disorders						
Anti-Parkinson's agents	bromocriptine	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	112
	cabergoline	clarithromycin	Inhibition of CYP3A4 and P-gp.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	113
Antiepileptic drugs	carbamazepine, phenytoin	doxycycline	Induction of CYP3A4.	Consider alternative or perform TDM.	2	116,117
	carbamazepine	ciprofloxacin	Inhibition of CYP3A4/1A2.	Consider alternative or perform TDM.	2	118
	phenytoin	TMP/SMX	Inhibition of CYP2C8.	Consider alternative or perform TDM.	2	116,119
	phenobarbital	doxycycline	Induction of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	115
Depression and psychiatric disorders						
Antidepressant, anxiolytic and antipsychotic agents	buspirone	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	125
	quetiapine	erythromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects. For clozapine, perform TDM.	2	122–124,129
	pimozide, trazodone	clarithromycin	Inhibition of CYP3A4.			
	clozapine	ciprofloxacin	Inhibition of CYP1A2.			
	diazepam	ciprofloxacin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust the dose of substrate.	3	127
Dyspepsia						
Antidyspepsia medications	aluminium hydroxide, sucralfate	quinolone, tetracyclines	Complex formation.	Avoid combination or administer quinolone at least 2 h before or 6 h after co-agents.	1	131–142
	lansoprazole	clarithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	147

Continued

Table 4. *Continued*

Comorbidity	Medication	Interacting AB	Mechanism	Management suggestions	Level of interaction[a]	Reference
	calcium carbonate	quinolone, tetracyclines	Complex formation.	Avoid co-administration or administer at interval of at least 2 h.	2	131,139
	bismuth subsalicylate	quinolone, tetracyclines	Complex formation.	Administration interval of at least 2 h.	3	143,205
HIV						
Anti-HIV drugs	didanosine	ciprofloxacin	Complex formation.	Avoid combination or administer quinolone at least 2 h before or 6 h after co-agents.	1	149,150
	saquinavir	erythromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	151
	lamivudine, didanosine	TMP/SMX	Inhibition of tubular secretion.	Monitor side effects and if necessary adjust dose of substrate.	3	152,153
Other						
Pulmonary arterial hypertension medications	bosentan	clarithromycin	Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	206
	ambrisentan	clarithromycin	Inhibition of CYP3A4 and P-gp.	Monitor side effects and if necessary adjust dose of substrate.	3	207
Insomnia medications	brotizolam, triazolam, zopiclone	erythromycin	Inhibition of CYP3A4.	Consider an alternative AB or other hypnotic drugs (not a CYP3A4 substrate).	2	208–210
	zolpidem	ciprofloxacin	Inhibition of CYP3A4.	Monitor side effects and if necessary choose alternative AB or other hypnotic drugs (not a CYP3A4 substrate).	3	211
Antifungal agents	voriconazole	erythromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects. For voriconazole, perform TDM and adjust dose if needed.	2	154,155
	itraconazole	ciprofloxacin	Inhibition of CYP3A4.			
Antineoplastic drugs	vinorelbine	clarithromycin	Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	179
Anti-gout drugs	colchicine	clarithromycin	Inhibition of CYP3A4.	Avoid combination or perform TDM and adjust dose if needed.	1	180
		azithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	180
	probenecid	ciprofloxacin	Inhibition of OAT.	Monitor side effects and if necessary adjust dose of substrate.	3	194,195
Anaesthesia drugs	midazolam	clarithromycin, erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	156–160
	ketamine	clarithromycin	Inhibition of CYP3A4.	Consider alternative or perform TDM and adjust dose if needed.	2	161
	alfentanil	erythromycin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	162–166
	ropivacaine	clarithromycin	Inhibition of CYP3A4.			
		ciprofloxacin	Inhibition of CYP1A2.			
	midazolam	roxithromycin	Inhibition of CYP3A4.			

Analgesics	oxycodone	clarithromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	167
Immunosuppressant drugs	cyclosporine	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and perform TDM.	1	168,169,181,182
	everolimus	erythromycin	Inhibition of CYP3A4 and/ P-gp.			
	tacrolimus	levofloxacin	Inhibition of CYP3A4 or P-gp.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	170
	cyclosporine	ciprofloxacin	Inhibition of CYP3A4.	Monitor side effects and, if necessary adjust dose of substrate.	3	171,172
Vasoactive agents	sildenafil	clarithromycin, erythromycin, ciprofloxacin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	173,174
Appetite suppressants	sibutramine	clarithromycin	Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	175,176
Emergency birth control	ulipristal acetate	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	178
Antimalarial agents	halofantrine	tetracycline	Probably by CYP3A4 inhibition.	Avoid combination or perform TDM and adjust dose if needed.	1	177
Muscle relaxants	tizanidine	ciprofloxacin	Inhibition of CYP1A2.	Avoid combination or perform TDM and adjust dose if needed.	1	183
Anti-diarrhoeals	loperamide	TMP/SMX	Inhibition of CYP2C8.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	186
Anaemia medications	iron supplements	quinolone, tetracyclines	Complex formation.	Avoid co-administration or administer at interval of at least 2 h.	2	212–220
Other metal cations	zinc sulfate	quinolone, tetracyclines	Complex formation.	Avoid co-administration or administer at interval of at least 2 h.	2	144,188,189
	calcium acetate, calcium carbonate, calcium polycarbophil, patiromer, lanthanum carbonate, sevelamer	quinolone, tetracyclines	Complex formation.	Administer at interval of at least 2 h.	3	139,190–193
Other ABs	linezolid	clarithromycin	Inhibition of P-gp.	Consider alternative or perform TDM and adjust dose if needed.	2	196
	dapsone	trimethoprim	Inhibition of CYP2C8.	Monitor side effects and if necessary adjust dose of substrate.	3	187
	neomycin	penicillin V	NA	Consider alternative or adjust dose of penicillin.	3	221

All detailed supporting information about each DDI is available in Tables S1 and S2.
OCT, organic cation transporter; OAT, organic anion transporter; MATE1, multidrug and toxin extrusion 1; TMP/SMX, trimethoprim/sulfamethoxazole; NA, not available yet.
[a]1, strong interaction; 2, substantial interaction; 3, moderate interaction; 4, weak or no interaction.

Lipid-lowering drugs. Lipid metabolism problems are among the most prevalent comorbidities in COPD patients.[14] The main pharmacological approach to the management of blood cholesterol levels is statin therapy.[33] Some ABs increase the plasma concentration of statins by several mechanisms. Statins such as simvastatin and atorvastatin are biodegraded by CYP3A4.[34,35] Therefore, potent CYP3A4 inhibitors (erythromycin and clarithromycin) increase the risk of statin-related side effects such as rhabdomyolysis.[34,35] Other statins, such as rosuvastatin, pravastatin and fluvastatin, are not CYP3A4 substrates.[36] However, the hepatic clearance of these statins is facilitated by anion-transporting polypeptides.[37] These influx transporters facilitate the transport 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.

Oral anticoagulants. Both coumarins and direct oral anticoagulants (DOACs) may interact with ABs. Multiple studies reported that DDIs between ABs and coumarins (warfarin, phenprocoumon, acenocoumarol) led to increased risks of haemorrhage.[39–58] Several interaction 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 macrolides) alter coumarin metabolism, which mainly involves CYP2C9 (trimethoprim/sulfamethoxazole) and CYP3A4 (macrolides).[60] Therefore, to choose alternative ABs or, if not possible, to monitor international normalized ratio (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 the P-gp transporter, their AUC values can be increased by ABs such as macrolides.[62,63] Therefore, when macrolides and DOACs are required in combination, careful monitoring of signs of bleeding is needed, and adjusting the dose of DOACs should be done if necessary.

Antiarrhythmic agents. Some antiarrhythmic agents, such as 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] The renal clearance of procainamide and digoxin is inhibited by trimethoprim.[66,67,72,73] The mechanism of interaction is inhibition of tubular secretion via inhibition of the 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 the P-gp transporter.[68–71] Clarithromycin could elevate the AUC of digoxin, which may cause toxicities.[68–71] Since quinidine, lignocaine, digoxin and procainamide are drugs with an NTI, avoiding ABs that can lead to DDIs with these drugs is recommended.[76,77] However, if their co-prescription is necessary, therapeutic drug monitoring (TDM) of these antiarrhythmic agents is strongly recommended.[77]

Respiratory diseases

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, are substrates of CYP3A4 and/or the P-gp transporter and have been shown to interact with macrolides.[78–87] Hence, one might consider other ABs for combination with asthma drugs, or closely monitor patients, especially in the case of theophylline, which is an NTI drug.[88] As theophylline is also metabolized by CYP1A2,[89] ciprofloxacin (a CYP1A2 potent inhibitor) should be avoided.[90–97]

Antimycobacterial agents

Tuberculosis and COPD share comparable risk factors and therefore can co-occur in individuals, particularly elderly patients.[98] Rifampicin and rifabutin (antimycobacterial agents) work as potent inducers of hepatic and intestinal CYP enzymes.[99] They can markedly reduce the activities of clarithromycin, doxycycline and trimethoprim/sulfamethoxazole by causing their rapid elimination.[100–104] Since rifampicin also exhibits other AB properties, such as activity against MRSA in combination with other drugs, rationalizing antimicrobial therapy should be considered accordingly.[105] Alternative ABs for treating COPD are also recommended to reduce the risk of treatment failures.

Moxifloxacin might be an alternative AB for clarithromycin, doxycycline and trimethoprim/sulfamethoxazole owing to its moderate or weak interaction with rifampicin.[106–109] Moxifloxacin is not metabolized by CYP450 and its interacting mechanisms with rifampicin might be facilitated by induction of other enzymes, such as 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 that rifampicin concentrations in blood are moderately elevated by co-trimoxazole.[104] It was assumed that the interaction was facilitated by inhibition of mixed-function oxidases, which are responsible for metabolizing rifampicin.[104] Thus, considering alternative ABs or monitoring the clinical and biochemical parameters for rifampicin-related hepatotoxicity is suggested when rifampicin and co-trimoxazole are combined.

It should be mentioned that not all the drugs for atypical *Mycobacterium* spp. were included in this review because selection was limited to ABs that are used frequently among COPD patients. For drugs outside the scope of this review, other references (e.g. statements of product characteristics) need to be considered.

Neurological disorders

Anti-Parkinson's drugs

Bromocriptine and cabergoline (dopamine agonists) are substrates of CYP3A4 and/or the 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 such combinations is recommended. However,

if this is not possible, adjusting the dose of these Parkinson's medications and closely monitoring side effects are needed.

Antiepileptic drugs

Carbamazepine, phenytoin and phenobarbital can 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 the half-life of doxycycline by stimulating the hepatic metabolism of doxycycline.[117] It is suggested that an alternative AB should be considered or that the dose of antiepileptic drugs should be adjusted while monitoring the AB activity of doxycycline.

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 an NTI drug and therefore avoiding using trimethoprim concomitantly or performing TDM of phenytoin is recommended when this DDI is not avoidable.[120]

Ciprofloxacin was reported to increase the AUC of carbamazepine by >50%.[118] Although it is not clear whether carbamazepine can be considered to be an NTI drug, a rising carbamazepine plasma concentration because of this DDI needs special caution.[121] Dose adjustment and TDM of carbamazepine are suggested to diminish potential toxicities.

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 the AUCs of these drugs substantially.[122–125] Considering alternative ABs 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 an NTI, can be altered by ciprofloxacin, which produces a significant increase in clozapine serum concentration.[129,130] Replacing ciprofloxacin or TDM of clozapine is an option that can be chosen in managing this DDI.

Dyspepsia

Drugs containing metal cations (e.g. antacids, sucralfate and bismuth salts) produced chemical interactions with some ABs, such as oral tetracyclines (e.g. tetracycline, doxycycline) and fluoroquinolones (e.g. ciprofloxacin, moxifloxacin).[131–144] Tetracyclines have a strong tendency to form chelates due to their structural features, which include many 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 decreases absorption of tetracycline and fluoroquinolones, and this reduced bioavailability may lead to ineffectiveness of these ABs.[131–144] Therefore, it is recommended that their combination should be avoided 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, replacement of antacids, sucralfate or bismuth salts with a proton pump inhibitor (PPI) is also favoured. Another alternative is to separate administration by using quinolone or tetracycline at least 2 h before or 6 h after the dyspepsia drugs.

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

HIV

HIV-positive patients have an ∼50% higher risk of developing COPD than HIV-negative patients.[148] Thus, the risk of co-prescriptions for treating these chronic conditions may also be high. A protease inhibitor (saquinavir) and NRTIs (didanosine and lamivudine) were found to clinically interact with ABs.[149–153]

Didanosine is very acid sensitive, and therefore didanosine formulations are supplemented with buffering mixtures containing magnesium hydroxide, dihydroxyaluminium 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 h before didanosine.[149,150]

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

Saquinavir 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 saquinavir while monitoring toxicities can be considered as a means of managing this DDI.

Other potential clinically significant DDIs

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 with by CYP3A4 inhibitors (macrolides).[154–182] Other drugs are CYP1A2 substrates (e.g. ropivacaine and tizanidine) and therefore potent inhibitors of CYP1A2, such as quinolones, significantly alter their metabolism and elevate their bioavailabilities.[164,183–185] Others are CYP2C8 substrates (e.g. loperamide for diarrhoea) and therefore trimethoprim (a potent CYP2C8 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 with a separation of at least 2 h from quinolones and tetracyclines.[139,144,188–193] Other interactions were facilitated by

drug transporters. A uricosuric agent (probenecid) interacts moderately with ciprofloxacin via competitive inhibition of organic anion transporters in renal tubules.[194,195] Moreover, linezolid, which is a substrate of the P-gp transporter, can potentially produce clinically significant interaction with P-gp inhibitors (macrolides).[196]

DDIs related to NTIs

Some ABs may interact with NTI drugs and therefore can produce serious ADRs. The NTI drugs in this review include 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 drugs sensitive to alterations in the normal gut flora (warfarin, phenprocoumon/acenocoumarol); a CYP2C8 substrate (phenytoin); substrates of the P-gp transporter (digoxin, linezolid); and a substrate of the organic cation transporter (procainamide).[76,77,88,120,197]

Discussion

Included articles

This study outlines the possible DDIs related to frequently prescribed ABs in COPD patients from clinical and observational studies. We only included well-designed studies (≥2 points) 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 of this point is ABs and oral contraceptive interactions; many cases of unintended pregnancies were reported 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 has finally been cancelled in related guidelines.[199]

Mechanisms of DDI

A DDI of potential clinical significance between an AB and a co-administered medication may occur in two situations: (i) the co-administered drug influences the absorption, distribution, metabolism and elimination (ADME) of the AB; and (ii) the AB influences the ADME of the co-administered medication. When the AB acted as a substrate, some co-administered drugs reduced the blood concentration of the AB and led to failure of the AB treatment to reduce COPD exacerbations. Other co-administered drugs increased the blood concentration of the AB, which could result in the termination of AB use because of an ADR, and therefore acted against the control of infection. Acting as inhibitors, ABs could also increase the blood concentrations of co-administered drugs, which may also produce an ADR and lead to termination of co-administered drugs, and therefore may lead to failure of treatment of comorbidities. Thus, 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 is well reported; however, potential drug interactions between drugs for these comorbidities and ABs used for COPD have received little specific attention. From this review, we found that many drugs (e.g. those used for heart and circulatory system diseases) should not be co-administered with related ABs, and other actions are necessary, such as dose adjustment, choosing an alternative drug and monitoring ADRs. These drug interactions may not only influence treatment options for clinical practitioners but also influence treatment effects for both COPD and comorbidities.

Information collected in this review can be used as input to improve the sensitivity and specificity of DDI 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, a small alteration of their pharmacokinetic parameters can produce fatal consequences.[88,120] Therefore, combination with particular ABs that have an ability to inhibit their clearance pathways should be avoided if 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 of this review are worth mentioning. 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 and 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 of pseudotumour cerebri in the case of combinations of doxycycline with vitamin A analogues.[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 real-world drug utilization data.[202] Secondly, selection of the 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 this may restrict the scope of application 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 DDI levels only offers a general consideration. The specific impact of a DDI is determined by many variables, such as different doses and formulations and the comorbidities of patients. Therefore, case-by-case analysis is important in clinical practice and a drug interaction handbook such as *Stockley's Drug Interactions*[203] further expands on these issues.

Conclusions

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 ABs in order 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 where potentially interacting drug combinations may be used. Furthermore, the information may highlight gaps in scientific knowledge about potential adverse effects from DDIs.

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Transparency declarations

None to declare.

Supplementary data

The detailed search terms and Tables S1 to S3 are available as Supplementary data at *JAC* Online.

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