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Original article

# Contraindicated drug–drug interactions associated with oral antimicrobial agents prescribed in the ambulatory care setting in the United States☆

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ABSTRACT

*Objectives:* Antimicrobial agents are commonly used in ambulatory care settings. Our objective was to examine national-level patterns of contraindications between oral antibacterial or antifungal agents and patients' other oral medications in the US ambulatory care setting.

*Methods:* This cross-sectional study included multiple year pooled data (2003–2011) from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey (NHAMCS Outpatient Department). Visits by adults (age ≥18 years) in ambulatory settings in the United States who were prescribed oral antibacterial or antifungal agents were evaluated for potential drug–drug interaction (DDI) contraindications. Findings with relative standard error >30% or unweighted sample size <30 were not reported because these were deemed unreliable estimates.

*Results:* From 2003 to 2011, there were 1 235 000 outpatient visits (proportion = 0.52%; 95% confidence interval (CI), 0.29–0.74) in which a patient was prescribed an antimicrobial agent associated with a contraindicated DDI. The most prevalent antimicrobials with contraindicated combination among outpatients were simultaneous use of macrolide-containing products (erythromycin or clarithromycin) with statin medication–containing products (simvastatin or lovastatin) (841 864 visits, proportion = 1.91%; 95% CI, 0.96–2.86). The next most common combination was use of fluoroquinolones with antiarrhythmic agents (amiodarone, sotalol, quinidine or procainamide) (365 622 visits, proportion = 0.19%; 95% CI, 0.06–0.32).

*Conclusions:* Providers should be aware of potential contraindicated DDIs when prescribing antibiotics, especially macrolides and fluoroquinolones. **K. Eljaaly, Clin Microbiol Infect 2019;25:620**



## Introduction

Antimicrobial agents are commonly used in patients in the ambulatory care setting [1]. The most common diseases they used for are respiratory conditions, skin/mucosal conditions and urinary tract infections [1]. Polypharmacy (receipt of five or more medications) is the strongest predictor of serious adverse drug events and drug–drug interactions (DDIs) [2–4]. Some antimicrobials have known contraindications as a result of drug interactions and should not be prescribed when these interactions are present. The increasing medication burden in patients with chronic disease has increased the risk of such coprescribing. Thus, recognition of these clinically relevant DDIs is crucial.

The extent to which antimicrobial related contraindicated DDI is prevalent is unknown. In addition, there is paucity of information regarding the most likely medication combinations with antibacterial or antifungal agents that result in contraindications. The objective of this study was to examine national-level patterns of contraindications between oral antibacterial or antifungal agents

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and patients' other oral medications in the US ambulatory care setting.

## Methods

This cross-sectional study included multiple year pooled data (2003–2011) from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS Outpatient Department) [5]. Nationally representative ambulatory medical care service utilization data from visits to non–federally employed, office-based physicians and outpatient departments of noninstitutional, general and short-stay hospital in the United States are collected in the NAMCS and NHAMCS [6]. These surveys are collected yearly using a multistage probability sampling design by the National Center for Health Statistics of the US Centers for Disease Control and Prevention. An initial list of contraindicated combinations of any oral antibacterial or antifungal agents with any oral medication was created after extensive screening of drug information software (Lexi-Comp Online and Micromedex databases) [7,8]. Subsequently, a second screening of the US Food and Drug Administration (FDA)-approved labelling of each contraindicated medication, whether it was the precipitant drug or the interacting drug, was performed to confirm the final list of contraindicated combinations (Table 1). The words 'contraindicated,' 'avoid' or 'should not be used' were used to identify the presence of contraindication within the FDA-approved labelling.

Visits by adults in NAMCS and NHAMCS who were prescribed an antibacterial or antifungal agent during an ambulatory care visit were identified. The presence of a contraindicated DDI between oral antibacterial/antifungal agents prescribed and patients' other oral medications was calculated looking both at all DDIs (the denominator was the prescription of any antibacterial/antifungal agent while the numerator was the coprescription of any contraindicated interacting medication) and at specific DDIs (the denominator was the prescription of specific antibacterial/antifungal agents while the numerator was the coprescription of specific contraindicated interacting medications). National estimates were obtained by adjusting for the complex survey design of NAMCS/NHAMCS. Findings with a relative standard error (RSE) of >30% (unweighted sample size <30) were not reported because these were deemed unreliable estimates. Sampling variability of an estimate that may arise by chance due to only few sample surveyed during data collection rather than the entire population is primarily measured by standard error. Percentage of RSE is calculated by the standard error as a percentage of the estimate. The National Center for Health Statistics considers >30% RSE as unreliable [9]. Unweighted sample size refers to the sample where the complex survey design of NAMCS/NHAMCS have not been adjusted to obtain the US nationally representative sample. Medication use was ascertained by using Multum Lexicon Code as well as the Generic Drug Code in the database. SAS 9.4 (SAS Institute, Cary, NC, USA) was used to conduct all analyses.

**Table 1**
List of contraindicated antimicrobials and other patient medications

| Contraindicated medication | Antimicrobial | Clinical relevance |
|---|---|---|
| Atorvastatin | Posaconazole | Rhabdomyolysis |
| Simvastatin, lovastatin | Erythromycin, clarithromycin, itraconazole, posaconazole | Rhabdomyolysis |
| Alfuzosin | Itraconazole, posaconazole | Torsades de pointes |
| Amiodarone, procainamide, quinidine, sotalol | Levofloxacin, gemifloxacin, moxifloxacin, ciprofloxacin, ofloxacin, norfloxacin, sparfloxacin, gatifloxacin, erythromycin, clarithromycin | Torsades de pointes |
| Cisapride | Erythromycin, clarithromycin, fluconazole, itraconazole, voriconazole | Torsades de pointes |
| Dofetilide | Erythromycin, clarithromycin, itraconazole, trimethoprim/sulfamethoxazole | Torsades de pointes |
| Dronedarone | Clarithromycin, itraconazole, voriconazole | Torsades de pointes |
| Erythromycin | Fluconazole | Torsades de pointes |
| Quinidine | Fluconazole, itraconazole, posaconazole, voriconazole | Torsades de pointes and hypotension |
| Quinine | Erythromycin | Torsades de pointes |
| Ivabradine, ranolazine | Clarithromycin, itraconazole | Torsades de pointes |
| Pimozide[a] | Erythromycin, clarithromycin, fluconazole, itraconazole, posaconazole, voriconazole | Torsades de pointes |
| Terfenadine, astemizole | Erythromycin, clarithromycin, fluconazole, voriconazole | Torsades de pointes |
| Eletriptan | Clarithromycin, itraconazole | Myocardial infarction and stroke |
| Ticagrelor | Clarithromycin, itraconazole, voriconazole | Dyspnea and bleeding |
| Methadone | Itraconazole | Respiratory depression and hypotension |
| Felodipine | Clarithromycin, itraconazole, voriconazole | Hypotension |
| Tizanidine | Ciprofloxacin | Hypotension and neurologic toxicity |
| Disulfiram | Metronidazole, tinidazole | Neuropsychiatric toxicity |
| Ergotamine | Erythromycin, clarithromycin, itraconazole, posaconazole, voriconazole | Ergotism |
| Phenelzine, isocarboxazid[a] | Linezolid | Serotonin syndrome |
| Eplerenone | Clarithromycin, itraconazole | Hyperkalaemia and nephrotoxicity |
| Everolimus | Itraconazole, voriconazole | Bone marrow suppression and hypokalaemia |
| Sirolimus | Erythromycin, clarithromycin, itraconazole, posaconazole, voriconazole | Bone marrow suppression and hypokalaemia |
| Erythromycin | Clindamycin | Antagonism |
| Carbamazepine, phenobarbital, rifampin, rifabutin[a] | Voriconazole | Reduced efficacy of voriconazole |
| Dronedarone, everolimus, ivabradine,[a] praziquantel, omeprazole, esomeprazole, ticagrelor, apixaban,[a] rivaroxaban, edoxaban,[a] dabigatran, ranolazine, quinine | Rifampin | Reduced efficacy of contraindicated medications |

[a] These drugs were not available in National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey Outpatient Department.

## Results

Looking at all contraindicated DDIs from 2003 to 2011, 1 235 000 ambulatory care visits (proportion = 0.52%; 95% confidence interval (CI), 0.29–0.74) involved prescribing of oral antibacterial or antifungal agent, which was contraindicated because of a drug interaction. The denominator in this case was the prescription of any antibacterial/antifungal agent. Looking at specific contraindicated DDIs, macrolide-containing products (erythromycin or clarithromycin) and fluoroquinolones were the most prevalent antimicrobials involved in these contraindicated combinations. The denominator in the former case was the prescription of erythromycin or clarithromycin, while the denominator in the latter case was the prescription of a fluoroquinolone. The most common contraindication was simultaneous use of macrolide-containing products with statin medication (simvastatin or lovastatin) (841 864 visits, proportion = 1.91%; 95% CI, 0.96–2.86). The next most common combination was fluoroquinolones with antiarrhythmic agents (amiodarone, sotalol, quinidine or procainamide) (365 622 visits, proportion = 0.19%; 95% CI, 0.06–0.32). Other medications did not reach reliable estimates.

## Discussion

In the US ambulatory care setting, an oral antibacterial or antifungal agent resulting in a contraindicated DDI was prescribed in more than a million visits during an 8-year time period. Providers should be especially cognizant of the potential for DDIs when prescribing macrolides and fluoroquinolones, which were the source of the majority of these DDIs.

The use of certain macrolides in combination with statins can lead to life-threatening rhabdomyolysis and subsequent acute kidney injury. Statins are major cytochrome P450 3A4 (CYP3A4) substrates, which are strongly inhibited by macrolides such as clarithromycin and erythromycin. This results in an increase in the systemic exposure to statins. For instance, the area under the curve of simvastatin increases by approximately 100% and 300%, respectively [10,11]. A similar increase in area under the curve is expected with lovastatin because of similar pharmacokinetics and metabolism via the CYP3A4 pathway [12,13].

The use of fluoroquinolones is contraindicated with some antiarrhythmic agents because both can cause QTc prolongation, potentially resulting in a life-threatening arrhythmia: torsades de pointes [14]. Although this interaction is listed as a contraindication according to FDA-approved labelling, some clinicians may consider using these agents simultaneously on the basis of patient-specific circumstances such as baseline risk, comorbidities and the availability of alternative therapies. Nonetheless, prescribers should be cautious about this interaction; they should assess the risk of arrhythmia and consider alternative antimicrobial agents, if possible, for patients receiving antiarrhythmic agents. If avoidance is not possible, electrocardiogram monitoring should be performed, and the shortest possible antimicrobial therapy course should be considered. It would have been interesting to evaluate the duration of therapy with antimicrobial therapy in these situations. However, NAMCS and NHAMCS are annual cross-sectional surveys and do not collect information related to the duration of prescriptions.

The primary limitation of this study is that we did not have information regarding the clinical impact of these contraindicated drug interactions because we were limited to information available in the data sets. It is possible that only a small subset of patients exposed to these interactions had an adverse event. Nonetheless, the incidence of the DDIs themselves is meaningful. Also, in some circumstances, the contraindications may not be absolute, depending on patient specific circumstances. This cannot be gauged from the data alone; clinical judgment may warrant prescribing a contraindicated combination when the benefits outweigh the risks. Finally, we were only able to include databases up through the year 2011 because this is the most recent year released by the Centers for Disease Control and Prevention. Therefore, it is unknown if there has been a more recent change in prescribing practices.

The most common contraindicated oral drug–antibacterial agent interactions in US ambulatory visits were macrolides (erythromycin/clarithromycin) in combination with statins (simvastatin/lovastatin), followed by fluoroquinolones in combination with antiarrhythmic agents. Providers should be aware of these potential contraindications when prescribing antibiotics.

## Transparency declaration

All authors report no conflicts of interest relevant to this article.

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