

ACCEPTED MANUSCRIPT

1 Contraindicated drug-drug interactions associated with oral antimicrobial agents**2 prescribed in the ambulatory care setting in the United States**

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12 **Short title:** Contraindicated drug-antimicrobial interactions

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

26 **Methods:** This cross-sectional study included multiple year pooled data (2003-2011) from the
27 National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory
28 Medical Care Survey (NHAMCS Outpatient Department). Visits by adults (age ≥ 18 years) in
29 ambulatory settings in US who were prescribed oral antibacterial or antifungal agents were
30 evaluated for potential drug-drug interaction contraindications. Findings with Relative Standard
31 Error $> 30\%$ or unweighted sample size < 30 were not reported as these were deemed unreliable
32 estimates.

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

41 **Conclusion:** Providers should be aware of potential contraindicated drug-drug interactions when
42 prescribing antibiotics, especially macrolides and fluoroquinolones.

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46 **Introduction**

47 Antimicrobial agents are commonly used in patients in the ambulatory care setting.¹ The most
48 common diseases they used for are respiratory conditions, skin/mucosal conditions, and urinary
49 tract infections.¹ Polypharmacy (being on ≥ 5 medications) is the strongest predictor of serious
50 adverse drug events and drug–drug interactions (DDIs).²⁻⁴ Some antimicrobials have known
51 contraindications as a result of drug interactions and should not be prescribed when these
52 interactions are present. The increasing medication burden in patients with chronic disease has
53 increased the risk of such co-prescribing. Thus recognition of these clinically relevant DDIs is
54 crucial.

55 The extent to which antimicrobial related contraindicated DDI is prevalent is unknown. In
56 addition, there is paucity of information regarding the most likely medication combinations with
57 antibacterial or antifungal agents that result in contraindications. The objective of this study was
58 to examine national-level patterns of contraindications between oral antibacterial or antifungal
59 agents and patients' other oral medications in the U.S ambulatory care setting.

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61 **Methods**

62 This cross-sectional study included multiple year pooled data (2003-2011) from the National
63 Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical
64 Care Survey (NHAMCS Outpatient Department).⁵ Nationally representative ambulatory medical
65 care service utilization data from visits to non-federally employed, office-based physicians and
66 outpatient departments of non-institutional, general and short-stay hospital in the U.S are
67 collected in the NAMCS and NHAMCS.⁶ These surveys are collected yearly using a multistage
68 probability sampling design by the National Center for Health Statistics (NCHS) of the Centers

69 for Disease Control and Prevention (CDC). An initial list of contraindicated combinations of any
70 oral antibacterial or antifungal agents with any oral medication was created after extensive
71 screening of drug information software (Lexi-Comp Online and Micromedex databases).^{7,8}
72 Subsequently, a second screening of Food and Drug Administration (FDA) approved labeling of
73 each contraindicated medication, whether it was the precipitant drug or the interacting drug, was
74 performed to confirm the final list of contraindicated combinations (Table 1). The words
75 “contraindicated”, “avoid”, or “should not be used” were utilized to identify presence of
76 contraindication within the FDA approved labeling.

77 Visits by adults in NAMCS and NHAMCS who were prescribed an antibacterial or antifungal
78 agent during an ambulatory care visit were identified. The presence of a contraindicated DDI
79 between oral antibacterial/antifungal agents prescribed and patients’ other oral medications was
80 calculated looking both at all DDIs (the denominator was the prescription of any
81 antibacterial/antifungal agent while the numerator was the co-prescription of any contraindicated
82 interacting medication) and at specific DDIs (the denominator was the prescription of specific
83 antibacterial/antifungal agents while the numerator was the co-prescription of specific
84 contraindicated interacting medications). National estimates were obtained by adjusting for the
85 complex survey design of NAMCS/NHAMCS. Findings with Relative Standard Error (RSE) >
86 30% (unweighted sample size < 30) were not reported as these were deemed unreliable
87 estimates. Sampling variability of an estimate that may arise by chance due to only few sample
88 surveyed during data collection rather than the entire population is primarily measured by
89 standard error. Percentage of RSE is calculated by the standard error as a percentage of the
90 estimate. NCHS considers >30% RSE as unreliable. Unweighted sample size refers to the sample
91 where the complex survey design of NAMCS/NHAMCS have not been adjusted to obtain the

92 U.S nationally representative sample. Medication use was ascertained by using Multum Lexicon
93 Code as well as Generic Drug Code in the database. SAS version 9.4 (SAS institute Inc., Cary,
94 NC, USA) was used to conduct all analyses.

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96 **Results**

97 Looking at all contraindicated DDIs from 2003 to 2011, 1,235,000 ambulatory care visits
98 (proportion = 0.52%, 95% CI 0.29 to 0.74%) involved prescribing of oral antibacterial or
99 antifungal agent, which was contraindicated due to a drug interaction. The denominator in this
100 case was the prescription of any antibacterial/antifungal agent. Looking at specific
101 contraindicated DDIs, macrolide-containing products (erythromycin or clarithromycin) and
102 fluoroquinolones were the most prevalent antimicrobials involved in these contraindicated
103 combinations. The denominator in the former case was the prescription of erythromycin or
104 clarithromycin, while the denominator in the later case was the prescription of a fluoroquinolone.
105 The most common contraindication was simultaneous use of macrolide-containing products with
106 statin medication (simvastatin or lovastatin) (841,864 visits, proportion = 1.91%, 95% CI 0.96 to
107 2.86%). The next most common combination was fluoroquinolones with antiarrhythmic agents
108 (amiodarone, sotalol, quinidine, or procainamide) (365,622 visits, proportion = 0.19%, 95% CI
109 0.06 to 0.32%). Other medications did not reach reliable estimates.

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111 **Discussion**

112 In U.S ambulatory care setting, an oral antibacterial or antifungal agent resulting in a
113 contraindicated DDI was prescribed in more than a million visits during an 8-year time period.

114 Providers should be especially cognizant of the potential for DDIs when prescribing macrolides
115 and fluoroquinolones, which were the source of the majority of these DDIs.

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

123 The use of fluoroquinolones is contraindicated with some anti-arrhythmic agents because both
124 can cause QTc prolongation, potentially resulting in a life-threatening arrhythmia - torsades de
125 pointes.¹⁴ Although this interaction is listed as a contraindication according to FDA approved
126 labeling, some clinicians may consider using these agents simultaneously based on patient
127 specific circumstances such as baseline risk, comorbidities, and the availability of alternative
128 therapies. Nonetheless, prescribers should be cautious about this interaction, assess the risk of
129 arrhythmia, and consider alternative antimicrobial agents, if possible, for patients on anti-
130 arrhythmic agents. If avoidance is not possible, ECG monitoring should be performed and the
131 shortest possible antimicrobial therapy course should be considered. It would have been
132 interesting to evaluate the duration of the therapy with antimicrobial therapy in these situations.
133 However, NAMCS and NHAMCS are annual cross-sectional surveys and do not collect
134 information related to the duration of prescriptions.

135 The primary limitation of this study is that we did not have information regarding the clinical
136 impact of these contraindicated drug interactions because we were limited to information

137 available in the datasets. It is possible that only a small subset of patients exposed to these
138 interactions had an adverse event. Nonetheless, the incidence of the DDIs themselves is
139 meaningful. Also, in some circumstances the contraindications may not be absolute depending
140 on patient specific circumstances. This cannot be gauged from the data alone, and clinical
141 judgment may warrant prescribing a contraindicated combination, when the benefits outweigh
142 the risks. Finally, we were only able to include databases until the year 2011 because this is the
143 most recent year released by the CDC. Therefore, it is unknown if there has been a more recent
144 change in prescribing practices.

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

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156 **Transparency declaration**

157 None of the authors has potential conflict of interest. No funding was received for this paper.

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Table 1. List of Contraindicated Antimicrobials and Patients' Other Medications

Contraindicated medications	Antimicrobials	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	Hyperkalemia and nephrotoxicity
Everolimus	Itraconazole, voriconazole	Bone marrow suppression and hypokalemia
Sirolimus	Erythromycin, clarithromycin, itraconazole, posaconazole, voriconazole	Bone marrow suppression and hypokalemia
Erythromycin	Clindamycin	Antagonism
Carbamazepime, 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

^aThese drugs were not available in the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS Outpatient Department)