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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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 (being on ≥5 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 co-prescribing. 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 and patients' other oral medications in the U.S 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 non-institutional, general and short-stay hospital in the U.S 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 (NCHS) of the Centers

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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

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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**

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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

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Quinine	Erythormycin	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	Mycocardial 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

[a]These drugs were not available in the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS Outpatient Department)