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An Evidence-Based Assessment of the Clinical Significance of Drug–Drug Interactions Between Disease-Modifying Antirheumatic Drugs and Non-Antirheumatic Drugs According to Rheumatologists and Pharmacists

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ABSTRACT

Background: Clinically relevant drug–drug interactions (DDIs) must be recognized in a timely manner and managed appropriately to prevent adverse drug reactions or therapeutic failure. Because the evidence for most DDIs is based on case reports or poorly documented clinical information, there is a need for better assessment of their clinical relevance.

Objective: This study evaluates the interdisciplinary agreement between rheumatologists and clinical (hospital) pharmacists in assessing the clinical relevance of DDIs with disease-modifying antirheumatic drugs (DMARDs) and non-DMARD medications.

Methods: Potential DDIs were identified from the medical literature using MEDLINE and EMBASE for the years 1968–2009. The following search terms were used for the key word, title, and abstract sections of the publications: *interaction(s), DMARD, disease-modifying antirheumatic drug(s), antirheumatic, rheumatology, rheumatoid arthritis*, and the names of the individual DMARDs of interest (*abatacept, adalimumab, anakinra, auranofin, aurothioglucose, aurothiomalate, D-penicillamine, etanercept, gold, [hydroxy]-chloroquine, interleukin-1 receptor antagonist, IL1-RA, infliximab, leflunomide, methotrexate, rituximab*, and *sulfasalazine/sulphasalazine*). Reference lists of the retrieved publications were searched for further information on potential DDIs. All pharmacodynamic or pharmacokinetic DDIs between a DMARD and a non-DMARD identified were included in the study, with the exception of evidence regarding DMARD doses higher than used in the treatment of rheumatoid arthritis and interactions with phytotherapeutic or homeopathic preparations. Using a standard information set for each DDI (eg, from product labeling, textbooks, and the medical literature), a group of rheumatologists and a group of clinical pharmacists independently assessed whether the individual drug–DMARD combinations interacted and whether they required immediate intervention. Both groups consisted of 3 members (2 men and 1 woman), aged 40 to 60 years, who had >5 years of clinical experience and were currently involved in clinical practice in large, nonacademic teaching hospitals in the Netherlands.

Results: Forty potential DDIs with DMARDs were retrieved and assessed by the 2 groups. For 30 (75%) of these, rheumatologists and clinical pharmacists agreed about the requirement for immediate intervention. Specifically, 17 drug combinations (43%) were judged to interact and to require immediate intervention, and 13 combinations (33%) were judged either

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not to interact or to interact but not to require immediate intervention. For 10 combinations (25%), rheumatologists and clinical pharmacists were not in agreement. Overall, agreement between the groups was good ($\kappa = 0.80$) for judging whether the drug combinations were interactions, and agreement was fair ($\kappa = 0.39$) for judging whether immediate intervention was required. Prospective analysis of the data showed that rheumatologists tended to recommend immediate intervention more often when the adverse reaction to the DDI involved an increased risk of toxicity of the DMARD. In contrast, clinical pharmacists more often advocated immediate intervention when the adverse reaction involved decreased effectiveness of the DMARD.

Conclusion: For a subset of DMARD–drug combinations, rheumatologists and clinical pharmacists differed in their assessments of clinical relevance. (*Clin Ther.* 2009;31:1737–1746) © 2009 Excerpta Medica Inc.

Key words: drug–drug interaction, disease-modifying antirheumatic drug, rheumatoid arthritis, assessment.

INTRODUCTION

Pharmacotherapy is the mainstay of treatment for rheumatoid arthritis. Because of advanced age and the presence of comorbid conditions in this population, patients may receive multiple medications and hence are at risk for drug–drug interactions (DDIs).[1,2] To prevent potential adverse drug reactions or therapeutic failure, clinically relevant DDIs must be recognized in a timely manner and managed appropriately.

Although information on potential DDIs is available from reviews,[3–6] product leaflets, textbooks,[7,8] and the medical literature, several barriers impede recognition of the clinical importance of a DDI. The evidence for most DDIs is based on case reports or poorly documented clinical information. Drug-interaction compendia are inconsistent in their grading of the relevance of DDIs.[9] Manual recognition of potentially relevant DDIs, in contrast to computer-generated alerts, has been reported to miss many DDIs that are potentially clinically relevant and to result in a large variety of detected DDIs among individual observers.[10] Although computerized drug-interaction alert systems (CISs) may improve sensitivity for the recognition of potentially relevant DDIs, they have a number of important drawbacks.[11–15] Pharmacists and doctors believe that these systems yield a large number of DDIs with questionable or unclear clinical relevance while failing to detect all relevant DDIs.[11] Furthermore, these systems fail to provide identifiable patient- and medication-related risk factors. These shortcomings allow users to doubt the quality of the system and to ignore DDI alerts.[13,15] For these reasons, a transparent and reproducible assessment of potential DDIs is essential before drug combinations are entered into a CIS.

The Working Group on Pharmacotherapy and Drug Information, responsible for the maintenance of the CIS of the Royal Dutch Association for the Advancement of Pharmacy, developed a structured assessment for potential DDIs in an effort to reach a transparent and reproducible assessment procedure. The assessment is based on the evaluation of 4 core parameters of DDIs: the quality of the evidence on the specific DDI; the severity of the adverse reaction to the DDI; patient, medication, or disease characteristics that increase the risk of adverse reactions to the drug combination; and the incidence of adverse reactions when the combination is given.[16] These 4 core parameters are equally weighted in a multidisciplinary assessment.[16] On the basis of this assessment, drug combinations are selected for incorporation into the CIS.

Although the perception of sensitivity and specificity of the alerts generated by the CIS may improve with the use of a structured assessment procedure, differences may exist in the assessment of clinical relevance between medical and pharmacologic specialties. When these differences are not considered, the sensitivity and specificity of the CIS alerts may be perceived as suboptimal. A search of the literature did not identify any studies on the difference between medical specialty groups in the assessment of the clinical relevance of DDIs in rheumatology. We therefore performed a study to compare and contrast the assessments of rheumatologists and clinical (hospital) pharmacists regarding the clinical relevance of DDIs with various disease-modifying antirheumatic drugs (DMARDs) and other medications.

METHODS

Selection of Potential Drug–Drug Interactions

Using product leaflets and textbooks,[7,8] we identified potential DDIs with drugs used as DMARDs. We also searched the medical literature using MEDLINE[17] and EMBASE[18] for the years 1968–2009, with the

following search terms for the key word, title, and abstract sections of the publications: *interaction(s), DMARD, disease-modifying antirheumatic drug(s), antirheumatic, rheumatology, rheumatoid arthritis,* and the names of the individual DMARDs of interest (*abatacept, adalimumab, anakinra, auranofin, aurothioglucose, aurothiomalate, D-penicillamine, etanercept, gold, [hydroxy]chloroquine, interleukin-1 receptor antagonist, IL1-RA, infliximab, leflunomide, methotrexate, rituximab,* and *sulfasalazine/sulphasalazine*). Reference lists of the retrieved publications were searched for further information on potential DDIs.

All potential DDIs with DMARDs were included except for the following. First, we excluded combinations of 2 DMARDs, DMARDs with systemic corticosteroids, and DMARDs with NSAIDs because, in most cases, these medications are combined by rheumatologists intentionally to improve clinical response. Although we are well aware of the (relative) contraindications for the combination of NSAIDs with methotrexate, anti–tumor necrosis factor-α antagonists with rituximab, or drugs with overlapping toxicity profiles (eg, hepatotoxicity), these combinations were not assessed in this study. Second, we excluded combinations when the evidence for potential DDIs was based on dose levels far higher than those used in the treatment of rheumatoid arthritis (eg, methotrexate or azathioprine at doses used in oncology, or chloroquine as an antimalarial agent). Third, we excluded combinations of DMARDs with food supplements or phytotherapeutic or homeopathic preparations. Finally, we excluded pharmaceutical DDIs (eg, incompatibilities in pharmaceutical containers with solutions for parenteral administration).

Assessment of Potential Drug–Drug Interactions

Standard Information Package for Each Interaction

For every potential DDI, a standard data set was prepared containing comprehensive information on the 4 core parameters of the DDI, as described earlier.[16] These included the following: (1) the quality level of the evidence on the drug combination, categorized from 0 to 4[16]; (2) a description of the adverse reaction from the combination, including the severity and the mechanism of the DDI; (3) characteristics of the patient (eg, age, sex), disease (eg, renal and hepatic function), or medication (eg, dose, route of administration) when the risk of an adverse reaction from the potential DDI is dependent on these characteristics; and (4) the incidence of the adverse reaction when the combination is administered, according to the literature. The quality level of evidence for DDIs was defined as follows[16]: category 0 indicated pharmacodynamic animal studies, in vitro studies with limited predictive value for the human in vivo situation, or "data on file"; category 1 indicated incomplete case reports (no rechallenge or dechallenge; presence of factors other than a DDI that explain the adverse reaction); category 2 indicated well-documented case reports or retrospective analyses of case series; category 3 indicated controlled interaction studies with surrogate end points; and category 4 indicated controlled interaction studies with clinically relevant end points. The standard data set also contained the main publications on the DDI. These publications could either support or deny the existence of the DDI. All of the information in the standard data set was provided electronically as well as on paper.

Expert Assessment

On the basis of the standard data set for each potential DDI, 3 rheumatologists and 3 clinical pharmacists were asked to assess the DDI individually. The rheumatologists and clinical pharmacists were selected on the basis of >5 years of clinical experience and current involvement in clinical practice. The rheumatologists and clinical pharmacists (2 men and 1 woman in both groups; aged 40–60 years) all worked in large, nonacademic teaching hospitals in the Netherlands.

The following 2 questions, which required a "yes" or "no" response, were used to assess the potential DDIs: (1) "On the basis of the information provided about the DDI, would you conclude that this combination of drugs will interact?" and (2) "When you judge this combination to interact, is any immediate intervention required?" *Immediate intervention* was defined as any action required at the moment the combination is recognized to prevent medication-related problems such as adverse drug reactions or suboptimal efficacy, as judged by the individual rheumatologist or clinical pharmacist on the basis of the evidence presented. Potential immediate interventions included the following: adjusted monitoring of therapy effectiveness or tolerability in the near future, adjusted provision of patient education about potential symptoms indicating adverse effects, appointments for therapeutic drug monitoring, dose adjustments, or prescription of an alternative drug.

Data Analysis

For both specialty groups (rheumatologists and clinical pharmacists), the data from the individual assessments were pooled separately. Outcomes per group were based on the opinion of the majority. On the basis of these assessments, the potential DDIs were divided into 3 groups: (1) drug combinations judged by both specialty groups as DDIs that require immediate intervention; (2) combinations judged by both specialty groups as either not interacting and therefore not requiring immediate intervention, or interacting but not requiring immediate intervention; and (3) combinations for which the rheumatologists and clinical pharmacists disagreed whether the combination interacted or whether immediate intervention was required.

The adverse reaction of each individual drug combination was prospectively grouped into 1 of 5 categories: (1) increased toxicity of the DMARD or (2) the non-DMARD, (3) decreased effectiveness of the DMARD or (4) the non-DMARD, or (5) other. When the adverse reaction of the DDI involved increased toxicity associated with both the DMARD and the non-DMARD individually, this toxicity was categorized as "increased toxicity of the DMARD."

Statistical Analysis

Assessments of the DDIs per specialty group were presented using 2 × 2 tables. To assess the interobserver variability, Cohen's κ was calculated. The κ values of <0.20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and 0.81 to 1.00 were classified as poor, fair, moderate, good, or very good agreement, respectively, between the specialty groups.[19] Differences in assessments of clinical relevance between the specialty groups per adverse-reaction category were analyzed using the nonparametric McNemar test in SPSS 13.0 (SPSS Inc., Chicago, Illinois). $P < 0.05$ was considered significant.

RESULTS

Selection of Potential Drug–Drug Interactions

Forty potentially interacting drug combinations with DMARDs were identified within the selection criteria. The highest level of evidence found for the potential DDIs was level 3 in 57%, level 2 in 5%, level 1 in 18%, and level 0 in 20%. Level-4 evidence was not found for any of the drug combinations. No evidence for DDIs with biologic agents was found.

Assessment of Potential Drug–Drug Interactions

Table I shows the assessment by the 2 specialty groups as to whether the drug combinations were interactions (ie, DDIs). The results represent good agreement between the groups (mean [SD] κ = 0.80 [0.11]). Within the groups, the 40 combinations were judged unanimously in 29 (73%) and 26 (65%) of the cases by clinical pharmacists and rheumatologists, respectively (data not shown).

Table I also shows the assessment by the 2 specialty groups as to whether the drug combinations required immediate intervention. The results represent fair agreement between the groups (mean [SD] κ = 0.39 [0.15]). Within the groups, the 40 combinations were judged unanimously in 27 (68%) and 17 (43%) of the cases by clinical pharmacists and rheumatologists, respectively (data not shown).

Tables II through **IV** display specific information on the drug combinations. For 30 (75%) of the drug combinations, rheumatologists and clinical pharmacists agreed about the requirement for immediate intervention. **Table II** details the 17 drug combinations (43%) judged by both groups to be DDIs and to require immediate intervention.[20–45] **Table III** details the 13 drug combinations (33%) that were judged by

Table I. Assessments of the drug combinations with disease-modifying antirheumatic drugs by the 2 specialty groups.

	Rheumatologists		
	No	Yes	Total
Assessment as a drug–drug interaction*			
Clinical pharmacists			
No	8	3	11
Yes	0	29	29
Total	8	32	40
Assessment of need for immediate intervention†			
Clinical pharmacists			
No	13	5	18
Yes	5	17	22
Total	18	22	40

*Mean (SD) κ = 0.80 (0.11) between the specialty groups.
†Mean (SD) κ = 0.39 (0.15) between the specialty groups.

Table II. Drug combinations with disease-modifying antirheumatic drugs (DMARDs) assessed by both specialty groups as drug–drug interactions requiring immediate intervention.

DMARD	Combining Agent	Level of Evidence*	Adverse Reaction	Ref
Azathioprine	Allopurinol	3	↑ Azathioprine toxicity	20, 21
	Doxorubicin	3	↑ Hepatotoxicity	22
	Warfarin	2	↓ Anticoagulant activity	23, 24
Chloroquine	Praziquantel	3	↓ AUC praziquantel by 65%	25
	Drugs that increase the QT interval	0	↑ Cardiac arrhythmia	–
D-penicillamine	Digoxin	3	↓ AUC digoxin by 40%–64%	26
	Iron salts	3	↓ AUC D-penicillamine by 35%–60%	27
Hydroxychloroquine	Cardiac glycosides	2	↑ C_{max} digoxin by 4-fold	28, 29
Leflunomide	Activated charcoal/resins	3	↓ Plasma $t_{1/2}$ of A77 1726 by 10-fold	30
	Warfarin	1	↑ Anticoagulant activity	31, 32
Methotrexate	Acitretin/retinoids	3	↑ Hepatotoxicity due to ↑ AUC MTX	33–35
	Cotrimoxazole/trimethoprim	3	↑ Bone marrow depression	36–39
	Isoniazid	3	↑ Hepatotoxicity	40, 41
	Probenecid	3	↑ C_{24h} MTX by 3- to 4-fold	42, 43
Sulfasalazine	Digoxin	3	↓ AUC digoxin by 50%	44
	Isoniazid	3	↑ Hepatotoxicity	40
	Talinolol	3	↓ AUC talinolol by 90%	45

Ref = references; ↑ = increase or increased risk; ↓ = decrease or decreased risk; A77 1726 = active metabolite of leflunomide; MTX = methotrexate.

*Category 0 = pharmacodynamic animal studies, in vitro studies with limited predictive value for the human in vivo situation, or "data on file"; category 1 = incomplete case reports (no rechallenge or dechallenge; presence of factors other than a drug–drug interaction that explain the adverse reaction); category 2 = well-documented case reports or retrospective analyses of case series; category 3 = controlled interaction studies with surrogate end points; category 4 = controlled interaction studies with clinically relevant end points.

both groups either not to interact or to interact but not to require immediate intervention.[46–58] **Table IV** outlines the 10 drug combinations (25%) for which the rheumatologists and clinical pharmacists disagreed.[59–70]

Table V shows the expert opinions about the need for immediate intervention according to the adverse-reaction category. Rheumatologists, compared with clinical pharmacists, tended to recommend immediate intervention more often for drug combinations with an increased risk of toxicity of the DMARD. Rheumatologists and clinical pharmacists tended to differ in their assessments of individual drug combinations when the adverse reaction involved decreased effectiveness of the DMARD; specifically, clinical pharmacists were more likely to judge the combination as requiring immediate intervention.

After excluding the drug combinations that did not interact and did not require immediate intervention according to both specialty groups, 27 of the 40 combinations remained. Both groups achieved a sensitivity of 81% for these combinations (ie, both groups identified 22 of 27 combinations as requiring immediate intervention). Specificity for both groups was 19% (ie, for 5 of

Table III. Drug combinations with disease-modifying antirheumatic drugs (DMARDs) assessed by both specialty groups as not requiring immediate intervention.*

DMARD	Combining Agent	Level of Evidence†	Adverse Reaction	Ref
Aurothiomalate	ACE inhibitors	1	Nitritoid reactions	46, 47
Azathioprine	Lamivudine	1	↑ Pancreatitis	48
	Mycophenolate mofetil	0	↑ Hematologic toxicity	49
	ACE inhibitors	3	↑ Neutropenia and ↑ anemia	50, 51
Chloroquine	Codeine	None	↓ Analgesic effectiveness of codeine	49
	Metronidazole	1	Acute dystonia	52
	Neuromuscular blocking agents	0	↑ Neuromuscular blockade	53
	Mefloquine	0	↑ QT-interval prolongation, ↑ convulsions, ↑ mefloquine plasma concentrations	54
D-penicillamine	Clozapine	0	↑ Agranulocytosis	55
	Oral contraceptives	1	↑ Macromastia	56
	Tricyclic antidepressants	0	↑ Myasthenia gravis	57
Gold salts	Chelating agents	0	Changes in gold distribution and elimination	49
Methotrexate	Theophylline	3	↓ Theophylline clearance	58

Ref = references; ACE = angiotensin-converting enzyme; ↑ = increase or increased risk; ↓ = decrease or decreased risk.
*The drug combinations were judged either not to interact or to interact but not to require immediate intervention.
† For explanation of categories, see **Table II**.

27 combinations, the group would generate an alert or take immediate action, whereas the other group would not require any immediate intervention).

DISCUSSION

For 30 of 40 (75%) potentially interacting drug combinations involving DMARDs, rheumatologists and clinical pharmacists agreed about the requirement for immediate intervention or no intervention at all. Overall, rheumatologists were more likely to judge a potential DDI as requiring immediate intervention when the drug combination increased the risk of DMARD toxicity, whereas clinical pharmacists were more likely to judge a potential DDI as requiring immediate intervention when the drug combination resulted in a decrease in effectiveness of the applied DMARD.

Our literature search identified only 40 potential DDIs among all possible drug combinations with DMARDs. A German study in a general population participating in a health-screening program found that only 7.5% of the total prescribed drug combinations had information on the existence of a potential DDI.[71] When translating these results to the population with rheumatoid arthritis, one may also expect underreporting of potentially clinically relevant DDIs with DMARDs. Guidelines for research on potential DDIs for newly registered drugs[72] may expand our knowledge of potential DDIs. However, drugs that have been marketed for several years may lack this information. This is reflected by the relatively high proportion (43%) of combinations in our study with evidence quality categorized as grade 0 to 2 and the lack of grade-4 evidence for any of the combinations.

In our study, *immediate intervention* was broadly defined as any action taken to prevent medication-related problems (eg, adverse drug reactions or suboptimal efficacy) or to avoid the interaction. Differences in judgment between the specialty groups may be due to differing perceptions about the degree to which the DDI can be controlled (eg, the likelihood of preventing the adverse reaction). For example, when the drug

Table IV. Drug combinations with disease-modifying antirheumatic drugs (DMARDs) for which rheumatologists and clinical pharmacists disagreed about whether the combination interacted or whether immediate intervention was required.

DMARD	Combining Agent	Level of Evidence*	Adverse Reaction	Immediate Intervention?		Ref
				Rheumatologists	Clinical Pharmacists	
Azathioprine	Cotrimoxazole	3	↑ Neutropenia/ thrombocytopenia	No	Yes	59
Chloroquine	Cimetidine	3	↓ Elimination of chloroquine	Yes	No	60
	Magnesium trisilicate/kaolin	3	↓ AUC chloroquine	No	Yes	61
D-penicillamine	Antacids	3	↓ AUC D-penicillamine by 30%–40%	No	Yes	62
	L-dopa	1	↑ AUC L-dopa by 50%	Yes	No	63
Leflunomide	Itraconazole	1	↑ Hepatotoxicity	Yes	No	64
	Rifampicin	3	↑ C_{max} A77 1726 by 40%	Yes	No	65
Methotrexate	Penicillins	3	↑ MTX toxicity	Yes	No	66, 67
Sulfasalazine	Ampicillin/ rifampicin	3	↓ AUC sulfapyridine by 60%–65%	No	Yes	68, 69
	Iron salts	3	↓ C_{5h} sulfasalazine	No	Yes	70

Ref = references; ↑ = increase or increased risk; ↓ = decrease or decreased risk; A77 1726 = active metabolite of leflunomide; MTX = methotrexate.
*For explanation of categories, see **Table II**.

Table V. Assessments of the need for immediate intervention according to adverse-reaction category for drug combinations with disease-modifying antirheumatic drugs (DMARDs) by the 2 specialty groups.

Adverse-Reaction Category	No. of Combinations in Category	Requiring Immediate Intervention		*P**
		Rheumatologists	Clinical Pharmacists	
Increased toxicity of DMARD	19	14	9	0.13
Decreased effectiveness of DMARD	7	2	6	0.13
Increased toxicity of non-DMARD	4	2	1	1.00
Decreased effectiveness of non-DMARD	6	5	5	1.00
Other	4	1	1	1.00

*Differences in assessments between the specialty groups per adverse-reaction category were analyzed using the nonparametric McNemar test.

combination shows an interaction based on decreased absorption from the gastrointestinal tract due to complexation (eg, chloroquine/magnesium trisilicate, D-penicillamine/antacids, D-penicillamine/iron salts, D-penicillamine/digoxin, or sulfasalazine/iron salts), the DDI can be controlled by adjusting the dosing times of the medications. Clinical pharmacists judged that all of these DDIs would have required immediate intervention, whereas rheumatologists considered immediate intervention to be required for only 2 of these interactions. These results highlight the differences in points of view between the specialty groups and the need for a multidisciplinary approach when assessing the relevance of a drug combination.

Our study has some limitations that should be addressed. First, the differences in results between the specialty groups may be specific to the field of rheumatology or the particular setting (ie, hospital). To our knowledge, no studies on this subject have been published in other fields of medicine that have evaluated DDIs. Second, no effort was made to reach consensus between the groups, so the results presented indicate the maximum contrast between the groups. Third, the rheumatologists and clinical pharmacists were not blinded to the objective of the study, and this may have been a source of bias. Despite these limitations, our study provides valuable information about differences in the assessment of the clinical relevance of DDIs between 2 specialties involved in the care of patients with rheumatoid arthritis.

CONCLUSIONS

Rheumatologists and clinical pharmacists differed in their assessments of clinical relevance for 10 out of 40 DMARD–drug combinations. To prevent drug-related problems, it may be necessary to eradicate discordant interdisciplinary attitudes and institute multidisciplinary judgment of the relevance of DDIs.

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REFERENCES

1. Doucet J, Chassagne P, Trivalle C, et al. Drug-drug interactions related to hospital admissions in older adults: A prospective study of 1000 patients. *J Am Geriatr Soc.* 1996;44:944–948.
2. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA.* 2003;289:1652–1658.
3. Haagsma CJ. Clinically important drug interactions with disease-modifying antirheumatic drugs. *Drugs Aging.* 1998; 13:281–289.
4. Furst DE. Practical clinical pharmacology and drug interactions of low-dose methotrexate therapy in rheumatoid arthritis. *Br J Rheumatol.* 1995;34(Suppl 2):20–25.
5. Vassilopoulos D, Camisa C, Strauss RM. Selected drug complications and treatment conflicts in the presence of coexistent diseases. *Rheum Dis Clin North Am.* 1999;25:745–777, x.
6. Munro RA, Sturrock RD. Slow-acting antirheumatic drugs. Drug interactions of clinical significance. *Drug Saf.* 1995; 13:25–30.
7. Hansten PD, Horn JR. *Drug Interactions: Analysis and Management*. St. Louis, Mo: Facts & Comparisons; 2002.
8. Baxter K, ed. *Stockley's Drug Interactions: A Source Book of Interactions, Their Mechanisms, Clinical Importance and Management.* 8th ed. London, UK: Pharmaceutical Press; 2008.
9. Vitry AI. Comparative assessment of four drug interaction compendia. *Br J Clin Pharmacol.* 2007;63:709–714.
10. Weideman RA, Bernstein IH, McKinney WP. Pharmacist recognition of potential drug interactions. *Am J Health Syst Pharm.* 1999;56:1524–1529.
11. Glassman PA, Simon B, Belperio P, Lanto A. Improving recognition of drug interactions: Benefits and barriers to using automated drug alerts. *Med Care.* 2002;40:1161–1171.
12. Barrons R. Evaluation of personal digital assistant software for drug interactions. *Am J Health Syst Pharm.* 2004;61: 380–385.
13. Magnus D, Rodgers S, Avery AJ. GPs' views on computerized drug interaction alerts: Questionnaire survey. *J Clin Pharm Ther.* 2002;27:377–382.
14. Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. *J Am Pharm Assoc (Wash).* 2001;41:200–204.
15. Chrischilles EA, Fulda TR, Byrns PJ, et al. The role of pharmacy computer systems in preventing medication errors. *J Am Pharm Assoc (Wash).* 2002;42:439–448.
16. van Roon EN, Flikweert S, le Comte M, et al. Clinical relevance of drug-drug interactions: A structured assessment procedure. *Drug Saf.* 2005;28:1131–1139.
17. National Center for Biotechnology Information (NCBI). PubMed. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi. Accessed November 20, 2008.
18. Elsevier B.V. EMBASE.com. http://www.embase.com. Accessed July 31, 2009.
19. Altman DG. Inter-rater agreement. In: Altman DG, ed. *Practical Statistics for Medical Research.* 1st ed. London, UK: Chapman and Hall; 1991:404.
20. Zimm S, Collins JM, O'Neill D, et al. Inhibition of first-pass metabolism in cancer chemotherapy: Interaction of

6-mercaptopurine and allopurinol. *Clin Pharmacol Ther.* 1983;34:810–817.
21. Boyd IW. Allopurinol-azathioprine interaction. *J Intern Med.* 1991;229: 386.
22. Minow RA, Stern MH, Casey JH, et al. Clinico-pathologic correlation of liver damage in patients treated with 6-mercaptopurine and Adriamycin. *Cancer.* 1976;38:1524–1528.
23. Khamashta MA, Cuadrado MJ, Mujic R. Effect of azathioprine on the anticoagulant activity of warfarin in patients with the antiphospholipid syndrome. *Arthritis Rheum.* 1998;41(Suppl):S171.
24. Ng HJ, Crowther MA. Azathioprine and inhibition of the anticoagulant effect of warfarin: Evidence from a case report and a literature review. *Am J Geriatr Pharmacother.* 2006;4: 75–77.
25. Masimirembwa CM, Naik YS, Hasler JA. The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. *Biopharm Drug Dispos.* 1994; 15:33–43.
26. Moezzi B, Fatourechi V, Khozain R, Eslami B. The effect of penicillamine on serum digoxin levels. *Jpn Heart J.* 1978;19:366–375.
27. Osman MA, Patel RB, Schuna A, et al. Reduction in oral penicillamine absorption by food, antacid, and ferrous sulfate. *Clin Pharmacol Ther.* 1983;33:465–470.
28. Leden I. Digoxin-hydroxychloroquine interaction? *Acta Med Scand.* 1982; 211:411–412.
29. McElnay JC, Sidahmed AM, D'Arcy PF. Chloroquine-digoxin interaction. *Int J Pharmaceut.* 1985;26:267–274.
30. Roethig H-J, Collins J, Harnisch L, et al. The effect of activated charcoal and cholestyramine on the pharmacokinetics of leflunomide. *Clin Pharmacol Ther.* 1996;59:204. Abstract.
31. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin [published correction appears in *BMJ.* 2003;326:432]. *BMJ.* 2002;325:1333.
32. Chonlahan J, Halloran MA, Hammonds A. Leflunomide and warfarin interaction: Case report and review of the literature. *Pharmacotherapy.* 2006;26:868–871.
33. Zachariae H. Methotrexate and etretinate as concurrent therapies in the treatment of psoriasis. *Arch Dermatol.* 1984;120:155.
34. Vanderveen EE, Ellis CN, Campbell JP, et al. Methotrexate and etretinate as concurrent therapies in severe psoriasis. *Arch Dermatol.* 1982; 118:660–662.
35. Lowenthal KE, Horn PJ, Kalb RE. Concurrent use of methotrexate and acitretin revisited. *J Dermatolog Treat.* 2008;19:22–26.
36. Steuer A, Gumpel JM. Methotrexate and trimethoprim: A fatal interaction. *Br J Rheumatol.* 1998;37:105–106.
37. Govert JA, Patton S, Fine RL. Pancytopenia from using trimethoprim and methotrexate. *Ann Intern Med.* 1992;117:877–878.
38. Ng HW, Macfarlane AW, Graham RM, Verbov JL. Near fatal drug interactions with methotrexate given for psoriasis. *Br Med J (Clin Res Ed).* 1987;295:752–753.
39. Sathi N, Dawson J. Methotrexate-induced pancytopenia associated with co-prescription of penicillin and trimethoprim. *Clin Rheumatol.* 2007;26:134–135.
40. Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. *Ann Rheum Dis.* 2003;62:1241–1242.
41. Mor A, Bingham CO III, Kishimoto M, et al. Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: Experience from an urban arthritis clinic. *Ann Rheum Dis.* 2008;67:462–465.
42. Basin KS, Escalante A, Beardmore TD. Severe pancytopenia in a patient taking low dose methotrexate and probenecid. *J Rheumatol.* 1991; 18:609–610.
43. Lilly MB, Omura GA. Clinical pharmacology of oral intermediate-dose methotrexate with or without probenecid. *Cancer Chemother Pharmacol.* 1985;15:220–222.
44. Juhl RP, Summers RW, Guillory JK, et al. Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther.* 1976;20:387–394.
45. Terhaag B, Palm U, Sahre H, et al. Interaction of talinolol and sulfasalazine in the human gastrointestinal tract. *Eur J Clin Pharmacol.* 1992;42:461–462.
46. Healey LA, Backes MB. Nitritoid reactions and angiotension-converting-enzyme inhibitors. *N Engl J Med.* 1989;321:763.
47. Isab AA. A reaction between captopril (a high blood pressure drug) and gold(I)-thiomalate. *J Inorg Biochem.* 1987;30:69–75.
48. Van Vlierberge H, Elewaut A. Development of a necrotising pancreatitis after starting lamivudine in a kidney transplant patient with fibrosing cholestatic hepatitis. A possible role of the interaction lamivudine and azathioprine. *Gastroenterology.* 1997;112(Suppl 4):1407.
49. Kary S, Buttgereit F, Burmester GR. Pharmacotherapy of rheumatic diseases in the aged [in German]. *Internist (Berl).* 2003;44:951–958.
50. Gossmann J, Thürmann P, Bachmann T, et al. Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients. *Kidney Int.* 1996;50:973–978.
51. Vanrenterghem Y, Ponticelli C, Morales JM, et al. Prevalence and management of anemia in renal transplant recipients: A European survey. *Am J Transplant.* 2003;3:835–845.
52. Achumba JI, Ette EI, Thomas WO, Essien EE. Chloroquine-induced acute dystonic reactions in the pres-

ence of metronidazole. *Drug Intell Clin Pharm.* 1988;22:308–310.
53. Tseng J. Clinical and experimental studies on the mechanism of neuromuscular blockade by chloroquine diorotate [in Japanese]. *Masui.* 1971; 20:491–503.
54. Supanaranond W, Suputtamongkol Y, Davis TM, et al. Lack of a significant adverse cardiovascular effect of combined quinine and mefloquine therapy for uncomplicated malaria. *Trans R Soc Trop Med Hyg.* 1997;91:694–696.
55. Clorazil (clozapine). *ABPI Data Sheet Compendium 1994-5*. London, UK: Datapharm Publications; 1994: 1376–1378.
56. Rose BI, LeMaire WJ, Jeffers LJ. Macromastia in a woman treated with penicillamine and oral contraceptives. A case report. *J Reprod Med.* 1990;35:43–45.
57. Ferro J, Susano R, Gómez C, de Quirós JF. Myasthenia induced by penicillamine: Does an interaction with tricyclic antidepressants exist [in Spanish]? *Rev Clin Esp.* 1993;192:358–359.
58. Glynn-Barnhart AM, Erzurum SC, Leff JA, et al. Effect of low-dose methotrexate on the disposition of glucocorticoids and theophylline. *J Allergy Clin Immunol.* 1991;88:180–186.
59. Bradley PP, Warden GD, Maxwell JG, Rothstein G. Neutropenia and thrombocytopenia in renal allograft recipients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med.* 1980;93:560–562.
60. Ette EI, Brown-Awala EA, Essien EE. Chloroquine elimination in humans: Effect of low-dose cimetidine. *J Clin Pharmacol.* 1987;27:813–816.
61. McElnay JC, Mukhtar HA, D'Arcy PF, et al. The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. *J Trop Med Hyg.* 1982;85:159–163.
62. Ifan A, Welling PG. Pharmacokinetics of oral 500-mg penicillamine: Effect of antacids on absorption. *Biopharm Drug Dispos.* 1986;7:401–405.
63. Mizuta E, Kuno S. Effect of D-penicillamine on pharmacokinetics of levodopa in Parkinson's disease. *Clin Neuropharmacol.* 1993;16:448–450.
64. Legras A, Bergemer-Fouquet AM, Jonville-Bera AP. Fatal hepatitis with leflunomide and itraconazole. *Am J Med.* 2002;113:352–353.
65. Leflunomide (HWA 486). Investigator's brochure. Wiesbaden, Germany: Hoechst Marion Roussel; 1998:4–5.
66. Herrick AL, Grennan DM, Aarons L. Lack of interaction between methotrexate and penicillins. *Rheumatology (Oxford).* 1999;38:284–285.
67. Nierenberg DW, Mamelok RD. Toxic reaction to methotrexate in a patient receiving penicillin and furosemide: A possible interaction. *Arch Dermatol.* 1983;119:449–450.
68. Houston JB, Day J, Walker J. Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol.* 1982;14:395–398.
69. Shaffer JL, Houston JB. The effect of rifampicin on sulphapyridine plasma concentrations following sulphasalazine administration. *Br J Clin Pharmacol.* 1985;19:526–528.
70. Das KM, Eastwood MA. Effect of iron and calcium on salicylazosulphapyridine metabolism. *Scott Med J.* 1973;18:45–50.
71. Bergk V, Gasse C, Rothenbacher D, et al. Drug interactions in primary care: Impact of a new algorithm on risk determination. *Clin Pharmacol Ther.* 2004;76:85–96.
72. The European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit, Committee for Proprietary Medicinal Products (CPMP). Note for guidance on the investigation of drug interactions. London, UK: CPMP/EWP; 1997. http://www.emea.europa.eu/pdfs/human/ewp/056095en.pdf. Accessed July 20, 2009.

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