Drug interactions among commonly used medications

Chart simplifies data from critical literature review

N. Renée Crowther, MSC Anne M. Holbrook, MD, PHARMD, MSC, FRCPC Robert Kenwright, BSC
Margaret Kenwright, AOCA

ABSTRACT

OBJECTIVE To simplify risk assessment, we have developed a way to present critically appraised drug interaction information through a chart.

DATA SOURCES Fifty drugs most frequently prescribed by Canadian family physicians and 16 drugs and substances that frequently interact with these drugs were the basis for a literature review. Drug interaction textbooks and MEDLINE (from 1966 to 1994) were searched for documented interactions. Reports of additive effects and animal or in vitro studies were excluded.

STUDY SELECTION All reports of interactions were evaluated for clinical effect, clinical significance, and quality of evidence.

SYNTHESIS Of the 464 drug-drug or drug-substance pairs evaluated, 387 (83.4%) demonstrated an interaction, 59 (12.7%) documented no effect, and 18 (3.9%) pairs had conflicting evidence. Five percent of interactions were of major clinical significance; only 1.3% were of major clinical significance and supported by good-quality evidence. By using symbols, colours, and legends in a "grid-map" format, a large amount of drug interaction information was reduced to a single-page chart suitable for a desk reference or wall mounting.

CONCLUSIONS Our chart organizes a large amount of drug interaction information in a format that allows for rapid appreciation of outcome, clinical significance, and quality of evidence.

RÉSUMÉ

OBJECTIF Simplifier l'évaluation des risques d'interactions médicamenteuses par l'élaboration d'une fiche qui présente l'information soumise à l'évaluation critique.

SOURCE DES DONNÉES Les 50 médicaments les plus fréquemment prescrits par les médecins de famille canadiens et les16 médicaments et substances qui interagissent fréquemment avec ces médicaments ont servi de base pour une recension de la littérature. Notre recherche des interactions documentées s'est effectuée dans les volumes de référence traitant des interactions médicamenteuses et dans MEDLINE (de 1966 à 1994). Nous avons exclu les rapports traitant des effets synergiques, les études in vitro et celles faites chez les animaux.

SÉLECTION DES ÉTUDES Tous les rapports d'interactions ont été évalués en fonction de trois critères : effet clinique, signification clinique et qualité des preuves.

SYNTHÈSE Parmi les 464 combinaisons médicamenteuses évaluées en paires, soit médicament-médicament, ou médicament-substance, 387 (83,4 %) ont interagi, 59 (12,7 %) n'ont manifesté aucun effet et 18 (3,9 %) ont donné des résultats contradictoires. Cinq pour cent des interactions avaient une signification clinique majeure ; seulement 1,3 % étaient à la fois très significatives cliniquement et démontrées par des preuves de bonne qualité. L'utilisation des symboles, des couleurs et des légendes a permis de réduire sur une fiche quadrillée de format page une grande quantité de renseignements sur les interactions médicamenteuses. Cette fiche peut être laissée sur le bureau ou affichée au mur.

CONCLUSIONS Notre fiche présente une grande quantité d'information concernant les interactions médicamenteuses dans un format qui permet de voir rapidement l'évaluation des résultats, la signification clinique et la qualité des preuves.

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Drug interactions can be defined as the pharmacologic or clinical response to the coadministration of two or more drugs or substances beyond that expected from the known effects of the drugs given individually. The outcome of a drug interaction can be synergistic, antagonistic, or idiosyncratic.

A drug or substance that interferes with or accentuates the absorption, distribution, or elimination of a second drug produces a pharmacokinetic interaction. A pharmacodynamic interaction occurs when drugs act on the same receptor, site of action, or physiologic system. While some drug interactions are beneficial (for example, the combination of amoxicillin and clavulanic acid), others are clinically harmful.

The search for and appraisal of drug interaction information at the time it is needed is a great problem for busy health professionals[1-3] and is a challenge for health service researchers and educators to resolve. The chances that patients will have a clinically significant drug interaction increase with the number of medications[4-9]; in some cases interactions are unavoidable. Thus groups already at risk of symptomatic morbidity because of age, multiple disease states, or serious organ dysfunction are also at risk for adverse effects from the drugs prescribed to treat these conditions.

Ideally, health professionals should have resources readily available to identify potential interactions.[1,3] Identification would then allow for dose modifications, extra surveillance, or selection of appropriate therapeutic alternatives to prevent or ameliorate the effect of an interaction. Many resources are available ranging from frequently updated reference books to drug interaction modules in computerized patient record systems. However, several drawbacks of these resources could account for their underuse.

First, the time required to locate and interpret potential drug interaction information is a great disadvantage and could contribute to the infrequent use of drug interaction textbooks in general practice. Computerized drug interaction software programs might reduce the time required to locate pertinent information.[10] Physicians' offices must be computerized, however, and the software must be accessible to physicians during patient visits. Unfortunately, few physician offices are computerized beyond billing purposes and even fewer have computers in patient examining rooms.[11]

Second, most resources lack information regarding the quality of the evidence supporting the drug interaction. Thousands of drug interactions have been reported in the literature, but only a few are certain to occur or have potential for great clinical harm. Reports on drug interactions are replete with small case series, single case reports, and extrapolations from animal and in vitro data. This evidence, when judged by standard criteria for rating quality of evidence for therapy or harm, is of low quality.[12,13]

Third, most resources do not distinguish between clinical and non-clinical outcomes, where a non-clinical outcome is defined as a modification in blood concentration or clearance of a substance in the absence of any clinically evident effect. This differentiation of non-clinical from clinical effects is important in determining an interaction's clinical relevance. Drug interactions should be evaluated using a hierarchical system that stratifies interactions based on their outcome, clinical significance, and quality of supporting evidence. To address the shortfalls of existing resources, we have developed an innovative means of presenting drug interaction information stratified on the basis of clinical effect, clinical significance, and quality of evidence.

Ms Crowther *is a doctoral student at the University of Toronto.* **Dr Holbrook** *is Associate Professor of Medicine at the Centre for Evaluation of Medicines in St Joseph's Hospital and in the Division of Clinical Pharmacology, Department of Medicine, at McMaster University in Hamilton.* **Mr and Ms Kenwright** *are at the Medwin Group Inc in Mississauga, Ont.*

METHODS

The 50 drugs most frequently dispensed from prescriptions written by Canadian family physicians in 1992 and 1993 (IMS Canada, Compuscript) provided the basis for a literature review on drug interactions. Individual drugs were organized into pharmacologic class, such as β-blockers and nonsteroidal anti-inflammatory drugs, when drug interaction profiles were similar. The original drug list was expanded to include other medications and substances that frequently interact with the selected drugs, including alcohol, food, and tobacco.

Data sources

Two reference books, *Evaluation of Drug Interactions*[14] and *Drug Interactions and Updates*,[15] were used. These references were selected because they are updated regularly and give detailed summaries of clinical outcome, mechanism of action, and supporting references. When more information or clarification was required to evaluate the interaction, the original papers were consulted. MEDLINE was

searched from 1966 to 1994 to identify other studies or interactions not reported in the textbooks, using MeSH headings "drug interactions," "English," "human," and the applicable MeSH heading or text word for the specific drug. Only interactions between the selected drugs were included. Interactions based on animal or in vitro studies were excluded.

Evaluation of interactions

Interactions were evaluated in three domains:

- clinical effect (includes outcome of interaction and clinical versus non-clinical effect),
- clinical significance, and
- quality of evidence.

Each interaction was evaluated independently by two reviewers (R.C. and A.H.) with disagreements resolved by review and consensus.

Clinical effect

Outcome of interaction: The outcome of an interaction was classified as augmentation, inhibition, no effect, or conflicting evidence. Any drug effect greater than expected in the presence of another drug or substance, or greater than the sum of the individual drugs' effect was classed as augmented. Any effect of a drug that was less than expected in the presence of another drug or substance was classed as inhibited. Additive or simple antagonist effects that were predictable based on pharmacology were not classed as an interaction and therefore not included, for example, the additive blood pressure–lowering effects of combining two antihypertensive agents or the obvious antagonistic effects of combining a β-blocker with a β-agonist. If two substances neither inhibited nor potentiated each other's clinical effect, this was classed as no effect.

If several reports of varying quality came to different conclusions regarding the possibility of interaction, the interaction supported by the highest quality of evidence was reported. For several drug pairs, reports of similar quality came to different conclusions regarding the possibility of interaction. These were classified as conflicting evidence. If a healthy volunteer study demonstrated a different type of interaction than did a patient-based study with the same quality of evidence, the latter study was given priority, as patient samples were considered to be more generalizable than volunteer samples.

Clinical versus non-clinical effect: For a drug interaction to rate as clinical, it had to produce some clinically evident effect like a symptom, sign, or laboratory evidence of clinical effect (eg, increased INR or decreased serum potassium). Drug interactions that caused only a change in the blood concentration or clearance of a drug, in the absence of a clinically evident effect, were rated non-clinical.

Clinical significance. An interaction's clinical significance was classified as major, moderate, or minor, depending on severity of outcome. If the clinical outcome required urgent medical attention or hospitalization, caused permanent damage, or was life threatening, it was considered major. If the interaction was likely only to interrupt usual activities or to require medical attention, it was classified as moderate. If the patient was unlikely to note any effect on usual activities or require medical attention, the interaction was considered minor.

Quality of evidence. The quality of evidence was judged as good, fair, or poor, depending on the methodologic quality of individual reports and the quantity of evidence supporting an interaction. The standard criteria for rating the quality of evidence[12] could not be used because most evidence for drug interactions is derived from low-quality studies, such as case series and case reports. Thus, criteria amalgamating standard levels of evidence rating with quantity of evidence and causation assessment were applied.[16,17] In general, a randomized, controlled trial or several studies demonstrating a clinical effect related to an interaction supported by documented pharmacokinetic or pharmacodynamic effects was considered high-quality evidence. An interaction supported by a small study or numerous case reports was considered fair, while a single case report was rated as poor.

Graphic presentation

After building a computerized database of the interactions, we wished to develop a comprehensive, user-friendly graphic presentation of the data. The choice of graphic format was based on clarity, accessibility during patient encounters, and brevity. After testing the usual text and tabular presentations, which failed on all three criteria, we developed a grid-map format (**Figure 1**).

The outcome of an interaction was characterized as **A** for augmentation, **I** for inhibition, ● for no effect, or ○ for conflicting evidence. Where no evidence existed for an interaction, the appropriate cell was left blank. Arrows pointing to the affected drug represented the direction of outcome. The number of arrows symbolized the degree of significance, with one (▲), two (▲▲), and three (▲▲▲) arrows

Figure 1. Grid-map chart listing potential interactions and their severity

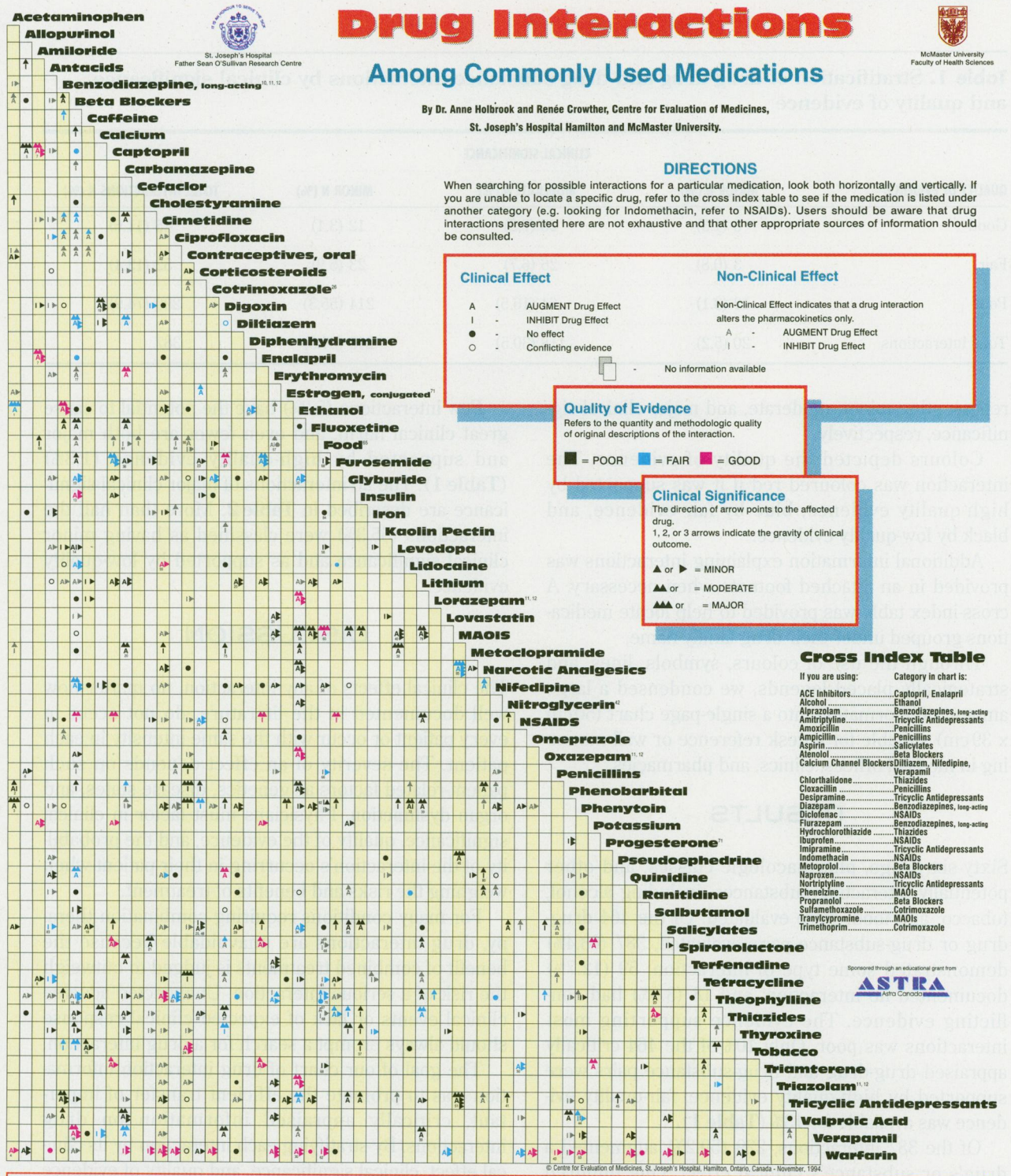

Table 1. Stratification of drug-drug and drug-substance interactions by clinical significance and quality of evidence

	CLINICAL SIGNIFICANCE			
QUALITY OF EVIDENCE	MAJOR N (%)	MODERATE N (%)	MINOR N (%)	TOTAL INTERACTIONS N (%)
Good	5 (1.3)	28 (7.2)	12 (3.1)	45 (11.6)
Fair	3 (0.8)	26 (6.7)	23 (5.9)	52 (13.4)
Poor	12 (3.1)	64 (16.5)	214 (55.3)	290 (74.9)
Total interactions	20 (5.2)	118 (30.5)	249 (64.3)	387

representing minor, moderate, and major clinical significance, respectively.

Colours depicted the quality of evidence. The interaction was coloured red if it was supported by high-quality evidence, blue by fair evidence, and black by low-quality evidence.

Additional information explaining interactions was provided in an attached footnote when necessary. A cross-index table was provided to help locate medications grouped under their drug family name.

Through the use of colours, symbols, lines, and strategically placed legends, we condensed a large amount of information into a single-page chart (50 cm x 39 cm) suitable for a desk reference or wall mounting in medical offices, clinics, and pharmacies.

RESULTS

Sixty-six drugs, pharmacologic classes, and other potentially interacting substances, including alcohol, tobacco, and food, were evaluated. Of the 464 drug-drug or drug-substance pairs evaluated, 387 (83.4%) demonstrated some type of interaction, 59 (12.7%) documented no interaction, and 18 (3.9%) had conflicting evidence. The evidence supporting most interactions was poor. Only 10% of the 464 critically appraised drug-drug and drug-substance pairs were supported by high-quality evidence; fair-quality evidence was available for 13% (**Table 1**).

Of the 387 interactions, 229 (59.2%) augmented a drug's or substance's clinical effect. One hundred forty-eight (38.2%) interactions inhibited the effect of a drug or substance. Ten (2.6%) interactions had a combination of augmentation and inhibition (eg, erythromycin and theophylline, where theophylline inhibits the effect of erythromycin and erythromycin augments the effect of theophylline). Thirty percent of the 387 interactions were classified non-clinical.

Few interactions (5.2%) have the potential to cause great clinical harm, and even fewer are both major and supported by high-quality evidence (1.3%) (**Table 1**). The 20 interactions of major clinical significance are described in **Table 2**. More than half the interactions (55.3%) were classified as having minor clinical significance and as supported by low-quality evidence.

DISCUSSION

The clinical effects of any interaction, no matter how well documented in the literature, do not occur in every patient or occur with the same intensity in each patient. The severity of an effect depends on such patient-related factors as genetics, disease states, and organ dysfunction. Physicians must factor in clinical significance, quality of the evidence, and the probability of the interaction's occurring in their patient when weighing the risks and benefits of treatment.

For many conditions requiring combination therapy, drug interactions are unavoidable because the benefit of combined treatments is judged to outweigh the risk of a serious interaction. Unexpected adverse clinical events or lack of expected clinical response should always prompt a search for a drug interaction.

The goal of our chart of drug interaction information was to promote the efficient transfer of important, critically appraised information on drug interactions. By stratifying each interaction by its clinical effect, clinical significance, and quality of evidence in one cell, clinicians have an immediate synopsis of that interaction. Using rows and columns, a particular drug can be quickly reviewed for all its potential interactions. Finally, use of standard colours and symbols allows for a general scan of quality and clinical severity of drug interaction reports. Clinicians are free to set their own thresholds for acceptable interactions.

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Table 2. Drug-drug and drug-substance interactions of major clinical significance

INTERACTION	CLINICAL EFFECT	QUALITY OF EVIDENCE
Theophylline and cimetidine	Augments theophylline effect	Good
Tobacco and oral contraceptives*	Augments tobacco effect	Good
Tyramine-containing foods and monoamine oxidase inhibitors†	Augments tyramine effect	Good
Warfarin and cimetidine	Augments warfarin effect	Good
Warfarin and erythromycin	Augments warfarin effect	Good
Acetaminophen and ethanol‡	Augments acetaminophen effect	Fair
Monoamine oxidase inhibitors and narcotic analgesics§	Augments MAOI and narcotic analgesic effects	Fair
Theophylline and ciprofloxacin‖	Augments theophylline effect	Fair
Acetaminophen and phenytoin¶	Augments acetaminophen effect	Poor
Allopurinol and captoril#	Augments allopurinol effect	Poor
Oral contraceptives and penicillins	Inhibits oral contraceptives' effect	Poor
Oral contraceptives and phenobarbital	Inhibits oral contraceptives' effect	Poor
Oral contraceptives and phenytoin	Inhibits oral contraceptives' effect	Poor
Oral contraceptives and tetracycline	Inhibits oral contraceptives' effect	Poor
Erythromycin and terfenadine**	Augments terfenadine effect	Poor
Ethanol and monoamine oxidase inhibitors†	Augments tyramine effect	Poor
Levodopa and metoclopramide††	Augments levodopa effect	Poor
Monoamine oxidase inhibitors and levodopa††	Augments MAOIs' effect	Poor
Monoamine oxidase inhibitors and pseudoephridine††	Augments MAOIs' effect	Poor
Monoamine oxidase inhibitors and tricyclic antidepressants	Augments MAOI and tricyclic antidepressant effects	Poor

**Potentiates tobacco-induced adverse cardiovascular effect.*
†Potential for serious hypertensive reaction with tyramine-containing food or beverages.
‡With high doses of ethanol, acetaminophen-induced hepatotoxicity can occur.
§Serious problem with meperidine; morphine appears safer.
‖Elderly patients are more likely to experience this interaction.
¶Potentiates acetaminophen-induced hepatotoxicity.
#Rare reports of Stevens-Johnson syndrome.
***Can cause cardiac toxicity.*
††Potential hypertensive crisis.

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Some cautions are appropriate when using this drug interaction chart.

- Absence of a reported interaction does not mean proof of no interaction. Many drugs have not been evaluated for their potential to interact with each other and should, therefore, not be presumed to have no clinical effect on each other.
- Interactions based on low-quality evidence or classified as conflicting evidence should not be completely discounted. Given the variability in patients, comorbidity, concomitant medication, and diet, some type of drug interaction could occur for any given drug pair.
- Users should be aware that interactions presented in the chart are not exhaustive and that other appropriate sources of information should be consulted. These interactions are based on information available at the end of 1994. We suspect that indexing within MEDLINE for reports of drug interactions is less than optimal.[18,19]
- It is difficult to incorporate new drugs or interactions into this format, and therefore the chart could become outdated. When new important information or new frequently prescribed medications need to be added to the chart, the entire chart must be reissued. However, an update of the literature review to 1997 did not uncover any new interactions of major clinical significance.
- Many other drugs, used less frequently, could interact with the listed drugs. Although requiring considerably more effort, it is important to document the interactions of these drugs as well, because their relatively uncommon use would render their interactions less familiar.

Conclusion

Despite a plethora of reports of drug interactions, very few are based on high-quality evidence, and even fewer are considered to be of major clinical significance. The Drug Interactions Among Commonly Used Medications chart has been designed as an informative drug interaction aid for physicians and other health professionals to consult at the time that it is needed most, during the physician-patient encounter.

To obtain a copy of the Drug Interactions among Commonly Used Medications chart, please contact Renée Crowther, Centre for Evaluation of Medicines, St Joseph's Hospital, 50 Charlton Ave E, Martha Wing H312, Hamilton, ON L8N 4A6; telephone (905) 522-1155, extension 5217.

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Correspondence to: *Renée Crowther, Centre for Evaluation of Medicines, St Joseph's Hospital, Martha Wing H312, 50 Charlton Ave E, Hamilton, ON L8N 4A6; telephone (905) 522-1155, extension 5217; e-mail:* **rcrowthr@fhs.csu.mcmaster.ca**

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