

# Drug interactions among commonly used medications

## *Chart simplifies data from critical literature review*

N. Renée Crowther, MSc Anne M. Holbrook, MD, PHARM D, 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 les 16 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.

*This article has been peer reviewed.*

*Cet article a fait l'objet d'une évaluation externe.*

*Can Fam Physician 1997;43:1972-1981.*

**D**rug 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<sup>1,3</sup> 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<sup>4,9</sup>; 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.<sup>1,3</sup> 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.<sup>10</sup> Physicians' offices must be computerized, however, and the software must be accessible to .....

**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.

physicians during patient visits. Unfortunately, few physician offices are computerized beyond billing purposes and even fewer have computers in patient examining rooms.<sup>11</sup>

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.<sup>12,13</sup>

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.

## 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  $\beta$ -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*<sup>14</sup> and *Drug Interactions and Updates*,<sup>15</sup> 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

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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  $\beta$ -blocker with a  $\beta$ -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.

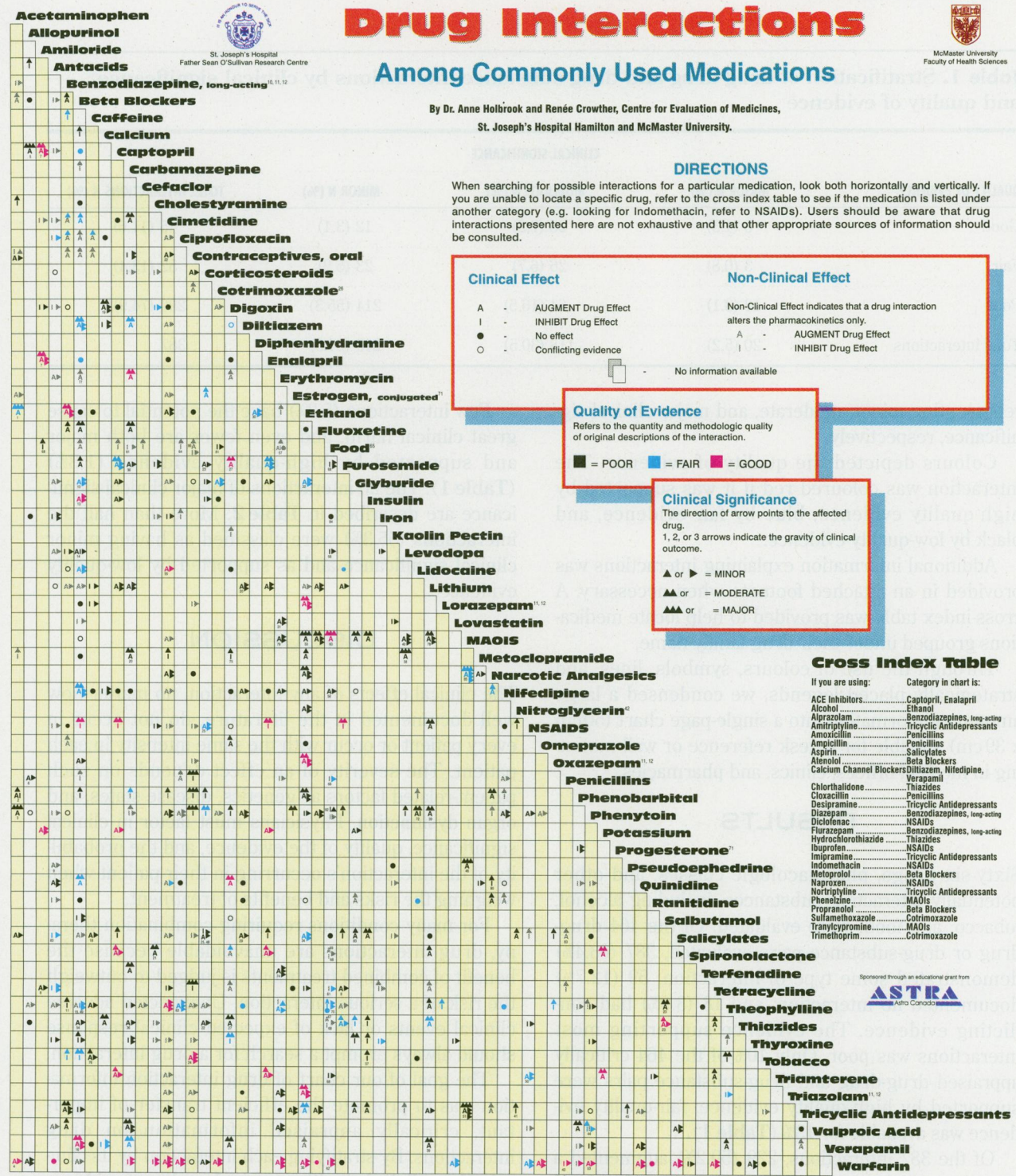
**Quality of evidence.** The quality of evidence was judged as good, fair, or poor, depending on the methodologic quality of individual reports and the quantity of evidence supporting an interaction. The standard criteria for rating the quality of evidence<sup>12</sup> could not be used because most 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.<sup>16,17</sup> 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**



# Drug Interactions

## Among Commonly Used Medications

By Dr. Anne Hobbrook and Renée Crowther, Centre for Evaluation of Medicines,  
St. Joseph's Hospital Hamilton and McMaster University.

### DIRECTIONS

When searching for possible interactions for a particular medication, look both horizontally and vertically. If you are unable to locate a specific drug, refer to the cross index table to see if the medication is listed under another category (e.g. looking for Indomethacin, refer to NSAIDs). Users should be aware that drug interactions presented here are not exhaustive and that other appropriate sources of information should be consulted.

#### Clinical Effect

- A - AUGMENT Drug Effect
- I - INHIBIT Drug Effect
- - No effect
- - Conflicting evidence

#### Non-Clinical Effect

- Non-Clinical Effect indicates that a drug interaction alters the pharmacokinetics only.
- A - AUGMENT Drug Effect
  - I - INHIBIT Drug Effect
  - - No information available

#### Quality of Evidence

Refers to the quantity and methodologic quality of original descriptions of the interaction.

- = POOR
- = FAIR
- = GOOD

#### Clinical Significance

The direction of arrow points to the affected drug.

1, 2, or 3 arrows indicate the gravity of clinical outcome.

- ▲ or ► = MINOR
- ▲▲ or ►► = MODERATE
- ▲▲▲ or ►►► = MAJOR

### Cross Index Table

If you are using:      Category in chart is:

ACE Inhibitors.....	Captopril, Enalapril
Alcohol.....	Ethanol
Alprazolam.....	Benzodiazepines, long-acting
Amitriptyline.....	Tricyclic Antidepressants
Amoxicillin.....	Penicillins
Ampicillin.....	Penicillins
Aspirin.....	Salicylates
Atenolol.....	Beta Blockers
Calcium Channel Blockers.....	Diltiazem, Nifedipine, Verapamil
Chlorthalidone.....	Thiazides
Cloxacillin.....	Penicillins
Desipramine.....	Tricyclic Antidepressants
Disipram.....	Benzodiazepines, long-acting
Diclofenac.....	NSAIDs
Flurazepam.....	Benzodiazepines, long-acting
Hydrochlorothiazide.....	Thiazides
Ibuprofen.....	NSAIDs
Imipramine.....	Tricyclic Antidepressants
Indomethacin.....	NSAIDs
Metoprolol.....	Beta Blockers
Naproxen.....	NSAIDs
Nortriptyline.....	Tricyclic Antidepressants
Phenazine.....	MAOIS
Propranolol.....	Beta Blockers
Sulfamethoxazole.....	Cotrimoxazole
Tranlycypromine.....	MAOIS
Trimethoprim.....	Cotrimoxazole



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|--|--|--|
| <p>1 With high doses of ethanol, acetaminophen-induced hepatotoxicity may occur</p> <p>2 Chronic phenobarbital use may potentiate hepatotoxicity in acetaminophen over dose. With usual doses of acetaminophen, long-term phenobarbital intake inhibits acetaminophen.</p> <p>3 Potentiate acetaminophen-induced hepatotoxicity</p> <p>4 With high dose acetaminophen only</p> <p>5 Rare reports of Stevens-Johnson syndrome</p> <p>6 Possibly higher incidence of ampicillin-associated rash</p> <p>7 Possible risk of hyperkalemia</p> <p>8 May elevate BUN levels</p> <p>9 Reported neuroleptic anaesthesia</p> <p>10 Induces Diazepam, Alprazolam, Flurazepam</p> <p>11 Benzodiazepines should not be administered if respiratory depression could not be tolerated</p> <p>12 Benzodiazepines are not recommended for long-term use</p> <p>13 Delays recovery from hypoglycemia, may mask hypoglycemic symptoms</p> <p>14 Potentiate anti-neuroleptic effect</p> <p>15 Beta blockers may antagonize bronchodilation</p> <p>16 Augments coronary vasoconstriction</p> <p>17 In general, caffeine has little or no effect on the action of antihypertensives</p>   | <p>18 Potentiate analgesic effect of aspirin</p> <p>19 Rare cases of cardiac arrhythmias with IV calcium</p> <p>20 May potentiate neurotoxicity (1 case report)</p> <p>21 Rare cases of hypertensive crisis in cardiac patients</p> <p>22 May potentiate estrogen effect</p> <p>23 May potentiate hypokalemia</p> <p>24 Potentiate ticlopidine-induced adverse cardiovascular effect</p> <p>25 May potentiate gastrointestinal ulceration</p> <p>26 Includes interaction for salbutamol and nitroglycerin</p> <p>27 Digoxin toxicity if potassium and magnesium levels low</p> <p>28 Rare report of nausea, tremor, shakiness, rigidity</p> <p>29 May potentiate anti-platelet effect</p> <p>30 Enhanced motor and mental impairment</p> <p>31 One case of mabdomyolysis - could be lovastatin-induced</p> <p>32 Potentiate a disulfiram-like reaction</p> <p>33 Alcoholic beverages containing tyramine may induce severe hypertension</p> <p>34 Potentiate gastrointestinal bleeding time</p> <p>35 With liver disease and with acute ethanol overdoses</p> <p>36 May potentiate risk of hypoglycemia</p> <p>37 May decrease subcutaneous absorption</p> | <p>38 Single case of hypertensive crisis with carbidoipine/levodopa</p> <p>39 May result in neurotoxicity</p> <p>40 Hypertensive crisis, but not if taking clobazam (Stammet)</p> <p>41 TCA-induced dry mouth may prevent dissolution of sublingual nitroglycerin</p> <p>42 Long-acting nifedipine (eg, sustained-release) may cause tolerance to nifedipine and nitroglycerin</p> <p>43 Reported for penicillase-resistant penicillins (eg, nafcillin, dicloxacillin)</p> <p>44 Vagionic acid may lower serum phenytoin levels initially, followed by a return to previous levels</p> <p>45 Inhibits progestin effect</p> <p>46 Rare report of hyperemesis gravidarum</p> <p>47 Increase chance of digoxin toxicity if salbutamol-induced hypokalemia</p> <p>48 May lower salicylate levels</p> <p>49 Propofol may increase theophylline serum levels</p> <p>50 Rarely associated with acute renal failure</p> <p>51 Rare reports of fever, myalgia and convulsions</p> <p>52 Reported for penicillase-resistant penicillins (eg, nafcillin, dicloxacillin) biphatic with later inhibition</p> <p>53 Statins with later inhibition</p> <p>54 May increase serum glucose in Type 2 Diabetics</p> |
| <p>55 Single dose of cimetidine may not alter ibuprofen's effect</p> <p>56 Described with food or grapefruit juice</p> <p>57 Erythromycin acetate and erythromycin ethylsuccinate augmented, erythromycin stearate inhibited, erythromycin base no effect</p> <p>58 Problem with high protein diets (2g/kg/day)</p> <p>59 Levodopa interacts with high protein diets (2g/kg/day)</p> <p>60 Potential for major hyperkalemic reaction with tyramine-containing food</p> <p>61 Food and dairy products containing high concentrations of calcium such as calcium, magnesium, iron</p> <p>62 High vitamin K content foods/animal feeds, large amounts of avocado</p> <p>63 Elderly patients are more likely to experience this interaction</p> <p>64 Dairy products</p> <p>65 High fat/cholesterol foods may increase hydrochlorothiazide absorption</p> <p>66 Except amoxicillin, penicillin V, ampicillin suspension</p> <p>67 High carbohydrate meals can increase hydrochlorothiazide absorption</p> <p>68 Folic acid increases absorption of drug</p> <p>69 Effect varies with frequency preparation and contents of diet</p> <p>70 Effect varies with frequency preparation and contents of diet</p> <p>71 See oral contraceptive interactions under "contraceptives, oral"</p> <p>72 May increase metabolism of ibuprofen but may also increase cardiac rate</p> | <p>Depression</p> <p>73 Phenytoin and lidocaine can have an additive effect on myocardial tissue that may result in excessive cardiac depression</p> <p>74 May cause cardiac toxicity</p> <p>75 Affects slow-dissolving digoxin only (not lanolin)</p> <p>76 May cause cardiac toxicity</p> <p>77 Effects less than additive but still greater than their individual effects</p> <p>78 Interaction reported for nafcillin only</p> <p>79 Four cases of neuroleptic malignant syndrome (poorly documented)</p> <p>80 Single case report of hypertension and atropine with phenazine</p> <p>81 Inhibits the metabolism of codeine to morphine</p> <p>82 Folic acid deficiency</p> <p>83 With high doses of aspirin (Dipleg)</p> <p>84 Ascorbic acid may potentiate absorption of iron in some patients</p> <p>85 Major problem with imipramine, moxipram appears safer</p> <p>86 Acetaminophen only</p>  |  |

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

QUALITY OF EVIDENCE	CLINICAL SIGNIFICANCE			TOTAL INTERACTIONS N (%)
	MAJOR N (%)	MODERATE N (%)	MINOR 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.

**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 captopril#	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 pseudoephedrine††	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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### Drug interactions among commonly used medications

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.<sup>18,19</sup>
- 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.

### Acknowledgment

The drug interaction chart was sponsored by Astra Pharma Canada Inc through an unrestricted educational grant. The company had no input into the drugs included in the chart, the evaluation of the interactions, or the chart design. Renée Crowther is funded by a Centre for Evaluation of Medicines-Canadian Drug Manufacturing Association-Medical Research Council studentship. Dr Holbrook received a research personnel grant from the Ontario Ministry of Health.

**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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# Ben Wicks'

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### MONOPRIL\* (fosinopril sodium) TABLETS 10 and 20 mg

**THERAPEUTIC CLASSIFICATION:**  
Angiotensin Converting Enzyme Inhibitor

**INDICATIONS AND CLINICAL USE:**

Mild to moderate essential hypertension. May be used alone or in association with thiazide diuretics. Use in renovascular hypertension not established. Use of antihypertensive agents other than thiazide diuretics has not been established. Adjunctive treatment in the management of symptomatic congestive heart failure. Initiate treatment under medical supervision. **When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected MONOPRIL should be discontinued as soon as possible.**

**CONTRAINDICATIONS:**

Hypersensitivity and a history of angioedema.

**WARNINGS:**

**Angioedema:** Discontinue. Observe until the swelling disappears. Where tongue, glottis or larynx are involved administer 0.3 to 0.5 mL epinephrine 1:1000.

**Hypotension:** Patients with severe congestive heart failure, ischemic heart or cerebrovascular disease, should start therapy under close medical supervision and be followed closely for the first weeks of treatment and whenever dose of MONOPRIL or diuretic is increased.

**Neutropenia/Agranulocytosis:** Monitor white blood cell counts.

**Use in Pregnancy:** ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Discontinue as soon as possible.

**PRECAUTIONS:**

**Renal Impairment:** Use with caution.

**Surgery/Anesthesia:** May augment the hypotensive effects of anesthetics and analgesics.

**Hyperkalemia and Potassium-Sparing Diuretics:** In clinical trials, elevated serum potassium (greater than 5.5 mEq/L) was observed in approximately 2.6% of hypertensive patients and were mostly self-resolving.

**Anaphylactoid reactions during membrane exposure:** Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., polyacrylonitrile (PAN)) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately.

**Anaphylactoid reactions during desensitization:** There have been isolated reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom.

**Valvular Stenosis:** Theoretically patients with aortic stenosis might be at risk of decreased coronary perfusion when treated with vasodilators as they do not develop much afterload reduction.

**Patients with Impaired Liver Function:** Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors. In most cases the changes were reversed on discontinuation of the drug. Use with caution in patients with pre-existing liver abnormalities.

**Cough:** Consider as part of the differential diagnosis.

**Nursing Mothers:** Should not be administered.

**Pediatric Use:** Not recommended.

**Use in Elderly:** No identified differences in response. Greater sensitivity is possible.

**DRUG INTERACTIONS**

**Agents Increasing Serum Potassium:** Administer cautiously and monitor frequently.

**Agents Causing Renin Release:** Antihypertensive effect is augmented.

**Lithium:** May result in increased serum lithium levels. Coadminister cautiously and monitor frequently.

**Antacids:** May impair absorption of fosinopril. If coadministration is indicated, separate dosing by two hours.

**Digoxin:** Bioavailability of fosinopril not altered.

**Furosemide:** Coadministration increased AUC of fosinopril by 26% and C<sub>max</sub> by 25%. Furosemide levels were decreased.

**Warfarin:** Bioavailability of fosinopril or warfarin not altered.

**Other:** Bioavailability of fosinopril not altered with chlorthalidone, nifedipine, propranolol, hydrochlorothiazide, cimetidine, metoclopramide and propantheline.

**ADVERSE REACTIONS:**

Severe adverse reactions occurring in 1548 hypertensive patients treated with MONOPRIL were: angioedema (1 case) and orthostatic hypotension (2.7%). Myocardial infarction (2 cases) and cerebrovascular accident (4 cases) occurred, possibly secondary to excessive hypotension in high risk patients. In 516 heart failure patients, the severe adverse reaction occurring with the highest frequency was angina pectoris (1.6%). In placebo-controlled hypertension trials (688 patients), the most frequent clinical adverse reactions were nausea/vomiting, diarrhea, fatigue, musculoskeletal pain, headache, dizziness and cough. Discontinuation of therapy due to adverse events was required in 4.1% of the 688 patients. Cough was the cause for discontinuation of therapy in 0.4% of these patients. In placebo-controlled CHF trials (361 patients), the most frequent adverse reactions were: dizziness, cough, headache and fatigue. Significant hypotension after the first dose of MONOPRIL occurred in 2.4% of patients, while 0.8% discontinued due to first dose hypotension. Discontinuation of therapy due to adverse events was 7.8% of 361 patients. Cough was the cause for discontinuation of therapy in 0.8% of these patients.

**DOSAGE AND ADMINISTRATION:**

Individualize dosage. Hypertension: Monotherapy 10 mg OD. Range: 10-40 mg OD (maximum 40 mg OD).

**Concomitant Diuretic Therapy:** Discontinue diuretic for two to three days before MONOPRIL.

**Heart Failure:** MONOPRIL is generally used in conjunction with a diuretic, with or without digoxin. Blood pressure and renal function should be monitored, both before and during treatment with MONOPRIL, because severe hypotension, and more rarely renal failure, have been reported (see WARNINGS - Hypotension, PRECAUTIONS - Renal Impairment). Initiation of therapy requires consideration of recent diuretic therapy, and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning treatment to reduce the likelihood of hypotension

(see PRECAUTIONS - Drug Interactions). In heart failure, the recommended initial dose of MONOPRIL is 10 mg OD, initiated under close medical supervision. If initial dose is well tolerated, it should be titrated over 1 to 3 weeks to 20-40 mg OD. The occurrence of hypotension after the initial dose may not preclude careful dose titration with MONOPRIL following effective management of hypotension. In severe congestive heart failure with or without renal insufficiency, therapy with MONOPRIL should be initiated with caution (see WARNINGS - Hypotension). A lower starting dose should be considered.

**Renal Impairment:** 10 mg OD. In such patients with heart failure, therapy should be initiated with caution.

**Hepatic Impairment and Normal Renal Function:** no dosage adjustment is necessary. In such patients with heart failure, therapy should be initiated with caution.

**AVAILABILITY:**

MONOPRIL 10 mg tablets are white to off-white, flat end, diamond shaped, compressed tablets with a partial bisect bar engraved with BMS on one side and MONOPRIL 10 on the other. MONOPRIL 20 mg tablets are white to off-white, oval shaped, compressed tablets engraved with BMS on one side and MONOPRIL 20 on the other. MONOPRIL 10 and 20 mg tablets are available in bottles of 100 tablets.

Full Product Monograph available upon request.

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2365 Côte-de-Liesse Rd.  
Saint-Laurent, Quebec  
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