Drug Interactions in the Elderly

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Polypharmacy and its dangers in the elderly are of increasing concern. The purpose of this study was to determine the incidence of drug with drug, drug with food, and drug with alcohol interactions in a population aged 60 years or greater. Four hundred patients were randomly selected from a university family medicine outpatient clinic population of 4,483 in this age group. A total of 292 drugs were involved for a total of 1,052 potential interactions: 310 drug–food, 316 drug–alcohol, and 426 drug–drug. Interactions were analyzed using The Drug Master *computer program and rated as to their clinical significance. Chart review revealed no serious actual interaction for any patient even though potential interactions could be categorized as highly significant for 27 percent of the drug–drug, 11 percent of the drug–alcohol, and 3 percent of the drug–food. Thirty-two percent of the total population were taking five or more drugs concurrently. The mean number of drugs for men was 3.75 and for women 4.22 ($P < .05$). Age and race differences were also noted in the number of drugs taken. The most common drugs and their interactions with drug, food, and alcohol are reviewed.*

Because of ongoing concern about the practice of polypharmacy, especially in the elderly, a university family practice outpatient population was studied for any potential or actual drug–drug interactions by analyzing the frequency, severity, and character of these interactions. As drug–food and drug–alcohol interactions frequently occur, these were also investigated. The objectives of this study were (1) to estimate the rates for drug–drug, drug–food, and drug–alcohol interactions in a family practice clinic population aged 60 years or older; (2) to compare the incidence of polypharmacy and interactions for cohort groups by age, sex, and race; and (3) to provide a discussion and descriptive summary of the most common drug interactions with other drugs, foods, and alcohol.

For the past 25 years there has been a dramatic rise in the use of prescription drugs, from 2.4 to 7.5 prescriptions per person annually. Among elderly patients the use is much higher—as many as 13 prescriptions a year.[1] Mitchell et al[2] reported a potential drug–drug interaction incidence rate of 32.5 percent for patients on more than single-drug therapy. They also reported an even higher rate of 47 percent potential interaction for the monitored ambulatory population studied. At least one potential drug–drug interaction was reported in 17 percent of the surgical patients studied by Durrence et al.[3] After studying all hospital patients at a private community hospital, Greenlaw and Zellers[4] reported potential drug interactions in about 9 percent of the patients per day. Chronic care facilities and nursing homes report drug interaction rates of 23 to 53 percent and drug utilization of 4.85 to 8.33 drugs per patient.[5–12] Studies report a 6 percent frequency of drug interaction in an ambulatory population with an average of 9.2 prescriptions per year per patient.[5–12] Brown et al[13] observed that the incidence of adverse reaction is increased when prescriptions are written on an as-needed basis. Lamy,[14] referring to Robinson's article,[15] indicates that most adverse drug interactions are predictable and avoidable. Lamy further states that the drugs that are most common offenders are the most commonly prescribed drugs, not the rarely used drugs.

May et al[16] reported that patients on five or fewer drugs have a 4 percent adverse response rate, whereas for patients on 16 to 20 drugs, the rate escalates to 54 percent. It can be expected, according to calculations by May and colleagues, that patients taking six to 10 drugs would have an adverse reaction rate of 10 percent.

While the literature addresses the dangers of multiple drug interactions, there is a paucity of information about these interactions when multiple drugs are admixed. Nearly all tables and computer designs reference only one drug with one other. No study reports the interaction of host factors and multiple drugs. It is rare to find references

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TABLE 1. NUMBER AND PERCENTAGE OF PATIENTS BY CATEGORY OF CONCURRENT DRUGS USED

Number of Drugs Taken Concurrently	Number of Patients	Percent
2	103	26
3	96	24
4	73	18
5	53	13
6	29	7
7 or more	46	12
Total	400	100

to the often important drug–food and drug–alcohol interactions. Indeed, as one author observed, patients are becoming "living chemistry sets."[17]

METHODS

A study was undertaken in which patient charts from a university family practice outpatient clinic were reviewed for drug interactions. Approved by the university Human Studies Committee, the chart review took approximately 12 weeks and covered visits made during the previous year. The contents of the medical records were searched for the types of medications and any reported adverse drug effects. These charts were pulled from a total patient population of 33,733, which included 5,281 patients aged 60 years and over. Of these 5,281 records, only 4,483 were accessible in the principal clinic studied. Those chosen for the survey were required to satisfy two criteria: (1) the patient had to be 60 years of age or older, and (2) the patient had to be taking two or more medications concurrently as documented in chart notes. The charts were pulled at random, and the first 400 patient charts that met these criteria were selected for the study. The charts were arranged into categories according to the number of medications being taken to form cohorts of two, three, four, five, six, and seven or more concurrent drugs used per patient.

Data collected from the charts included the patients' age, sex, race, number of medications, and the names of the medications. All medications listed in the charts, including vitamins, potassium, calcium, aspirin, and any over-the-counter medications were counted along with all prescription items in the survey.

For the purpose of counting the number of medications each patient was taking, each medication listed was counted as one, even if it contained a combination of two or more chemical compounds. For example, Dyazide, though composed of triamterene and hydrochlorothiazide, was counted as one medication. These compound preparations, however, were analyzed for adverse reactions by the computer according to their component drugs.

Screening was done by a computer program entitled, *The Drug Master* by Thomas Shreve.[18] This program was used on an ITT XP microcomputer equipped with a 20-megabyte hard disk. Fifteen hundred drugs make up the database of this program, which offers the possibility of entering for interaction analysis up to 15 drugs at one time. The program automatically performs an interaction analysis not only between the drugs entered but also between those drugs and food and alcohol. A drug list for each of the 400 patients was entered into the computer. A rating of low, moderate, or high clinical significance was assigned to each interaction, and a computer hard-copy printout giving the potential drug–drug, drug–food, and drug–alcohol interactions was obtained. Potential interactions were also cross-referenced with the 1986 *Physicians' Desk Reference,*[19] the *Physicians' Desk Reference for Nonprescription Drugs,*[20] *The Medical Letter,*[21] *Facts and Comparisons,*[22] Goodman and Gilman's *The Pharmacological Basis of Therapeutics,* ed 7,[23] and current literature as noted in the references. Student's *t* test was used for statistical analysis of data and alpha levels (P) were set at .05.

RESULTS

Of the 400 patients selected for this study, about two thirds were female and one third were male. About 87 percent of the group were aged 65 years or older with an age range from 60 to 100 years. Racial distribution reflected that of the general clinic population, with 41 percent black and 44 percent white. The race of the remaining 14 percent could not be determined from the charts.

Comparisons between patient groups using Student's *t* tests revealed significant differences at the .05 level between men and women on the mean number of drugs taken (3.75 and 4.22, respectively). Number of drugs taken also differed between (1) patients aged 75 years and over and those who were younger than 75 years (4.3 and 3.8, respectively) and (2) white patients and black patients, with white patients taking significantly more drugs.

This sample of patients was using 292 different drugs at the time of data collection. The number of drugs per patient ranged from 2 to 16 with the average number per patient being 4.1. The cohort groups are described in Table 1 by number of drugs taken concurrently. In this sample, 32 percent were taking five or more drugs concurrently.

Even though all patients were taking at least two or more drugs, 96 (24 percent) were not at risk for drug interaction with food, alcohol, or other drugs. In Table 2, the sample is described by the type of potential of inter-

actions; patients with potential drug–drug interactions represented almost one half of the sample (42 percent).

A list of the most commonly prescribed drugs in the study is shown in Table 3. As might be expected, the most commonly prescribed drugs included hydrochlorothiazide (128 times), digoxin (73 times), furosemide (69), and antacids (64).

For this sample there were 1,052 potential interactions. When described according to type of interaction, drug with drug interactions accounted for 40 percent of the potential interactions, followed by drug with alcohol (30 percent), and drug with food (29.5 percent). A summary of the potential interactions by type of interaction is shown in Table 4.

Drug with drug interactions are further described in Table 5. As could be expected, drugs prescribed most commonly were also highest in frequency of potential drug with drug interactions. The drugs accounting for the largest percentages of potential drug with drug interactions were digoxin (24 percent), furosemide (16 percent), and oral antidiabetic agents (9 percent).

While number of drugs taken concurrently is of interest for potential interactions, so also is the clinical significance of those interactions. The number and percentage of each type of potential interaction by the clinical significance levels (low, moderate, or high) are contained in Table 6. For this sample, 15 percent of all potential drug interactions were rated as having high clinical significance, 44 percent were of moderate significance, and 41 percent were of low significance.

No one source was sufficient to obtain all the information necessary to describe potential drug interactions. Table 7 includes descriptions of the drug with alcohol or food interactions, and Table 8 includes alphabetical descriptions of the drug with drug interactions. These tables are meant to be informative and do not reflect the incidence of interaction in this study.

TABLE 2. NUMBER AND PERCENTAGE OF PATIENTS BY INTERACTION TYPE

Interaction Categories	Number	Percent
Patients without potential interaction	96	24
Patients with only potential drug–food or -alcohol interactions	137	34
Patients with potential drug–drug interactions	167	42

TABLE 3. MOST COMMONLY PRESCRIBED DRUGS FOR 400 PATIENTS

Most Commonly Prescribed Drugs	Number of Times Prescribed
Hydrochlorothiazide	128
Digoxin (Lanoxin)	73
Furosemide (Lasix)	69
Antacids	64
Nitroglycerin	55
Potassium chloride	53
Methyldopa (Aldomet)	37
Ibuprofen (Motrin)	36
Hydrochlorothiazide/triamterene (Dyazide)	32
Prazosin (Minipress)	28
Multivitamin	28
Oral antidiabetic agents	28
Propranolol	27
Theophylline (Theo-Dur)	21
Diazepam (Valium)	18
Doxepin (Sinequan)	17
Phenytoin (Dilantin)	16
Insulin	16
Nifedipine (Procardia)	15
Haloperidol (Haldol)	13

TABLE 4. NUMBER AND PERCENTAGE OF INTERACTIONS BY TYPE

Type of Interaction	Number	Percent
Potential drug–food interactions	310	29.5
Potential drug–alcohol interactions	316	30
Potential drug–drug interactions	426	40.5
Total	1,052	100

DISCUSSION

In general, drug interactions are of four kinds: desirable, undesirable, insignificant, and unknown. Drug interactions can cause several types of pharmacological responses. These responses include enhancement of the effects of one or the other drug, development of totally new effects, inhibition of the effects of one or the other drug, and no change in the response.[23] These drug interactions may occur through many mechanisms, such as the following:

1. Decreased or increased intestinal absorption
2. Decreased renal excretion
3. Direct competition for some receptor sites
4. Displacement from carrier proteins
5. Interference with synthesis of enzyme, coenzyme, or carrier
6. Hormonal effects on genetic systems (eg, vitamin and mineral binders)
7. Effects due to vehicle or to components in drug formulation[24]

TABLE 5. DRUGS MOST COMMONLY INVOLVED IN DRUG–DRUG INTERACTIONS

Drug	Number of Potential Drug–Drug Interactions	Percent of the Potential Drug–Drug Interactions (426)	Percent of Total Population (400)*
Digoxin	101	24	18
Furosemide	69	16	13
Oral antidiabetic agents	38	9	7
Antacids	34	8	6
Beta blockers	28	6.5	5.5
Hydrochlorothiazide	27	6	6
Hydrochlorothiazide/ triamterene	15	3.5	3
Phenytoin sodium	14	3	3
Cimetidine	12	3	3
Nifedipine	10	2	1
Promethazine hydrochloride	10	2	1
Doxepin hydrochloride	7	2	1
Indomethacin	7	2	1
All others	42	13	11

** Percentages do not sum to 100, because not all patients had drug interactions, and those that did may have been taking multiple drugs with the potential for multiple interactions*

TABLE 6. INTERACTION TYPE BY CLINICAL SIGNIFICANCE

Clinical Significance	Low No. (%)	Moderate No. (%)	High No. (%)
Potential drug–food interactions (n = 310)	230 (74)	72 (23)	8 (3)
Potential drug–alcohol interactions (n = 316)	40 (13)	242 (77)	34 (11)
Potential drug–drug interactions (n = 426)	158 (37)	153 (36)	115 (27)

Many of these mechanisms were found to be involved in the potential drug–food interactions generated by this study as well as drug–drug interactions.

It should be noted that potential drug interactions with food, alcohol, or other drugs are not the same as actual interactions. Nor are all actual interactions severe or even undesirable. The reduced absorption of erythromycin with food, for example, may have minimal or no serious consequences.

No serious actual drug interaction problems were seen, but 27 percent serious potential interactions were identified. This result could be attributed to good teaching and heightened awareness of physicians about these effects. The paucity of knowledge, however, that exists concerning drug–drug, drug–food, drug–alcohol, and drug–host interactions is alarming. Even worse was the discovery of a poor cataloging of potential mischief. In an extensive effort to find a creditable computer program for this study, very little was available. It was surprising to discover that several major hospitals and clinic pharmacies, and most clinic and nurses' stations, had no ready computer program at hand.

It should be no surprise that commonly used drugs are the major offenders. Apparently physicians give more diligent thought to seldom used medications when they are employed. It was found, as Lamy[14] and others point out, that drug interactions are predictable and preventable. "First do not harm" is an axiom never more appropriate than now when applied to drug therapy.

While analyzing the results, several seemingly irrational drug combinations were observed. For example, hydrochlorothiazide is known to alter glucose metabolism. Hypertensive patients with diabetes mellitus could first be given a trial of prazosin or captopril to try to avoid adverse reactions that might alter glucose homeostasis. While captopril is known to control only 50 percent of patients' blood pressure, it is essential to begin with a minimum therapy while trying to maintain glucose homeostasis. Even though captopril or prazosin might not control all blood pressure, and even though some patients might require a diuretic, it seems wise to avoid, if possible, any drug that alters glucose metabolism in a diabetic. Such errors were found to be common in therapeutics in this study.

Equally troubling was the combination of hydrochlorothiazide or furosemide with digoxin, which occurred 48 times. It is well known that this combination can lead to hypokalemia and conduction block or arrhythmias, from which fatalities have resulted. Even the repairing of the potassium deficit with potassium chloride would be unwarranted if digoxin were not indicated. Digoxin therapy often poses an undesirable and unjustified risk to the patient. There is no pharmacological dictum, "Once digitalis, always digitalis." More consideration needs to be given to criteria for initiating digoxin, but more especially, patients should be considered for discontinuation of digitalis at periodic intervals. Since neither potassium chloride nor potassium-sparing diuretics are without harm and pose considerable expense, more thought should be given to their combination with digoxin. With the growing array of antihypertensive medications, unloading agents for failure, and new antiarrhythmic drugs, serious thought should be given to avoiding treating a patient with digitalis in whom there is a strong potential for problems.

The patients at the greatest risk for potential drug in-

teraction from this study, and the studies of others,[25,26] are those with cardiovascular disease, diabetes, liver disease, and kidney disease. Patients with cardiovascular disease may experience heart failure, arrhythmias, and hypotension; those with diabetes might have interference with glucose homeostasis; patients with liver disease have impaired detoxification; and those with kidney disease have impaired excretion.

More attention needs to be given to the irrational, dangerous, and often unsuspected combination of over-the-counter drugs with prescription medications. There were 121 cases of patients (30 percent of total patients) taking one or more over-the-counter drugs along with their prescription medications. Williams et al[27] reported that it is not uncommon to find elderly patients taking five or more prescription drugs plus several over-the-counter drugs. This study showed that more often than not, combining prescription and nonprescription drugs led to potential interactions. The most commonly used over-the-counter preparations were analgesics, antacids, laxatives, vitamins, cough syrups, cold medicines, and allergy medications. The potential for sedation, malabsorption of drugs, counteracting effects, etc, from the use of over-the-counter drugs is significant and needs to be noted. Even the findings of this study represent an underreporting of the utilization of over-the-counter medications because such use is often episodic and not noted in medical records.

Drug–food and drug–alcohol incompatibilities are well recognized and can be prevented.[28] Even so, there were many potential drug–food and drug–alcohol interactions found in this study. Food delays or reduces the absorption of many drugs including aspirin, acetaminophen, digoxin, furosemide, tetracycline, phenobarbital, penicillin, amoxicillin, and erythromycin. Nitrofurantoin, propranolol, propoxyphene, metoprolol, hydralazine, and spironolactone are better absorbed when taken with food. Certain drugs, such as diuretics, laxatives, antacids, glucocorticoids, and nonnarcotic analgesics, cause depletion of minerals including calcium, potassium, magnesium, zinc, iron, and phosphates.[29]

There were 316 potential drug–alcohol interactions identified in this study that in general potentiated sedation or gastric erosion. Little or no documentation was found on the charts as to whether the patient was consuming alcohol. The lethality of tranquilizers and hypnotics combined with alcohol is well known. Alcohol injury of the liver and decreased detoxification can only compound with hepatotoxic drugs.

There were 310 potential drug–food interactions, by far the most common being decreased absorption. Less than casual attention was given to such drug–food combinations as erythromycin–food, tetracycline–food, and theophylline–food. In general, inadequate attention may be paid by physicians to drug–food interactions even though they are well known. This problem may be especially compounded because prescribing habits often relate drug ingestion to meal times as a way to increase compliance and gastric tolerance. Much could be done to alleviate these problems by pharmacist auxiliary labeling to call attention to possible interactions with other drugs, food, or alcohol.

The Medical Letter reports[21] that very little is known about the combined effects of more than two drugs. Nearly all studies reference one drug with one other as to side effects and untoward responses.

Little is also known about the diseased host's response to multiple drug therapy. Congestive heart failure, for example, may cause chronic congestion of the liver with reduced detoxification, as in the case of theophylline. Worse still is the effect in an aged, diseased host. There are many physiological changes associated with aging that alter host response to drugs.

1. *Protein binding.* Most drugs compete for binding sites on plasma proteins. This may result in significant changes in plasma concentration of the free drug. With age, there is approximately a 20 percent fall in serum albumin, which results in more of the free drug.

2. *Absorption.* Certain drugs can inhibit or enhance the rate or extent of absorption of another drug. In the elderly decreased absorption occurs for some drugs, although most are readily absorbed.

3. *Receptor sites and responses.* Interactions at specific and nonspecific receptor sites can occur between drugs. Sometimes altered receptor responses occur in elderly people.

4. *Metabolism.* Accelerated or inhibited metabolism of some drugs can result in interactions. In the elderly, liver blood flow is decreased causing detoxification and microsomal activity to be decreased.

5. *Renal excretion.* Alterations in renal excretion can be responsible for some drug interactions. Renal excretion is decreased in the elderly because of a decline in glomerular filtration rate (GFR). The GFR is reduced by more than one half in persons aged between 30 and 80 years.

6. *Body water, pH, and electrolytes.* Alterations in body water, pH, and electrolyte concentrations may lead to drug interactions. With age total body water decreases, leading to diminished volume of distribution for water-soluble drugs; hence, their concentration increases. Also, carcass fat is increased in the elderly, which increases the lipid storage and prolongs half-life of lipophilic drugs.[23] In general, the elderly exhibit alterations in absorption, pharmacokinetics, pharmacodynamics, receptor response, and effect.

A critical assessment of this study would focus on the quality of the computer database for drug interaction analysis. Some significant drugs were missing from the

TABLE 7. DRUG INTERACTIONS WITH FOOD OR ALCOHOL[18–23]

Drug	Food or Alcohol	Effect	Significance
Acetohexamide	Alcohol	May cause a disulfiram-like reaction; may also cause unpredictable alterations in blood sugar levels	Moderate–high
Acetaminophen	Food	Delay absorption	Low
	Alcohol	Increase risk of developing hepatotoxicity	Moderate–low
Alprazolam	Alcohol	Additive central nervous system depression	Moderate–high
Ampicillin	Food	Decrease oral absorption	Low
Theophylline, anhydrous	High-protein foods	Decrease theophylline effect	Moderate
Aspirin	Food	Delay rate of absorption	Low
	Alcohol	Additive gastric irritation and bleeding	Moderate
Aspirin/antacid	Food	Delay rate of absorption	Low
	Alcohol	Additive gastric irritation and bleeding	Moderate
Aspirin/codeine phosphate	Alcohol	Additive gastric irritation and bleeding	Moderate
Bisacodyl	Milk products	May cause coating to prematurely dissolve and result in gastric irritation	Moderate
Butalbital/aspirin/caffeine	Alcohol	Additive gastric irritation; sedation	Moderate
	Food	Delay rate of absorption	Low
Calcium carbonate	Milk or dairy products	Can produce hypercalcemia	Low
Captopril	Food	Decrease bioavailability of by greater than 50%	Moderate
Carbidopa/levodopa	High-protein foods	Decrease effect of levodopa	Low
Chlordiazepoxide	Alcohol	Additive central nervous system depression	Moderate–high
Chlordiazepoxide/clidinium bromide	Alcohol	Additive central nervous system depression	Moderate–high
Chlorpromazine hydrochloride	Alcohol	Additive sedative effect	Low
Chlorpropamide	Alcohol	May cause a disulfiram-like reaction; there may also be unpredictable alterations in blood glucose levels	Moderate–high
Chloryl hydate	Alcohol	Additive central nervous system depression	High
Cimetidine	Food	Delay absorption	Low
Clonazepam	Alcohol	Additive central nervous system depression	Moderate–high
Clorazepate dipotassium	Alcohol	Additive central nervous system depression	Low
Diazepam	Alcohol	Additive central nervous system depression	Moderate–high
Dicloxacillin	Food	Decrease absorption	Low
Digoxin	Food	Decrease oral absorption and lower peak serum concentration	Low
Erythromycin	Food	Decrease oral absorption	Low
Fluphenazine hydrochloride	Alcohol	Additive sedative effect	Low
Flurazepam	Alcohol	Additive central nervous system depression	Low
Griseofulvin	Fatty foods	Increase absorption	Low
Insulin	Alcohol	Increase hypoglycemic effect	High
Isocarboxazid	Tyramine-containing foods	Excessive tyramine can cause hypertension, tachycardia, and arrhythmias	High
Isoniazid	Food	Decrease oral absorption	Low
	Alcohol	Additive hepatotoxicity and may decrease response to isoniazid	Low
Levodopa	High-protein foods	Decrease absorption	Low
Lithium carbonate	Food	Serum lithium levels may vary in inverse proportion to sodium intake	Moderate
Lorazepam	Alcohol	Additive central nervous system depression	Moderate–high

TABLE 7. DRUG INTERACTIONS WITH FOOD OR ALCOHOL,[18–23] CONTINUED

Drug	Food or Alcohol	Effect	Significance
Meprobamate	Alcohol	Additive central nervous system depression	Moderate–high
Nitrofurantoin/macrocrystals	Food	Minimizes gastric irritation and may increase bioavailability of nitrofurantoin	Moderate
Nitroglycerin	Alcohol	Additive hypotension; may progress syncope	Moderate
Oxazepam	Alcohol	Additive central nervous system depression	Moderate–high
Oxtriphylline	High-protein foods	Decrease effect	Moderate
Oxycodone	Food	Delay absorption	Low
Oxycodone/acetaminophen	Food	Delay absorption	Low
	Alcohol	Increase risk of developing hepatotoxicity	Moderate
Penicillin V potassium	Food	Decrease oral absorption	Low
Pentobarbital	Alcohol	Additive and potentially lethal central nervous system depression	High
Phenobarbital	Alcohol	Additive central nervous system depression	High
Phenytoin	Alcohol	Additive sedative and anticonvulsive effects	Low–moderate
Prochlorperazine	Alcohol	Additive sedative effect	Low
Propoxyphene/acetaminophin	Food	Delay absorption	Low
	Alcohol	Increase risk of developing hepatotoxicity	Moderate
Propoxyphene	Food	Inhibit absorption	Low
Propoxyphene—APC	Food	Delay absorption	Low
Quinidine gluconate	Foods that alkalize urine	May increase quinidine reabsorption and blood serum levels leading to quinidine toxicity	Moderate
Rifampin	Food	Decrease oral absorption	Low
Salsalate	Food	Delay absorption	Low
	Alcohol	Additive gastric irritation and bleeding	Moderate
Temazepam	Alcohol	Addition central nervous system depression and may increase oral absorption	Moderate–high
Tetracycline	Dairy products, iron preparations, antacids, laxatives containing magnesium	Inhibit absorption	High
Theophylline	High-protein foods	Enhance metabolism of theophylline and decrease its effect	Moderate
Thioridazine	Alcohol	Additive sedative effect	Low
Tolazamide	Alcohol	May cause disulfiram-like reaction; may also cause unpredictable alterations in blood glucose levels	Moderate–high
Tolbutamide	Alcohol	May cause disulfiram-like reaction	Moderate
Triavil	Alcohol	Additive sedative effect	Low
Trifluoperazine	Alcohol	Additive sedative effect	Low
Warfarin	Foods containing vitamin K	May antagonize effect	Low
Xanthine derivatives	High-protein foods	Enhance metabolism of theophylline and decrease its effects	Moderate

computer program, and drugs were analyzed only in pairs, as already noted, not one against a group of others. Better computer programs are needed as well as increased availability and applications in medical settings.

Forms placed in the front of each clinic record for the accurate recording of all drugs used, along with the dates of beginning and ending the drug, were seldom used. This omission would compound prescribing error, especially

TABLE 8. DRUG–DRUG INTERACTION[18–23]

Primary Drug	Other Drugs	Effect	Significance
Amitriptyline	Chlorpheniramine	Potentiate the anticholinergic and sedative effects	Moderate
Antacid	Isoniazid	May inhibit oral absorption of isoniazid	Low
	Thioridazine	May inhibit oral absorption of phenothiazines	Low
	Cimetidine	Decrease absorption of cimetidine	Low
	Hydrocortisone	Decrease absorption of prednisone	Low
	Quinine sulfate	Decrease absorption of quinine	Low
	Phenytoin	*	
	Ferrous sulfate	Decrease absorption of iron preparations	Low
Aspirin/codeine	Prednisone	Increase risk of gastrointestinal ulceration	Moderate
	Furosemide	Salicylate toxicity may occur at lower doses	Low
Atenolol	Chlorpropamide	Enhance hypoglycemic effect	Moderate
	Digoxin	Enhance bradycardia	Low
	Xanthine derivatives	Antagonistic effects	
Chlordiazepoxide/ clidinium	Digoxin	May increase absorption and lead to digitalis toxicity	High
	Amitriptyline	Additive anticholinergic side effects	Low
Chlorpropamide	Trimethoprim/sulfamethoxazole	Increase hypoglycemic effect	Low
	Hydrochlorothiazide	Increase blood glucose and may antagonize action of antidiabetic agent	Moderate
	Allopurinol	Increase hypoglycemic effect	Low
	Choline magnesium	Increase hypoglycemic effect	Moderate
	Aspirin	Increase hypoglycemic effect	Moderate
	Triamterene/hydrochlorothiazide	*	
	Levothyroxine sodium	May require increase in dosage of the oral antidiabetic agent when thyroid therapy is initiated	Moderate
Cimetidine	Temazepam	Increase sedative effects	Moderate
	Antacid	Decrease oral absorption	Low
	Sucralfate	Decrease activity of sucralfate	Moderate
	Iron preparations	Cimetidine may inhibit expected hematologic response	Low
Desipramine hydrochloride	Dicyclomine hydrochloride	Additive anticholinergic effects	Low
	Trifluoperazine	Additive anticholinergic effects	Low
Digoxin	Hydrochlorothiazide	Depletion of potassium by thiazide diuretics can lead to digitalis toxicity	High
	Furosemide	Depletion of potassium by furosemide can lead to digitalis toxicity	High
	Erythromycin	Increase bioavailability of digoxin	High
	Trimethoprim/sulfamethoxazole	Decrease bioavailability of digoxin	Moderate
	Nifedipine	Increase effect of digoxin and could lead to toxicity	High
	Timolol	Potentiate bradycardia	Low
	Triamterene/hydrochlorothiazide	Depletion of potassium by thiazide diuretics can lead to digitalis toxicity	High
	Quinidine	Increase serum digoxin levels	High
	Alpha-methyldopa	May cause sinus bradycardia, lightheadedness, forgetfulness, disorientation, and possibly syncope	Low
	Phenylbutazone	May increase digoxin effect	Moderate
	Tetracycline	Increase bioavailability of oral digoxin	High
	Isoproterenol	Increase risk of cardiac arrhythmias	Low
	Bumetanide	May cause hypokalemia with possible cardiac arrhythmias	High
	Antacid	Decrease absorption of digoxin	Moderate
	Spironolactone hydrochlorothiazide	Depletion of potassium by thiazide diuretics can lead to digitalis toxicity	High

TABLE 8. DRUG–DRUG INTERACTION,[18–23] CONTINUED

Primary Drug	Other Drugs	Effect	Significance
Digoxin	Pentobarbital sodium	Decrease serum digoxin levels	Moderate
	Atenolol	*	
	Dicyclomine	May increase absorption and effect of digitalis	High
	Metaproterenol sulfate	Increase risk of cardiac arrhythmias	Low
	Phenobarbital	Decrease serum digoxin levels	Moderate
	Chlordiazepoxide/clidinium	*	
	Phenylbarbital/belladonna alkaloids	Increase absorption and effect of digitalis	High
	Nadolol	Potentiate bradycardia	Low
	Propranolol	Potentiate bradycardia	Low
Doxepin	Isoproterenol	May result in severe hypertensive crisis or cardiac arrhythmias	Moderate
	Terbutaline sulfate	May result in severe hypertensive crisis or cardiac arrhythmias	Moderate
	Dyphenhydramine hydrochloride	Additive sedative effects	Moderate
	Fluphenazine	Additive sedative effects	Low–moderate
	Haloperidol	Additive sedative effects	Low–moderate
Erythromycin	Xanthine derivatives	May inhibit hepatic metabolism of theophylline and lead to toxicity	Moderate
Fenoprofen calcium	Furosemide	Can inhibit diuretic or antihypertensive effects of furosemide	Moderate
	Aspirin	Additive stomach irritation	Low
Fluphenazine	Trihexyphenidyl hydrochloride	Additive anticholinergic side effects	High
Furosemide	Prednisone	Increased hypokalemic effect	Moderate
	Indomethacin	Can inhibit diuretic, natriuretic, and antihypertensive effects of furosemide	Moderate
	Sulindac	Can inhibit diuretic or antihypertensive effects of furosemide	Low
	Insulin	Decrease insulin effect	Low
	Ibuprofen	Can inhibit diuretic or antihypertensive effects of furosemide	Low
	Aspirin/antacid	Possible salicylate toxicity and also the diuretic effect of furosemide may be decreased	Low
	Aspirin	Possible salicylate toxicity and also the diuretic effect of furosemide may be decreased	Low
	Aspirin, Empirin w codeine	Possible salicylate toxicity and also the diuretic effects of furosemide may be decreased	Low
	Chloral hydrate	Seating, flushing, uneasiness, hypertension and/or tachycardia	Low
	Ibuprofen	May inhibit diuretic effect of furosemide	Low
	Meclofenamate	May inhibit diuretic effect of furosemide	Low
	Digoxin	*	
	Phenytoin	*	
	Aspirin/codeine	*	
	Naproxen	May inhibit diuretic effect of furosemide	Moderate
	Lithium	Furosemide can increase serum lithium levels and lead to toxicity	Moderate
	Tolbutamide	Decrease effect of the oral antidiabetic agent	Low
	Phenylbutazone	Can inhibit diuretic or antihypertensive effects of furosemide	Moderate
Glyburide	Metoprolol	Decrease hypoglycemic effect, also beta-blocker masks tachycardia during hypoglycemia	Moderate
Hydrochlorothiazide	Chlorpropamide	Antagonize antidiabetic effect	Moderate
	Tolbutamide	Antagonize antidiabetic effect	Moderate
	Hydrocortisone	Increase hypokalemic effect	Moderate
	Allopurinol	May cause hyperuricemia and thus may antagonize effect of allopurinol	
	Glipizide	Loss of control leading to increased blood glucose levels	Low–moderate
	Tolbutamide	Antagonize action of the antidiabetic agent	Moderate

Table continued

TABLE 8. DRUG–DRUG INTERACTION,[18–23] CONTINUED

Primary Drug	Other Drugs	Effect	Significance
Hydrochlorothiazide	Digoxin	*	
Hydrochlorothiazide/ triamterene	Prednisone	Increased hypokalemic effect	Moderate
	Chlorpropamide	Thiazide diuretics tend to increase blood glucose and may antagonize the action of the antidiabetic agent	Moderate
	Insulin	Decrease insulin effect	
	Hydrocortisone	Hypokalemic effect of thiazide diuretics is increased by corticosteroids	Moderate
	Tolbutamide	Thiazide diuretics tend to increase blood glucose and may antagonize the action of the antidiabetic agent	Moderate
	Potassium chloride	Severe hyperkalemia may result	
	Digoxin	*	
Imipramine	Methscopolamine	Additive anticholinergic side effects	Low
Indomethacin	Hydrochlorothiazide/timolol	Decrease antihypertensive effect of the beta-blocker	Moderate
	Triamterene	Possible renal failure (avoid concurrent use if possible)	High
	Metaprolol	*	
	Propranolol	*	
	Furosemide	*	
Isocarboxazid	Other psychotropic agents	Potentiating effects	High
Meclizine	Doxepin hydrochloride	Additive anticholinergic and sedative effects	Moderate
Methyldopa	Promethazine/codeine	May inhibit effect of methyldopa	Moderate
Metoprolol tartrate	Glyburide	Decreased hypoglycemic effect	Moderate
	Cimetidine	Substantial elevations in serum levels of propranolol	Moderate
	Prochlorperazine/isopropamide	Additive hypotensive effect	Low–moderate
	Terbutaline sulfate	May increase blood pressure	
	Chlorpropamide	Enhance hypoglycemic effect	Moderate
	Indomethacin	Decrease antihypertensive effect	Moderate
	Theophylline	Antagonistic effect	Moderate
Nifedipine	Nadolol	Increase risk of cardiovascular side effects	High
	Nitroglycerin	Vasodilation	Low
	Timolol	Increase risk of cardiovascular side effects	High
	Digoxin	*	
	Propranolol	*	
	Pindolol	Increase risk of cardiovascular side effects	High
Pentobarbital	Diphenoxylate hydrochloride/atropine sulfate	Potentiate sedative effects of barbituates	Low
	Quinidine	Quinidine plasma levels may be reduced in inadequate levels	Moderate
	Digoxin	*	
Perphenazine/amitriptyline	Butalbital/aspirin/caffeine	Barbiturate can increase metabolism of tricyclics	Moderate
	Butalbital/aspirin/caffeine	Additive central nervous system depression	Low
Phenobarbital	Hydroxyzine pamoate	Additive sedative effect	Moderate
	Oxycodone hydrochloride/oxycodone terephthalate/aspirin	Additive respiratory and central nervous system depression	Moderate
	Codeine	Additive respiratory and central nervous system depression	Moderate
	Promethazine	Additive central nervous system depression	Moderate
	Digoxin	*	
	Thioridazine	Additive central nervous system depression	Low
Phenylpropanolamine	Pindolol	Possible increase in blood pressure	Moderate
	Maprotiline hydrochloride	Possible hypertensive crisis or cardiac arrhythmias	Moderate
Phenytoin	Chlorpromazine hydrochloride	May increase serum phenytoin levels and also thorazine lowers seizure threshold	Low
	Furosemide	Decrease effect of furosemide	Low
	Aspirin/aluminum glycinate/magnesium carbonate	May increase serum phenytoin levels	Low
	Salsalate	May increase serum phenytoin levels	Low
	Butalbital/aspirin/caffeine	May increase serum phenytoin levels	Low

TABLE 8. DRUG–DRUG INTERACTION,[18–23] CONTINUED

Primary Drug	Other Drugs	Effect	Significance
Phenytoin	Oxycodone hydrochloride/oxycodone terephthalate/aspirin	May increase serum phenytoin levels	Low
	Aspirin	May increase serum phenytoin levels	Low
	Antacid	Decrease absorption	
	Trifluoperazine	May increase serum phenytoin levels with possible toxicity	Low
	Cimetidine	May increase effects of phenytoin with possible toxicity	High
	Sucralfate	Decrease pharmacological effects with possible toxicity	High
Potassium chloride	Captopril	Captopril can cause potassium retention and may lead to hyperkalemia	Moderate
	Amiloride hydrochloride-hydrochlorothiazide	Possible hyperkalemia	
	Hydrochlorothiazide/triamterene	*	
Prazosin	Atenolol	Increase hypotension	Moderate
	Nadolol	Increase hypotension	Moderate
Promethazine	Thioridazine	Possible somnolence and liver toxicity	Low
	Phenobarbital/belladonna alkaloids	Additive central nervous system depression and anticholinergic effects	Moderate
	Amitriptyline	Additive sedative and anticholinergic effects	Low
	Phenobarbital	*	
	Propranolol	*	
Propranolol	Prazosin	Increase in severity and duration of hypotension	Moderate
	Promethazine	Additive hypotensive effect	Low
	Fluphenazine	Additive hypotensive effect	Low–moderate
	Antacid	Decreased absorption	Low
	Indomethacin	Decreased antihypertensive effect	Moderate
	Nifedipine	Increased risk of cardiovascular side effects due to synergism between the two drugs	High
	Hydralazine	May increase serum levels of both drugs	Moderate
	Antacid	Decrease absorption of propranolol	Low
Rifampin	Isoniazid	Additive hepatotoxicity	High
	Diazepam	Increase metabolism of benzodiazepines	Low
	Theophylline anhydrous	Increase metabolism of theophylline	Moderate
Spironolactone/ hydrochlorothiazide	Acetylsalicylic acid	Decrease effect of spironolactone	Low
Theophylline	Metaproterenol sulfate	Increase arrhythmias and cardiac necrosis	Moderate
	Terbutaline sulfate	Increase arrhythmias and cardiac necrosis in animals	Moderate
Thioridazine	Atenolol	Additive hypotensive effects	Low–Moderate
	Butalbital/aspirin/caffeine	Additive central nervous system depression	Low
Timolol	Tolbutamide	Enhance hypoglycemic effect	Moderate
	Calcium carbonate	Decrease absorption	Low
	Prazosin	Enhance hypoglycemic effect	Moderate
Tolazamide	Trimethoprim/sulfamethoxazole	Enhanced hypoglycemic effect	Moderate
Tolbutamide	Trimethoprim/sulfamethoxazole	Increase hypoglycemic effect	Moderate
	Furosemide	Decrease antidiabetic effect	Low
	Aspirin/alumina/magnesia	Increase hypoglycemic effect	Moderate
	Atenolol	Enhance hypoglycemic effect	Moderate
	Allopurinol	Increase hypoglycemic effect	Low
Triamcinolone	Prednisone	Potential adrenal supression	Low
	Aspirin/aluminum glycinate/magnesium carbonate	May increase renal excretion of salicylates and increase risk of gastrointestinal ulceration	Moderate
	Chlorothiazide	Possible hypokalemia	Moderate
Trifluoperazine	Triazolam	Additive sedative effects	
	Amitriptyline	Potentiates the anticholinergic and sedative effects	Moderate
	Benztropine mesylate	Additive anticholinergic side effects	Low
	Primidone	Additive central nervous system depression	Low
Warfarin	Ibuprofen	Gastric irritation, bleeding	Moderate

* *See interaction for "Other Drug" in "Primary Drug" column*

where patients are seen by many physicians over time. Even still, there were few potentially serious interactions.

Adequate computer databases are strongly recommended for each clinic, nurses' station, and hospital pharmacy. Such computerized information would be inadequate if in hospital pharmacies only. Since the incidence of serious reactions is low and predictable, the cost of continuous, prospective monitoring would not be justified.

Avoidance of combinations of drugs known to cause mischief should be adhered to. Adding corrective drugs to the regimen increases cost and interaction and decreases compliance.

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