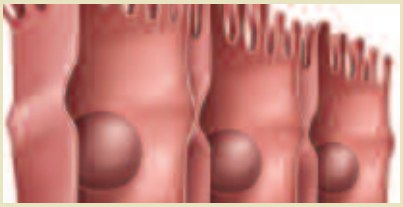
abstract



Many medications have the potential to interact with alcohol, and older patients may be at greater risk of experiencing adverse effects due to issues of comorbidity and polypharmacy. Even small amounts of alcohol consumed by an older person who is taking multiple medications can have serious consequences. A retrospective analysis linked prescription claim records with self-reported alcohol use. Results showed that 77% of older adults used at least one alcohol-interactive medication, and 19% of alcohol-interactive drug users reported concomitant alcohol use. Because many individuals are unaware of the risks posed by alcohol and medications, it is important for clinicians to warn patients about potential interactions.

Key words: *older adults, alcohol, prescription drug use, alcohol-drug interactions, concomitant use of alcohol and prescription drugs*

Alcohol and Prescription Drug Interactions Among Aging Adults

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Introduction

Clinicians who provide care to older patients are well aware of the special safety concerns that surround pharmacotherapy for this age group. In general, older patients are more likely to be frail, suffer from multiple chronic conditions, or have other patient factors that may complicate drug therapy. Such factors necessitate careful consideration of appropriate dosages or therapy combinations. An important issue that may be overlooked, however, is that of alcohol-drug interactions. Alcohol use—whether episodic or chronic—can significantly alter the bioavailability of prescription drugs and seriously compromise the therapeutic goals of drug therapy. Clinicians and patients alike must therefore be aware of the potential for alcohol to interact with medications. It is important for clinicians to ask patients about any alcohol use as part of the medical history.

The mechanisms of alcohol-drug interactions include both pharmacokinetic and pharmacodynamic processes.[1,2] In pharmacokinetic interactions, either alcohol or the drug alters the absorption or distribution of the other substance. For example, alcohol and the medication may directly compete for metabolism through the cytochrome P450 enzyme system (Figure 1). Depending on the specific mechanisms involved, pharmacokinetic interactions may result in increased or decreased bioavailability of either alcohol or the prescribed drug.

For example, the alcoholism treatment agent disulfiram works therapeutically by means of a pharmacokinetic interaction with alcohol. By inactivating aldehyde dehydrogenase, disulfiram produces high blood levels of the alcohol metabolite acetaldehyde, causing extreme flushing and nausea. In contrast to pharmacokinetic interactions, pharmacodynamic drug interactions are not characterized by altered drug metabolism, but involve situations in which alcohol and a medication have similar therapeutic effects. Pharmacodynamic interactions can result in clinically significant adverse additive or synergistic effects, most frequently involving central nervous system (CNS) depression. Such interactions may produce dangerous sedation and psychomotor skill impairment. Table 1 summarizes the potential for alcohol interactions for commonly prescribed medication classes.

Although alcohol-prescription drug interactions are important for all age groups, older adults are at greatest risk for adverse effects, especially for interactions involving CNS depression. As noted this may lead to dizziness, falls, or other accidents.[2,3] Although older adults typically have low rates of heavy drinking,[4,5] many older adults have patterns of alcohol consumption that nevertheless exceed current guidelines.[5] Older adults are also more likely to use multiple alcohol-interactive drugs, which increases the likelihood of interaction. Even small amounts of alcohol consumed by an

older person who is taking multiple medications can have serious consequences.[6,7]

Although much is known about the use of alcohol by aging adults,[5,8] and a lesser—but growing—amount of information is known about the risks of alcohol-interactive drugs, surprisingly little is known about the prevalence of concomitant alcohol and drug use in this population segment, or about specific patterns of exposure.[9,10]

This article highlights results from a research study on potential alcohol-drug interactions that was recently published in the Journal of the American Geriatrics Society (JAGS).[11] The goal of the JAGS study was to characterize alcohol-interactive drug exposure and concomitant alcohol use by therapeutic class, and to examine factors associated with concomitant use.

Outline of the JAGS Study

Subjects in the JAGS study were enrolled in Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PA-PACE) program, a state-funded program providing prescription benefits to older adults with low-to-moderate incomes. All new and renewal PA-PACE enrollment applications include an optional Survey on Health and Well-Being, which addresses topics including health status

Table 1: Potential Interactions of Alcohol with Commonly-Prescribed Medications

Therapeutic Class	Commonly Prescribed Medications	Interaction Potential
Antihistamines	Cetirizine Desloratadine Promethazine Diphenydramine	Alcohol enhances the central nervous system (CNS) depressing effects of antihistamines (sedation, impaired psychomotor skills). Although newer nonsedating antihistamines have lower potential for interaction, CNS depression can still occur.
Anti-infectives	Erythromycin Cephalosporins Metronidazole Ketoconazole	Erythromycin may increase gastric emptying and speed alcohol absorption. Cephalosporins, metronidazole, and ketoconazole may produce disulfiram-like flushing reactions, leading to nausea, vomiting, headache, and tachycardia.
Antineoplastics	Methotrexate	Alcohol may increase the potential for methotrexate-induced liver damage.
Anticoagulants	Warfarin	Alcohol may increase anticoagulation.
Beta-blockers	Metoprolol Carvedilol	Alcohol may increase the likelihood of dizziness or drowsiness, and may cause flushing or tachycardia.
Calcium channel blockers	Amlodipine Diltiazem	Alcohol can increase the hypotensive effects of these medications and may cause dizziness or drowsiness.
Vasodilators	Isosorbide mononitrate Nitroglycerin	Alcohol can produce additive vasodilation, leading to hypotension, dizziness, and fainting.
Nonsteroidal Anti-inflammatories (NSAIDs)	Acetylsalicyclic acid (ASA) Ibuprofen Naproxen Meloxicam Diclofenac Celecoxib	Alcohol enhances ASA's potential for gastric mucosal damage and bleeding time prolongation. With all NSAIDs, alcohol increases the risk of gastrointestinal bleeding. Although gastrointestinal (GI) effects are lower with COX-2 products, risk still exists.
Narcotic analgesics	Propoxyphene/acetaminophen Hydrocodone/acetaminophen Oxycodone/acetaminophen Acetaminophen/codeine Oxycodone Fentanyl	Many combination products include acetaminophen. Chronic alcohol use increases the activity of enzymes that metabolize acetaminophen, leading to greater concentrations of hepatotoxic metabolites. With all narcotic analgesics, alcohol enhances CNS depression, leading to increased sedation and potential respiratory depression.

Table 1, continued: Potential Interactions of Alcohol with Commonly Prescribed Medications

Therapeutic Class	Commonly-Prescribed Medications	Interaction Potential
Antidepressants	*Tricyclics:* Amitriptyline Nortriptyline Imipramine *MAO Inhibitors:* Tranylcypromine Phenelzine *SSRIs:* Sertraline Escitalopram Paroxetine Fluoxetine Citalopram	All antidepressants, including newer agents, produce some degree of CNS depression, which is enhanced by alcohol. Tricyclic antidepressants, especially amitriptyline, pose the greatest potential for excessive sedation. MAO inhibitors can produce severe hypertension if taken with tyramine-containing alcoholic beverages. Although SSRIs still confer some risk of enhanced CNS depression, they may offer the safest alternatives with respect to alcohol interactions.
Anxiolytics, sedatives, and hypnotics	*Barbiturates:* Phenobarbital Benzodiazepines: Lorazepam Alprazolam Diazepam *Other anxiolytics and sedatives:* Zolpidem Buspiron Eszopiclone Meprobamate	Alcohol and barbiturates display pharmacodynamic interactions in the form of additive CNS depression. Alcohol also interacts pharmacokinetically with phenobarbital, slowing the drug's metabolism and increasing the potential for overdose. Alcohol and benzodiazepines have additive CNS depressant effects, leading to increased sedation and impaired psychomotor skills. All other anxiolytics, sedatives, and hypnotics can also be expected to interact with alcohol, causing CNS depression.
Gastrointestinal drugs	*H2–Receptor Agonists:* Cimetidine Ranitidine Nizatidine Other GI agents: Metoclopramide	H2RAs may reduce first-pass gastric alcohol metabolism, potentially producing higher blood alcohol levels. Metoclopramide may increase gastric emptying and enhance the sedative effects of alcohol.
Antidiabetic agents	Insulin Sulfonylureas Chlorpropamide Glipizide Glyburide Other oral agents Metformin	In general, alcohol can produce hypoglycemia in patients taking either insulin or oral diabetes drugs. Alcohol combined with sulfonylureas may produce a disulfiram-like reaction. With metformin, alcohol may increase the risk of lactic acidosis.

Sources: Hansten et al., 2003[1] and Weathermon et al., 1999.[2]

Table 2: Alcohol-Interactive Drug Exposure and Prevalence of Alcohol Use by Therapeutic Class (n=83,321)

Therapeutic Class	% of Users Exposed to AI Drugs	Alcohol Use among Individuals Using AI Drugs in Class (%)
Antihistamines	76.6	20.1
Anti-infectives	16.4	16.3
Antineoplastics	21.3	17.8
Autonomic drugs	23.4	17.7
Blood coagulants/anticoagulants	1.8	14.0
Cardiovascular agents		
Angiotensin-receptor blockers	32.0	19.6
Beta-blockers	17.3	19.0
Calcium channel blockers	66.8	18.9
Misc. antihypertensives	96.8	19.9
Vasodilators	99.9	14.6
Other cardiovascular agents	0.6	18.8
Total, all cardiovascular agents	50.1	18.4
CNS agents		
NSAIDs	100.0	20.2
Narcotic analgesics	100.0	16.7
Antiseizure drugs	100.0	13.5
Antidepressants/antipsychotics	100.0	16.0
Anxiolytics/sedatives/hypnotics	100.0	16.8
Antimanic agents/lithium	100.0	16.8
Other CNS agents	65.5	17.5
Total, all CNS agents	99.0	18.0
Electrolytic agents	0.8	18.8
Antitussive agents	69.2	18.0
Eye, ear, nose & throat (EENT) drugs	15.5	18.7
Gastrointestinal drugs	16.8	14.1
Hormones	39.4	12.8
Antidiabetic agents	87.8	12.8
Smooth muscle relaxants	26.9	16.2
All other drugs	15.9	19.8
Total, all therapeutic classes	77.4	18.7

and health behaviours and yields annual response rates above 70%. The sample consisted of 83,321 renewing cardholders who were using one or more prescription drugs at the time of survey completion.

In 2001, the Survey on Health and Well-Being asked respondents to describe how frequently they use alcohol and included the following choices: (1) every day, (2) several times a week, (3) several times a month, (4) once a month or less, (5) former drinker, and (6) never used alcohol. A second question asked respondents to enter the number of drinks they have on the days they drink. Current drinkers were defined as individuals who chose one through four on the first question. Using the standard quantity-frequency (QF) approach,[12] drinkers were categorized as light, moderate, or heavier drinkers.

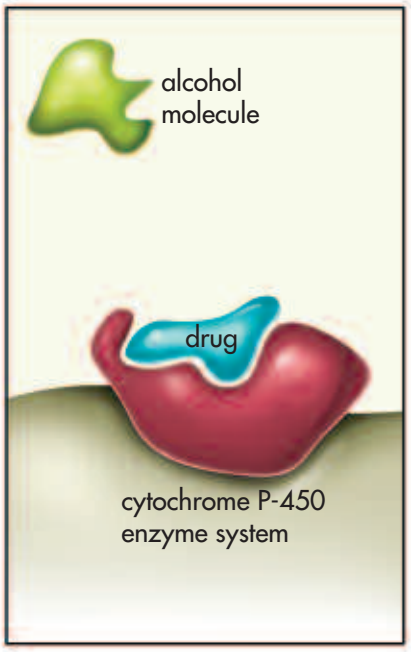
We focussed on medication use at the time of survey completion by identifying all prescriptions filled by respondents within a 45-day window prior to their survey completion date. Prescription drug claims were categorized into 26 therapeutic classes, based on the American Hospital Formulary Service[13] system (see Table 2). Each drug's potential for alcohol interactivity was assessed using a database of medication warning labels provided by First DataBank, Inc.[14] Drugs having at least one of four possible alcohol-warning codes were categorized as alcohol-interactive (AI); drugs with none of the codes were categorized as non-AI. Concomitant use of alcohol and AI drugs was defined as having one or more AI drug claims in the 45-day window prior to reporting alcohol use on the survey.

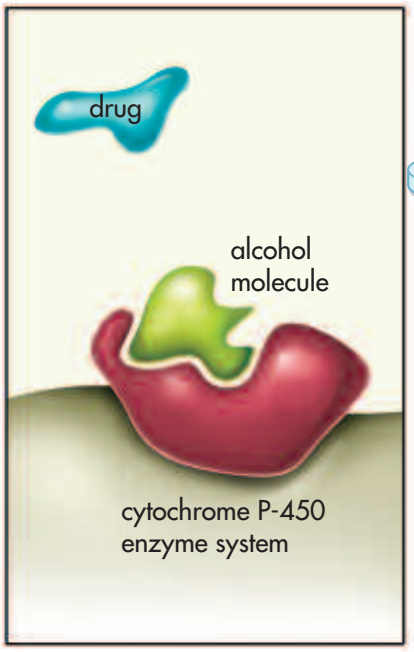
Multinomial logistic regression was used to examine factors associated with light, moderate, and heavier drinking among persons using one or more AI drugs. Interpretation of results for a specific risk factor is based on the odds of being, for example, a heavier drinker using AI drugs rather than a nondrinker using AI drugs. More details of the statistical methods are provided in the JAGS publication.[11]

Results and Interpretation

Participants' ages ranged from 65 to 106, with a mean of 79 years. The over-

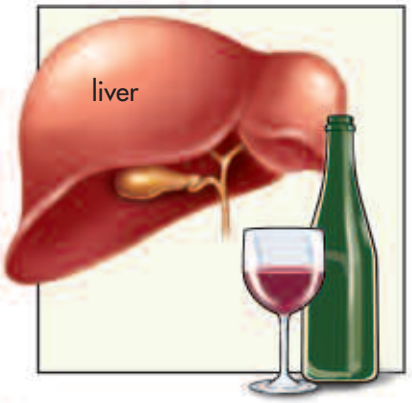
Figure 1:
Mechanisms of Alcohol-drug Interactions

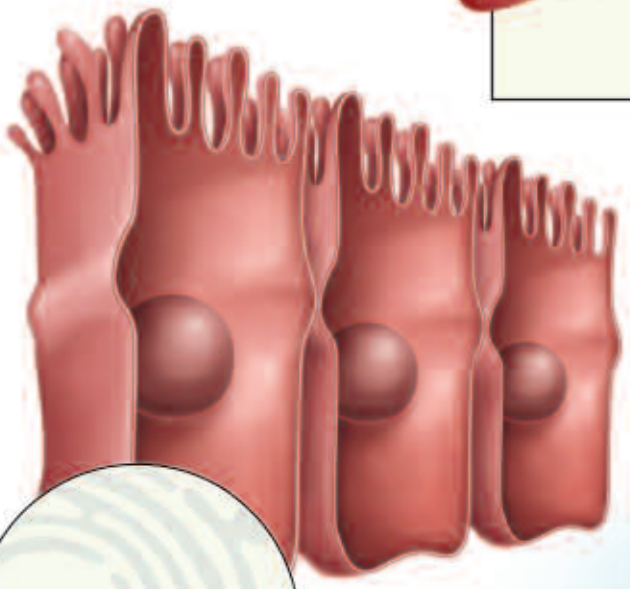




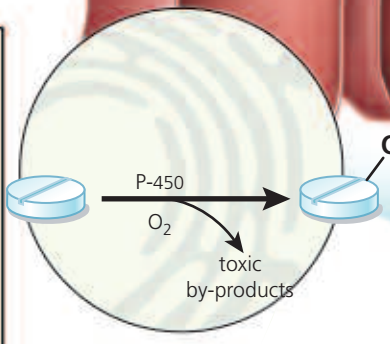
pharmacokinetics
In pharmacokinetic interactions, either alcohol or the drug alters the absorption or distribution of the other substance. Alcohol and medication may directly compete for metabolism through the cytochrome P-450 enzyme system. This may result in increased or decreased bioavailability of either alcohol or the prescribed drug.

drug metabolism
Most drug metabolism takes place in the liver. Portal blood coming from the intestine is processed by the liver before draining into the systemic circulation.



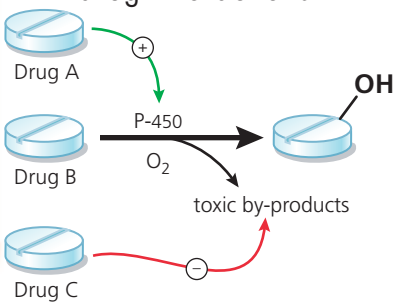


hepatocytes
The cytochrome P-450 systems are found in the smooth endoplasmic reticulum of hepatocytes.

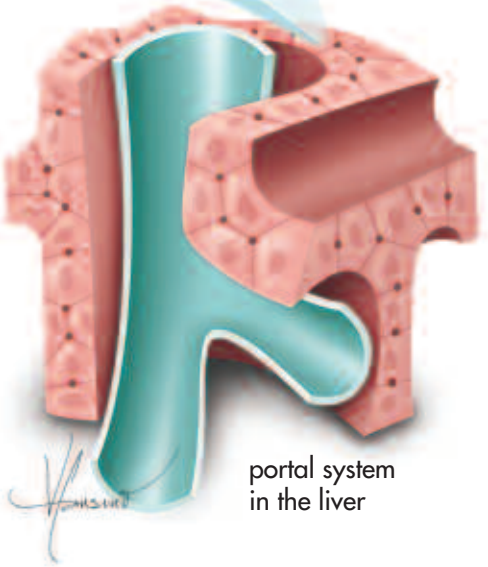


The liver takes up drugs and oxidizes them using cytochrome P-450 enzymes in the smooth endoplasmic reticulum.

Medical consequences of drug interactions



- Drug A may induce a P-450 enzyme that eliminates Drug B faster
- Drug C may inhibit an enzyme that eliminates toxic side compounds



portal system in the liver

Key Points

- Even small amounts of alcohol consumed by an older person who is taking multiple medications can have serious consequences.
- In the JAGS study, 77% of all older prescription drug users were exposed to at least one alcohol-interactive drug.
- Older patients may be unaware of the risks of alcohol-drug interactions and may have difficulty reading or understanding warnings on medication labels.
- Clinicians should warn older patients about alcohol use, especially heavier use, which can make alcohol-drug interactions more likely.
- Older adults may not realize that not only prescribed but also over-the-counter-medications may adversely interact with alcohol.

all prevalence of alcohol use was 20.3%. Among drinkers, 7% reported drinking every day or nearly every day, 8% reported drinking several times a week, 13% reported drinking several times a month, and 72% reported drinking once a month or less. Respondents consumed an average of 1.44 drinks per day (range=1–12) on the days they drank. Using the QF categories, 74% of drinkers were light drinkers, 20% were moderate drinkers, and 6% were heavier drinkers. Among current drinkers with at least one concomitant AI claim, 44.9% used one AI drug, 28.6% used two, 14.1% used three, 6.9% used four, and 5.5% used five or more in combination with alcohol.

Approximately three-quarters (77%) of all prescription drug users were exposed to one or more AI drugs (n=64,515), but exposure varied by therapeutic class (Table 2). We found six classes in which AI drug exposure was 100%, nine classes with exposure rates greater than 50%, and 13 classes with exposures less than 50%. This variation in exposure has important implications for clinicians, who may be able to reduce risk for some adverse reactions by considering alternative therapies for patients who drink. However, some therapies require the use of AI drugs (e.g., psychotropics), and clinicians should be vigilant in warning patients about alcohol use, especially heavier use.

Concomitant alcohol and AI drug use also varied by therapeutic class (Table 2). Considering all therapeutic classes, 19% of AI drug users reported concomitant alcohol use. The most common combination of alcohol and AI drugs occurred with NSAIDs (20.2%). The next most frequent classes of AI drugs used with alcohol were prescription antihistamines (20.1%) and miscellaneous antihypertensives (19.8%). Individuals using hormones were the least likely to use alcohol (12.8%), followed by those using antiseizure medications (13.5%) and blood coagulants/anticoagulants (14.0%). Additional analyses conducted for heavier drinking also showed some variability by therapeutic class. Current drinkers using AI miscellaneous antihypertensives (9.5%), eye, ear, nose, and throat (EENT) drugs (7.8%), and calcium channel blockers (6.3%) were the most likely to report heavier use; drinkers using other CNS agents (2.4%), blood coagulants/anticoagulants (3.7%), and antidiabetic agents (3.8%) were the least likely to report heavier use.

Additional findings regarding the relationship between alcohol use and the number and types of drugs taken give some cause for optimism, albeit guarded, regarding the dissemination and efficacy of alcohol warnings. In comparison with nondrinkers taking AI drugs, drinkers were 9 to 21 percent less likely to drink with each additional AI drug taken, depending on their level of alcohol consumption. Each additional non-AI drug, however, decreased the odds of alcohol consumption by only 2 to 10 percent. These results suggest that there is a greater reduction in the likelihood of concomitant alcohol use among individuals using AI drugs, relative to individuals using non-AI drugs.

The results of the multinomial logistic regression model demonstrated that there are some differences in the factors that identify classification in the various levels of concomitant use. Being younger, male, white, community-dwelling, single/widowed, divorced, higher educated, and in better physical health distinguished drinkers at all levels from nondrinkers. Alternatively, persons using multiple AI medications were significantly less likely to use alcohol, with the lowest risk observed for heavier use (OR=0.79 for each additional AI drug). One particularly important finding was that while individuals reporting poor physical health were less likely to use alcohol, at all levels, in combination with AI drugs, there was no difference in moderate or heavier concomitant alcohol use according to self-rated mental health. This suggests that older adults using AI drugs do not limit alcohol consumption in response to mental health problems in the same way that they do for physical health problems.[15]

Although we cannot determine the reasons why a proportion of our sample chose to use alcohol in combination with AI drugs, prior research has shown that many aging individuals are unaware that drinking places them at risk for harmful interactions.[6] One possible explanation for the knowledge gap surrounding AI risk may relate to pharmacy practices. Because the procedures and sources used to generate warnings vary by pharmacy and because there is not 100% concordance among sources, some AI medications may be dispensed without a warning label. Even if an alcohol warning label is placed on the bottle or listed in the package insert, health literacy and language proficiency issues may result in a failure to understand the warning.[16] In addition, the size of the label and the font size used may not be readable by older persons. A clear implication, therefore, is that clinicians should talk with their patients about alcohol and warn patients who are prescribed AI drugs about alcohol-drug interactions.

Even patients who are aware that alcohol can interact with drugs may place themselves at risk. Many patients believe that alcohol-drug interactions can only occur when alcohol is taken in close temporal proximity with prescription drugs. Patients may not understand that drug therapy is often designed to achieve some steady-state level of medication needed to produce desired therapeutic effects, and that alcohol consumption—even if well before or after a scheduled drug dose—can result in a change in the bioavailability of the drug. In other cases, such as interactions involving alcohol and acetaminophen, chronic alcohol consumption can increase the levels of enzymes that metabolize acetaminophen, resulting in altered drug pharmacokinetics even on days when alcohol is not consumed.[2] Older patients also frequently use over-the-counter (OTC) medications and may not realize that these products may interact with alcohol. Clinicians can help by informing their patients about these risks.

Conclusions

The JAGS study showed that many older adults use alcohol in combination with AI prescription drugs. While studies of alcohol consumption patterns have shown that drinking declines with age,[4] research has also shown that the average amount of alcohol consumed by older persons who continue drinking does not change over time.[19] This is a timely health problem, as demographic projections and alcohol use trends indicate that newer cohorts of aging individuals (e.g., "Baby Boomers") are more likely to drink and have heavier drinking habits than previous generations.[20] Moreover, as the number of older adults using prescription drugs continues to grow, so will the absolute number using AI prescription drugs. The combination of increased prevalence of alcohol use[20] and the likelihood of greater numbers of aging adults exposed to AI drugs suggests that risks due to alcohol-drug interactions will increase. Clinicians and other members of the health care community should strive to screen their older patients for alcohol use and provide verbal warnings in order to minimize the risk of adverse consequences.

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