PHARMACIST'S LETTER / PRESCRIBER'S LETTER

Detail-Document #240106

–This Detail-Document accompanies the related article published in–

PHARMACIST'S LETTER / PRESCRIBER'S LETTER

January 2008 ~ Volume 24 ~ Number 240106

Alcohol-related Drug Interactions

Many drugs interact with alcohol resulting in undesirable outcomes. There are two types of alcohol-drug interactions: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions occur when alcohol alters the metabolism or excretion of the drug or vice versa. Pharmacodynamic interactions refer to the additive effects of alcohol and certain drugs, particularly in the central nervous system (CNS) (e.g., sedation) without affecting the pharmacokinetics of the drug.[2] Alcohol is primarily metabolized in the liver by several enzymes. The most important enzymes are aldehyde dehydrogenase and CYP2E1. In people consuming alcohol only occasionally, CYP2E1 metabolizes only a small fraction of the ingested alcohol. In contrast, chronic heavy drinking can increase CYP2E1 activity up to ten-fold, resulting in higher proportion of alcohol being metabolized by CYP2E1 rather than alcohol dehydrogenase.[5] Therefore, in some cases, the effect of alcohol on the interacting drug may be different depending on chronic or acute alcohol use. There are a number of classes of drugs that can potentially interact with alcohol (e.g., antibiotics, antidepressants, sedative/hypnotics, opioids, anticoagulants, etc). The included chart summarizes common alcohol-medication interactions including precautions and recommendations for alcohol consumption.

Abbreviations: CNS=central nervous system; GI=gastrointestinal; MAOIs=monoamine oxidase inhibitors; NSAIDs= nonsteroidal anti-inflammatory drugs.

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Analgesics (non-opioids)		
Aspirin, NSAIDs (e.g., ibuprofen, etc)	• Increased risk of GI hemorrhage. • Aspirin or NSAIDs and alcohol each damage the gastric mucosal barrier. The combination can result in additive or synergistic effects.	• Warn patients of the increased risk for GI bleeding when aspirin or NSAIDs are taken with alcohol, especially if taken on an empty stomach. • Tell patients to avoid taking aspirin within 8 to 10 hours of heavy alcohol use.
Acetaminophen (*Tylenol*, *Paracetamol*, etc)	• Chronic alcoholics are more susceptible to acetaminophen-induced hepatotoxicity. • Acute alcohol intoxication might reduce the formation of toxic acetaminophen metabolites. • Prolonged intake of large amounts of alcohol may cause enzyme induction and enhance the formation of hepatotoxic metabolites of acetaminophen while lowering serum acetaminophen concentration.	• Warn patients who chronically consume several alcoholic drinks a day or more to avoid taking large or prolonged doses of acetaminophen. (Do not exceed 4 g/24 hr).

More. . .

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Analgesics (Opioids)[b]		
Alfentanil (*Alfenta*)	• Chronic alcohol consumption may increase the risk of pharmacodynamic tolerance to alfentanil. • The exact mechanism of interaction is unknown.	• Consider higher doses of alfentanil in patients who regularly consume alcohol.
Long-Acting Morphine (*Kadian*[6], *Avinza*[7])	• Increased morphine release rate and absorption, which may lead to potentially fatal doses. • Alcohol interacts with the extended-release mechanism and causes a dose dumping effect. • In an *in vitro* study, alcohol was found to affect *Kadian*'s extended release mechanism. However, *in vivo* studies done in the U.S. showed that dose dumping is not a problem.[6]	• Tell patients to avoid alcohol and alcohol-containing drugs (*NyQuil*, etc). • Alcohol is contraindicated according to Canadian *Kadian* monograph.[21]
Long-Acting Oxymorphone (*Opana ER*[8])	• Enhanced CNS depression, which can potentially result in respiratory depression, hypotension, coma, and in some cases, death.[9] • An *in vivo* pharmacokinetic study showed an increased absorption of oxymorphone in the presence of alcohol.	• Tell patients to avoid alcohol and alcohol-containing drugs (*NyQuil*, etc).
Meperidine (*Demerol*)	• Excessive CNS depression and impaired psychomotor performance. • Alcohol may affect the distribution of meperidine, but the clinical importance of this effect is not established.	• Tell patients to limit alcohol intake to avoid excessive CNS depression. • Monitor for excessive CNS depression if the combination is used.

Drug/Drug Class[a]	Effect(s) and Proposed Mechanism(s)[1-5]	Recommendations/ Comments[c,1-5]
Analgesics (Opioids)[b] Con't		
Methadone[22,23] (*Dolophine*)	• Excessive CNS depression and impaired psychomotor performance. • The combination of methadone and alcohol has been implicated in fatalities due to increased risk for respiratory depression. • Acute alcohol ingestion can slow methadone metabolism, thereby increasing risk of methadone toxicity. • Due to methadone's prolonged half-life, the risk of accidental overdose and potential for drug interactions is higher.	• Tell patients to avoid alcohol. • Monitor for excessive CNS depression and signs and symptoms of respiratory depression if the combination is used.
Propoxyphene (*Darvocet-N*)	• Overdoses of propoxyphene combined with alcohol have been associated with fatal reactions. • Alcohol appears to increase propoxyphene bioavailability by reducing its first-pass metabolism.	• Tell patients to avoid acute excessive alcohol intake. • Monitor for excessive CNS depression if the combination is used.
Antidepressants		
Tricyclic Antidepressants (e.g., amitriptyline, etc)	• Excessive CNS depression and impaired psychomotor performance. • Acute alcohol ingestion may inhibit the first-pass hepatic metabolism of tricyclic antidepressants. • Prolonged intake of large amounts of alcohol may stimulate the hepatic metabolism of tricyclic antidepressants. • Imipramine and desipramine elimination is increased in detoxified alcoholics.	• Warn patients taking tricyclic antidepressants of enhanced CNS depression, especially within the first week of treatment and with the more sedating tricyclics such as amitriptyline and doxepin.

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Antidepressants Con't		
MAOIs (e.g., phenelzine [*Nardil*], isocarboxazid [*Marplan*], tranylcypromine [*Parnate*])	• Severe hypertensive response when taken with alcoholic beverages containing tyramine. • No known mechanism for interaction between alcohol itself and MAOIs. • Some alcoholic beverages may contain considerable amounts of tyramine (e.g., some red wines and beers), whose metabolism is severely impaired in the presence of MAOIs.	• Tell patients to avoid alcohol. • If alcohol is ingested, use products that are unlikely to contain significant amounts of tyramine (e.g., vodka, white wine) and ingest small amounts initially. • Warn patients that the effects of non-selective MAOIs may persist for two weeks after they are discontinued.
Antidiabetics		
Sulfonylureas	• Disulfiram-like reaction has been reported in patients on chlorpropamide who drank alcohol. (Theoretical risk with other sulfonylureas.) The exact mechanism of interaction is unclear. • Acute alcohol use increases the risk of severe hypoglycemia. • Alcohol may prolong glipizide's effect on blood glucose by delaying glipizide absorption and elimination. • Chronic alcohol ingestion may decrease the half-life of tolbutamide by decreasing absorption and increasing hepatic metabolism of tolbutamide.	• Tell patients to avoid alcohol consumption in excess of an occasional drink to prevent hypoglycemia. • Monitor for hypoglycemia if the combination is used. • Counsel patients on sulfonylureas to avoid alcohol if they experience flushing or headache.
Insulin	• Enhanced glucose-lowering action of insulin. • Enhanced release of insulin following a glucose load and inhibition of gluconeogenesis.	• Tell patients to limit alcohol consumption and avoid drinking on an empty stomach. • Monitor for hypoglycemia if the combination is used.
Metformin[12,13] (*Glucophage,* etc)	• Theoretically, an increased risk for lactic acidosis. • Potentiate metformin effect on lactate metabolism.	• Tell patients to limit alcohol consumption. • Monitor for signs and symptoms of lactic acidosis if the combination is used.

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Antihistamines		
First generation antihistamines (e.g., diphenhydramine, chlorpheniramine, hydroxyzine, etc)	• Enhanced CNS depression and impaired psychomotor performance. • Interactions are more pronounced in elderly patients. • There are no documented cases with nonsedating antihistamines.	• Tell patients to limit alcohol consumption. • Monitor for signs and symptoms of CNS depression if the combination is used.
Antihypertensives		
Alpha-1-adrenergic blockers (prazosin)	• Hypotension, especially in Asians. • Asians may be more susceptible because they are more likely than whites to be deficient in aldehyde dehydrogenase. When such patients ingest alcohol, the vasodilatory alcohol metabolite acetaldehyde accumulates and reduces blood pressure. • Theoretically, a similar interaction with alcohol can occur with other alpha-1-adrenergic blockers (e.g., doxazosin, terazosin, etc).	• Tell patients to limit or avoid alcohol intake, especially in patients who flush after alcohol ingestion.
Verapamil (*Calan*, etc)	• Increases alcohol concentrations and prolongs intoxication. • Verapamil appears to inhibit alcohol metabolism and it may also decrease the first-pass metabolism of alcohol.	• Warn patients of the potential for enhanced effects of alcohol when combined with verapamil.
Anti-infectives		
Cephalosporins (cefoperazone [*Cefobid*], cefotetan [*Cefotan*], Canada only: moxalactam [*Moxam*], cefamandole [*Mandol*])	• Disulfiram-like reactions. • These cephalosporins contain a moiety that is structurally related to disulfiram and may inhibit aldehyde dehydrogenase, thereby leading to accumulation of acetaldehyde, a metabolite of alcohol.	• Tell patients to avoid alcohol while taking these cephalosporins and for 2 to 3 days after discontinuing the drug.
Doxycycline	• Chronic alcohol ingestion may reduce the serum concentration of doxycycline. • Chronic ingestion of large amounts of alcohol can induce hepatic enzymes and increase doxycycline metabolism.	• Consider tetracycline in an alcoholic patient when a tetracycline is needed or increase the doxycycline dose.

Drug/Drug Class[a]	Effect(s) and Proposed Mechanism(s)[1-5]	Recommendations/ Comments[c,1-5]
Anti-infectives Con't		
Erythromycin	• Alcohol appears to slow gastric emptying, thereby delaying absorption of erythromycin (no significant effect on efficacy noted). • Erythromycin may increase alcohol absorption when low doses of alcohol are administered.	• Warn patients of enhanced alcohol effects if the combination is used.
Isoniazid	• Increased risk of hepatotoxicity in the presence of chronic alcohol consumption on a daily basis. • The exact mechanism of interaction is unclear.	• Tell patients to limit or avoid alcohol. • Alcoholic patients should be monitored carefully for INH hepatitis.
Ketoconazole (*Nizoral*, etc)	• Disulfiram-like reaction. • The exact mechanism of interaction is unclear.	• Tell patients to limit or avoid alcohol consumption. • Warn patients that alcohol consumption might cause flushing, headache, and nausea.
Metronidazole (*Flagyl*)	• Disulfiram-like reaction. • Metronidazole inhibits aldehyde dehydrogenase, which leads to accumulation of acetaldehyde, a metabolite of alcohol. • Vaginal preparations have also been reported to interact with alcohol.	• Tell patients to avoid alcohol or alcohol-containing drugs while taking metronidazole and for at least 1 day after stopping the drug. • Monitor for flushing, nausea, and vomiting if the combination is used.
Tinidazole (*Tindamax*)	• Disulfiram-like reaction. • Tinidazole inhibits aldehyde dehydrogenase, which leads to accumulation of acetaldehyde, a metabolite of alcohol.	• Manufacturer recommends avoiding alcohol or preparations with propylene glycol during tinidazole therapy and for 3 days following its discontinuation. • Monitor for flushing, nausea, and vomiting if the combination is used.

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Antipsychotics		
Phenothiazines (e.g., chlorpromazine, fluphenazine, prochlorperazine, etc)	• Excessive CNS depression and impaired psychomotor performance. • Increased risk for extrapyramidal symptoms. • Alcohol may lower the threshold of resistance to neurotoxic effects by depleting dopamine or calcium.	• Discourage alcohol intake. • Warn patients receiving neuroleptics of the risk for CNS depression and impaired psychomotor performance.
Atypical antipsychotics[16,17] (quetiapine [*Seroquel*], aripiprazole [*Abilify*] , olanzapine [*Zyprexa*], risperidone [*Risperdal*], ziprasidone [*Geodon*], paliperidone [*Invega*], clozapine [*Clozaril*])	• Excessive CNS depression and impaired psychomotor performance. • Enhanced orthostatic hypotension when olanzapine and alcohol are taken together.	• Tell patients to avoid alcohol use beyond the occasional one or two drinks.
Sedatives-Hypnotics		
Barbiturates (e.g., phenobarbital, pentobarbital, secobarbital, etc)	• Excessive CNS depression and impaired psychomotor performance. • There are reports of death associated with concomitant use of alcohol and barbiturates due to mechanisms other than excessive CNS depression. • Acute intoxication with alcohol appears to inhibit pentobarbital metabolism, while chronic alcohol ingestion appears to enhance the hepatic metabolism of pentobarbital.	• Tell patients to avoid alcohol since tolerance is unpredictable and deaths have been reported. • Monitor for excessive CNS depression if the combination is used.

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Sedatives-Hypnotics Con't		
Benzodiazepines (e.g., diazepam, lorazepam, etc)	• Excessive CNS depression and impaired psychomotor performance. • Alcohol has been reported to increase aggression or amnesia and/or reduce the anxiolytic effects of some benzodiazepines. • Alcohol may increase the absorption of diazepam and reduce its hepatic metabolism. • Patients with alcoholic liver disease may eliminate benzodiazepines more slowly than those with normal liver function.	• Warn against moderate to large amounts of alcohol. • Small amount of alcohol especially if taken with food probably causes little additive CNS depression unless alertness is required (e.g., driving). • Keep in mind that some benzodiazepines (e.g., flurazepam, clonazepam, etc) used at night for sedation are still present in appreciable amounts the next morning and the interaction continues. • Monitor for excessive CNS depression if the combination is used.
Non-benzodiazepine hypnotics[18-20] (zolpidem [*Ambien*, etc], zaleplon [*Sonata*], eszopiclone [*Lunesta*], zopiclone [*Imovane*, Canada only])	• Increased risk of 'sleep-driving' (i.e., driving not fully awake with amnesia of the event). • The exact mechanism of interaction is unknown. May be due to additive CNS depressant effect.	• The manufacturers warn against concurrent use with alcohol.
Chloral Hydrate	• Excessive CNS depression and impaired psychomotor performance. • *In vitro* studies showed that the metabolite of chloral hydrate, trichloroalcohol, inhibits the metabolism of alcohol. • Alcohol appears to stimulate the formation of trichloroalcohol and inhibit its conjugation with glucuronide.	• Tell patients to limit alcohol intake. • Monitor excessive CNS depression if the combination is used. • Disulfiram-reaction is rare, but has been reported.
Ramelteon (*Rozerem*)	• Enhanced CNS depression and impaired psychomotor performance. • The exact mechanism of interacation is unknown.	• Manufacturer warns against concurrent use of ramelteon and alcohol.[25]

Drug/Drug Class[a]	Effect(s) and Proposed Mechanism(s)[1-5]	Recommendations/ Comments[c,1-5]
Sedatives-Hypnotics Con't		
Meprobamate	• Excessive CNS depression and impaired psychomotor performance. • Acute use of alcohol appears to inhibit meprobamate metabolism, while chronic alcohol ingestion appears to induce hepatic metabolism of meprobamate.	• Limit intake of alcohol to avoid excessive CNS depression. • Monitor for excessive CNS depression if the combination is used.
Immunosuppressive		
Methotrexate (*Rheumatrex*)	• Increased risk of methotrexate-induced liver injury. • Most cases involve regular use of moderate to large amounts of alcohol • Exact mechanism of interaction is not known but may be due to additive hepatotoxicity.	• Tell patients to avoid regular consumption or excessive amounts of alcohol. • The manufacturer advises against initiating methotrexate in patients who drink alcohol excessively.[24]
Pimecrolimus[10] (*Elidel*)	• Facial flushing. • The exact mechanism of interaction is unknown.	• Warn patients of increased risk of alcohol-induced facial flushing. • If flushing occurs, caution patients to avoid alcohol while using pimecrolimus.
Tacrolimus[11] (*Prograf*)	• Facial flushing. • The exact mechanism of interaction is unknown.	• Warn patients of increased risk of alcohol-induced facial flushing. • If flushing occurs, caution patients to avoid alcohol while using tacrolimus.
Other Agents		
Acitretin (*Soriatane*)	• Increased duration of teratogenic potential in women. • Alcohol increases the transesterification of acitretin to etretinate, a teratogen which can remain in the body for years.	• Tell women of reproductive potential to completely avoid alcohol and alcohol-containing drugs while taking acitretin and for 2 months after the drug is stopped.
Disulfiram (*Antabuse*)	• Flushing, hypotension, nausea, tachycardia, vertigo, dyspnea, esophageal rupture, and blurred vision. • Deaths have also been reported. • Disulfiram inhibits aldehyde dehydrogenase which leads to accumulation of acetaldehyde, a metabolite of alcohol.	• Tell patients to avoid ANY alcohol, alcohol-containing drugs, or propylene glycol.

Drug/Drug Class[a]	**Effect(s) and Proposed Mechanism(s)**[1-5]	**Recommendations/ Comments**[c,1-5]
Other Agents Con't		
Metoclopramide (*Reglan;* Canada: *Maxeran*)	• Additive sedative effects. • Increases absorption rate of alcohol, probably by speeding gastric emptying.	• Warn patients of the potential for an enhanced alcohol effect. • Monitor for excessive CNS depression if the combination is used.
Nitroglycerin	• Hypotension. • Additive vasodilatory effects.	• Tell patients to limit alcohol intake. • Monitor for hypotension (e.g., lightheadedness, fainting) in patients receiving the combination.
Phenytoin (*Dilantin*, etc)	• Chronic alcohol abuse may reduce serum phenytoin concentrations. • Alcohol induces the hepatic metabolism of phenytoin.	• Monitor for a decreased anticonvulsant effect in heavy drinkers.
Procarbazine (*Matulane*)	• Facial flushing. • Procarbazine inhibits aldehyde dehydrogenase in animal studies.	• Tell patients to avoid alcohol if they develop facial flushing with procarbazine.
Propofol (*Diprivan*)	• Alcoholic patients may require higher doses of propofol. • The exact mechanism of interaction is unknown. • In a small study (n=20), alcoholic patients required 30% higher doses of propofol to induce general anesthesia compared to nonalcoholics.	• Be aware that higher doses of propofol may be needed in alcoholic patients.
Warfarin (*Coumadin*, etc)	• Enhanced anticoagulant effects with acute alcohol intoxication. • Reduced anticoagulant effects in chronic alcoholics. • Acute excessive alcohol intake may inhibit warfarin metabolism. • Increase in warfarin metabolism with chronic heavy drinking is likely due to alcohol- induced stimulation of hepatic enzymes.	• Monitor INRs if patient has more than 3 alcoholic drinks a day or if there is a significant change in the amount of alcohol intake. • Warn patients of increased risk of falls when under the influence of alcohol, which may result in bleeding injuries.

a. Note that only drug interactions that require actions to reduce risk are included. This list is not all-inclusive.
b. Expect the combination of alcohol and any opioids to result in enhanced CNS depression.
c. In general, experts consider moderate alcohol consumption to be one drink per day for adult women and two drinks a day for adult men.[14,15,26] One drink is defined as a 12-oz beer, a 4-oz glass of wine, or a 1.5-oz glass of distilled spirits.[14]

Project Leader in preparation of this Detail-Document: *Wan-Chih Tom, Pharm.D.*

References

1. Hansten PD, Horn JR. *Drug interactions analysis and management*. St. Louis, MO: Facts and Comparisons Publishing Group. 2007.
2. Tatro DS. *Drug interaction facts*. St. Louis, MO: Facts and Comparisons Publishing Group. 2007.
3. Gordis E, Alcohol-medication interactions. National Institute on Alcohol Abuse and Alcoholism. No. 27 PH 355 January 1995. http://pubs.niaaa.nih.gov/publications/aa27.htm. (Accessed December 2, 2007).
4. Alcohol-drug interactions. UHS health Promotion Office. University of Rochester. http://www.rochester.edu/uhs/healthtopics/Alcohol/interactions.html. (Accessed December 2, 2007).
5. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health* 1999;23:40-54
6. Personal communication, medical information department. Alpharma Pharmaceutical Piscataway NJ, 08854 (December 11, 2007).
7. Product information for *Avinza*. King Pharmaceutical. Bristol, TN 37620. October 2006.
8. Product information for *Opana ER*. Endo Pharmaceuticals. Chadds Ford, PA 19317. September 2007.
9. Buse JB Personal communication, medical information department. Endo pharmaceuticals. Chadds Ford, PA 19317. December 11, 2007.
10. Product information for *Elidel*. Novartis Pharmaceuticals. East Hanover, NJ 07936. January 2006.
11. Lubbe J, Milingou M. Tacrolimus ointment, alcohol and facial flushing. *N Engl J Med* 2004;351:2740.
12. Product information for *Glucophage, Glucophage XR*. Bristol-Myers Squibb. Princeton NJ, 08543. (October 2000).
13. Schaffalitzky de Muckadell OB, Mortensen H, Lyngsoe J. Metabolic effects of glucocorticoid and alcohol administration in phenformin- and metformin-treated obese diabetics. *Acta Med Scand* 1979;206:269-73. [Abstract].
14. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007;115:114-26.
15. American Diabetes Association, Alcohol. http://www.diabetes.org/type-1-diabetes/alcohol.jsp. (Accessed December 11, 2007).
16. Product information for *Zyprexa*. Eli Lilly and Company. Indianapolis, IN 46285. October 1, 2007.
17. Product information for *Abilify*. Bristol Myers Squibb Company. Princeton, NJ 08543. November, 2007.
18. Product information for *Lunesta*. Sepracor Inc. Marlborough, MA 01752. April 2007.
19. Product information for *Ambien CR*. *Sanofi-Aventis*. Bridgewater, NJ 08802.
20. Product information for *Sonata*. Wyeth Pharmaceutical. Philadelphia, PA 19101.
21. Product monograph for *Kadian*. Abbott Laboratories, Limited. Vaughan, Ontario L4K 4T7.
22. Methadone: focus on safety. Pharmacist's Letter/Prescriber's Letter 2006;22(9):220902.
23. Product information for *Dolophine*. Roxane Laboratories, Inc. Columbus, OH 43216. October 2006.
24. Product information for *Rheumatrex*. Stada Pharmaceuticals, Inc. Cranbury, NJ 08512. February 2003.
25. Product information for *Rozerem*. Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015. April 2006.
26. U.S. Dept Health & Human Services. Guide to lowering blood pressure. May 2003 (document 03-5232). http://www.nhlbi.nih.gov/health/public/heart/hbp/hbp_low/hbp_low.pdf. (Accessed December 17, 2007).

Cite this Detail-Document as follows: Alcohol-related drug interactions. Pharmacist's Letter/Prescriber's Letter 2008;24(1):240106.

PHARMACIST'S LETTER

Evidence and Advice You Can Trust…

PRESCRIBER'S LETTER

3120 West March Lane, P.O. Box 8190, Stockton, CA 95208 ~ TEL (209) 472-2240 ~ FAX (209) 472-2249