Current Psychiatry

Protect against drug-drug interactions with anxiolytics

Safe use of benzodiazepines, buspirone, and propranolol

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Patients with anxiety disorders are at risk for drug-drug interactions (DDIs) with anxiolytics because they often take medications for comorbid medical or psychiatric illnesses.[1-3] Prescribing anxiolytics for them without contemplating both physiology and chemistry leads to what Osler called "popgun pharmacy, hitting now the malady and again the patient," while "not knowing which."[4]

To help you "hit" the anxiety instead of the patient,[1] we explain the pharmacokinetics and pharmacodynamics of benzodiazepines, buspirone, and propranolol. Practical tables provide information at a glance about which combinations

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Box

3 variables explain a drug's clinical effect

Clinical effect	=	Affinity for site of action (pharmacodynamics)	X	Concentration at site of action (pharmacokinetics)	X	Patient's biology (genetics, age, disease, internal environment)

Pharmacodynamics
What a drug does to the body (actions that mediate its efficacy and adverse effects)

Pharmacokinetics
What the body does to a drug (absorption, distribution, metabolism, elimination) that determines its concentration at the site of action

Patient's biology
Why patients respond differently to the same dose of the same medication (internal environment includes what patients consume, such as foods and co-prescribed drugs)

to avoid and which have potential clinical effects (*Box 1*) you could use to your patients' advantage.

BENZODIAZEPINES

Benzodiazepines provide an anxiolytic effect by increasing the relative efficiency of the gamma-aminobutyric acid (GABA) receptor when it is stimulated by GABA.[5] As a class, benzodiazepines are efficacious for treating panic disorder, social anxiety disorder, generalized anxiety disorder, alcohol withdrawal, and situational anxiety.

Oxidative metabolism. Some benzodiazepines require biotransformation in the liver by oxidative metabolism; others—such as lorazepam, oxazepam, and temazepam—undergo only glucuronidation reactions and do not have active metabolites (*Table 1*).[6-8]

Diazepam is a classic example of the first group; its oxidative metabolism is mediated by cytochrome P-450 (CYP) enzymes 1A2, 2C8/9, 2D19, and 3A3/4. Others in this group—alprazolam, clonazepam, midazolam, and triazolam—depend on CYP 3A3/4 for oxidative metabolism.

Benzodiazepines that undergo oxidative metabolism are more likely than those that do not to be influenced by old age, liver disease, or

Table 1

Benzodiazepines: How metabolized and half-lives

Benzodiazepine	Metabolism	Half-life (includes metabolites)
Alprazolam	Oxidation 3A3/4	8 to 12 hrs
Chlordiazepoxide	Oxidation 3A3/4	10 to 20 hrs
Clonazepam	Oxidation 3A3/4	18 to 50 hrs
Clorazepate	Oxidation 3A3/4	40 to 100 hrs
Diazepam	Oxidation 1A2, 2C8/9,2C19, 3A3/4	20 to 70 hrs
Lorazepam	Conjugation	10 to 20 hrs
Oxazepam	Conjugation	5 to 15 hrs

Source: References 5-7.

Table 2

Clinical effects of drug-drug interactions with benzodiazepines

Pharmacodynamic
Respiratory depression with alcohol, barbiturates, tricyclic and tetracyclic drugs, dopamine receptor antagonists, opioids, antihistamines
With mirtazapine ↑ sedation
With lithium, antipsychotics, and clonazepam → ataxia and dysarthria
With clozapine → delirium
Pharmacokinetic
Cimetidine, disulfiram, isoniazid, estrogen, oral contraceptives ↑ diazepam, chlordiazepoxide plasma concentrations
Nefazodone and fluvoxamine ↑ plasma concentration of triazolam, alprazolam
Carbamazepine ↓ alprazolam plasma concentration
Food, antacids ↓ benzodiazepine plasma concentrations
Cigarette smoking ↑ benzodiazepine metabolism
Benzodiazepines ↑ plasma concentrations of digoxin, phenytoin

co-administration of other drugs that increase or decrease hepatic CYP enzyme function. Some (midazolam and triazolam) have high first-pass metabolism before reaching systemic circulation.

Pharmacodynamic DDIs. Giving benzodiazepines with other CNS depressants—such as barbiturates, tricyclics and tetracyclics, dopamine receptor antagonists, opioids, or antihistamines, or alcohol—can cause potentially serious oversedation and respiratory depression (*Table 2*).

Patients with anxiety disorders may use alcohol to self-medicate their anxiety, especially in social situations. Acute and chronic alcohol use with psychotropics may trigger toxic interactions, including fatal poisoning. Combining benzodiazepines with alcohol, opioids, or mirtazapine potentiates sedation through central H-1 antagonism and GABA promotion.[2] Acute alcohol ingestion also delays the oxidative metabolism of many drugs.[9]

Using benzodiazepines with lithium or antipsychotics may cause ataxia and dysarthria, and benzodiazepines with clozapine can cause delirium.

At-risk patients. Benzodiazepine use is a significant predictor of falling, especially in elderly persons taking more than one sedative. In a controlled study of hospitalized older patients, 84 (46%) of 181 who fell were taking one or more benzodiazepine, compared with 48 (27%) of 181 age-matched controls who did not fall.[10] The message: seek an alternative to benzodiazepines to sedate older patients, especially those taking another CNS depressant.

Alprazolam and DDIs. Alprazolam is commonly prescribed, despite its high potential for abuse and association with dangerous DDIs:

- A study of 172 deaths involving oxycodone showed that 117 patients died from combined drug toxicity. Benzodiazepines (detected in 96 cases) were the most common co-intoxicants and were led by alprazolam.[11]
- Benzodiazepine abuse is common among clients at methadone maintenance clinics and was reported in 3 fatal drug overdoses caused by co-ingestion of methadone and alprazolam.[12]
- Cocaine and methadone were the most common co-intoxicants with alprazolam in a study of 87 deaths attributed to combined drug toxicity.[13]
- In a study of patients who overdosed with benzodiazepines, 22% of those who took alprazolam required ICU admission. This was twice the rate of ICU admission after overdose with other benzodiazepines.[14]

These studies indicate that alprazolam may be more toxic than other benzodiazepines in overdose and when used with other drugs. We recommend that you exercise great care when prescribing alprazolam, particularly for patients who may be at risk of deliberate self-poisoning and lethal DDIs.

Pharmacokinetic DDIs. Diazepam and chlordiazepoxide plasma concentrations increase in combination with drugs that inhibit CYP enzymes, including cimetidine, disulfiram, isoniazid, estrogen, and oral contraceptives.[15]

Nefazodone—a CYP 3A3/4 inhibitor—can increase plasma concentrations of triazolam and alprazolam to potentially toxic levels. Nefazodone's manufacturer recommends lowering triazolam dosages by 75% and alprazolam dosages by 50% when used with nefazodone.[3]

Carbamazepine—a CYP 3A3/4 inducer—induces both its own and other drugs' metabolism. It can lower plasma concentrations of alprazolam, clonazepam, midazolam, and triazolam, which are metabolized by 3A3/4. Smoking, food, and antacids also may decrease benzodiazepine plasma concentrations.

As perpetuator drugs, benzodiazepines might increase digoxin plasma concentration, probably because of reduced digoxin renal clearance.[16] Diazepam may inhibit CYP 2C9 and/or 2C19 by being an alternate substrate for enzyme-binding sites,[15,17] increasing the concentration of other drugs such as phenytoin.

Table 3

Clinical effects of drug-drug interactions with buspirone

Pharmacodynamic
DO NOT use buspirone with monoamine oxidase inhibitors (MAOIs); allow 2-week washout after stopping an MAOI before starting buspirone
Pharmacokinetic
Food ↑ buspirone C_{max} and AUC 2-fold
Renal impairment ↑ buspirone plasma concentration 2-fold
Hepatic impairment ↑ buspirone C_{max} and AUC 15-fold and ↑ half-life 2-fold
Verapamil, diltiazem, erythromycin, itraconazole ↑ buspirone plasma concentration
Rifampicin ↓ buspirone plasma concentration 10-fold
Buspirone ↑ haloperidol plasma concentration
Erythromycin, itraconazole, nefazodone, grapefruit juice ↑ buspirone plasma concentration

C_{max}: maximum drug concentration
AUC: area under the curve (mathematical calculation of the body's total exposure to a drug over time)

BUSPIRONE: COMPLICATED PHARMACOLOGY

One of buspirone's major clinical advantages is that it does not pharmacodynamically or pharmacokinetically affect benzodiazepines. Buspirone, the only azaspirodecanedione marketed in the United States, has complex central 5-HT effects.[18,19] Because it is a partial 5-HT1A agonist, buspirone's net effect depends on 5-HT concentration at the receptor:

- If 5-HT concentration is low, buspirone will act as an agonist.
- If 5-HT concentration is high, buspirone—being a partial agonist—will antagonize the effect of excessive 5-HT.

Buspirone also acts at postsynaptic and presynaptic 5-HT1A receptors, which mediate different physiologic mechanisms in the brain. Finally, buspirone may act more as a full agonist at postsynaptic than at presynaptic 5-HT1A receptors.[20]

Buspirone's pharmacology is further complicated by its conversion via oxidative metabolism into an active metabolite—1-pheyl-piperazine

(1-PP). Buspirone is a CYP 3A3/4 enzyme substrate, so it is extensively metabolized as it crosses the duodenum and passes through the liver. As a result, the parent drug has low bioavailability and is principally converted into 1-PP before entering systemic circulation.[6]

1-PP works differently than the parent drug. As an alpha-2-adrenergic antagonist, 1-PP increases the firing rate of adrenergic neurons in the locus ceruleus by blocking a receptor in presynaptic feedback system.

Which traits of buspirone and its active metabolite produce the drug's anxiolytic effect? It might be one of these, all of them, or some other unknown trait.

Pharmacodynamic DDIs. Presumably because of its effects on serotonin release at 5-HT1A receptors, buspirone may cause hypertensive episodes when used with monoamine oxidase inhibitors (MAOIs) (*Table 3, page 23*). This is why a 2-week washout is recommended between discontinuing an MAOIs and starting buspirone.[21]

In theory, buspirone might cause serotonin syndrome when combined with MAOIs. Rare cases of serotonin syndrome have been reported in patients taking buspirone and selective serotonin reuptake inhibitors (SSRIs) and/or trazodone.[6] On the other hand, using buspirone to augment SSRIs can cause therapeutic DDIs. Some researchers have added buspirone when patients have not benefited from SSRI monotherapy because:

- buspirone affects 5-HT mechanisms
- drugs that affect serotonin reuptake inhibition, 5HT1A receptors, and 5HT2 receptors may have synergy.[20]

Pharmacokinetic DDIs. Avoid combining buspirone with verapamil, diltiazem, erythromycin, or itraconazole because competitive enzyme inhibition will substantially increase buspirone's plasma concentration.[21]

Some SSRIs—such as high-dose fluoxetine and usual doses of fluvoxamine—may increase buspirone serum concentration by inhibiting CYP 3A4.[6] Consider this clinical effect before you combine an SSRI with buspirone. Using buspirone with fluoxetine, paroxetine, or bupropion also increases serum 1-PP. This increase, which occurs when CYP 2D6 slows 1-PP clearance, could cause euphoria, mania, or seizures.[20]

Coadministering rifampin can lower buspirone plasma concentrations almost 10-fold because rifampin induces CYP 3A3/4.[22]

As a perpetuator, buspirone can increase haloperidol plasma concentrations, but probably not to a clinically important extent. In an open trial, Goff[23] added buspirone, mean dosage 23.8 mg/d, to a stable regimen of haloperidol in 7 patients with schizophrenia. Although haloperidol's mean plasma concentration increased by 26% after 6 weeks, this modest change would be difficult to detect in clinical practice.

Huang et al[24] found no clinically significant pharmacokinetic interaction between buspirone, 10 mg tid, and haloperidol, 10 to 40 mg/d, during 6 weeks of coadministration in 27 patients with schizophrenia.

Coadministering rifampin can lower buspirone plasma concentrations almost 10-fold

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Table 4

How to avoid drug interactions with three common anxiolytics*

DO	DO NOT
When prescribing benzodiazepines ...	
Advise patients not to combine benzodiazepines with alcohol	Use with other CNS depressants or nefazodone
Talk to patients about potential for abuse/dependency, and monitor benzodiazepine use	Use in elderly patients or in patients with high potential for substance abuse
When prescribing buspirone ...	
Allow a 2-week washout between discontinuing an MAOI and starting buspirone	Use with MAOIs, verapamil, diltiazem, erythromycin, or itraconazole
Consider adding buspirone when SSRI monotherapy has not adequately helped patients with anxiety	Co-administer with rifampin
Combine with benzodiazepines, if needed	
When prescribing propranolol ...	
Educate patients using insulin for diabetes mellitus that propranolol may inhibit recovery from insulin-induced hypoglycemia, cause bradycardia, or mask tachycardia	Combine with medications with strong hypotensive effects
	Coadminister with strong CYP 2D6 or 1A2 inhibitors
Recheck anticonvulsant plasma concentrations after starting propranolol	Add to calcium inhibitors for patients with ↓ myocardial contractility and A-V nodal conduction

* Before prescribing any anxiolytic, review all co-prescribed medications for potential DDIs
DDI: drug-drug interaction
MAOI: monoamine oxidase inhibitor
SSRI: selective serotonin reuptake inhibitor

PROPRANOLOL: BETA-BLOCKING ANXIOLYTIC

Propranolol is prescribed off-label for anxiety disorders more often than other beta blockers. It may help patients with situational or performance anxiety.

Beta-adrenergic blockers competitively antagonize norepinephrine and epinephrine at the beta-adrenergic receptor. These cardiovascular agents can reduce many of anxiety's peripheral manifestations, such as tachycardia, diaphoresis, trembling, and blushing. All beta blockers share this pharmacologic effect, but their pharmacokinetics differ greatly. Some depend on a single CYP enzyme for clearance (metoprolol, by CYP 2D6), whereas others, such as propranolol, are metabolized by multiple CYP enzymes.

Pharmacodynamic DDIs. Drugs that block alpha-1 adrenergic receptors potentiate beta blockers' blood pressure-lowering effects and increase the risk of orthostatic hypotension. This is probably

why haloperidol can potentiate propranolol's hypotensive effects.[6] Other alpha-1 adrenergic antagonists—though not normally classified as such—include some tertiary amine tricyclic antidepressants (amitriptyline and imipramine) and some antipsychotics (quetiapine).

Reports have associated hypertensive crises and bradycardia with coadministration of beta blockers and MAOIs.[21] Depressed myocardial contractility and A-V nodal conduction may occur when beta blockers are combined with calcium channel inhibitors.[21] Beta blockers also can decrease IV anesthetic dose requirements because they decrease cardiac output.[25]

In patients using insulin for diabetes mellitus, propranolol inhibits recovery from insulin-induced hypoglycemia and may cause hypertension and bradycardia. Beta blockers also can mask the tachycardia that usually accompanies insulin-induced hypoglycemia.

Pharmacokinetic DDIs. Propranolol has an extensive first-pass effect, being metabolized in the liver to active and inactive compounds that interact with CYP enzymes 1A2, 2C18, 2C19 and 2D6.[6]

Coadministering strong CYP 2D6 inhibitors such as bupropion, fluoxetine, or paroxetine can reduce propanolol clearance, increasing its effect and risking cardiac toxicity[6] (*Table 4*). CYP 1A2 inhibitors such as amiodarone and fluoroquinolones or CYP 2C19 inhibitors such as fluvoxamine also increase serum concentrations of propranolol.

On the other hand, CYP inducers such as barbiturates, phenytoin, and cigarette smoking can increase propranolol elimination and decrease its serum levels.[26] Hyperthyroidism may enhance propranolol's presystemic clearance but has little effect on its half life.[27]

As a perpetuator, propranolol produces small increases in diazepam concentration, suggesting that the beta-blocker inhibits diazepam metabolism. This interaction can impair kinetic visual acuity, which is correlated with the ability to discriminate moving objects in space.[26]

Propranolol increases plasma concentrations of antipsychotics, anticonvulsants, theophylline, and levothyroxine (*Table 5*)—possibly because of the beta blocker's negative inotropic effects (decreased cardiac output reduces hepatic and renal blood flow).

Table 5

Clinical effects of drug-drug interactions with propranolol

Pharmacodynamic

With MAO inhibitors → hypertensive crisis and bradycardia

With calcium channel inhibitors → ↓ myocardial contractility and A-V nodal conduction

↓ intravenous anesthetic dose requirements

↓ diazepam metabolism

↓ median effective dosage of valproate and diazepam; might improve antiepileptic potential of valproate

Pharmacokinetic

↑plasma concentration of antipsychotics, anticonvulsants, theophylline, levothyroxine

Barbiturates, phenytoin, and cigarette smoking ↑propranolol elimination

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Related resources

- Cytochrome P450 interactions. www.drug-interaction.com.
- FDA. Food and drug interactions. http://vm.cfsan.fda.gov/~lrd/fdinter.html.
- Psychiatric drug interactions. www.preskorn.com.

DRUG BRAND NAMES

Alprazolam • Xanax
Bupropion • Wellbutrin
Buspirone • BuSpar
Carbamazepine • Carbatrol, others
Chlordiazepoxide • Librium
Cimetidine • Tagamet
Clonazepam • Klonopin
Clorazepate • Tranxene
Clozapine • Clozaril
Diazepam • Valium
Fluoxetine • Prozac
Fluvoxamine • Luvox
Haloperidol • Haldol
Itraconazole • Sporanox
Lorazepam • Ativan
Midazolam • Versed
Mirtazapine • Remeron
Oxazepam • Serax
Paroxetine • Paxil
Phenytoin • Dilantin
Propranolol • Inderal
Quetiapine • Seroquel
Rifampin • Rifadin, Rimactane
Triazolam • Halcion
Valproate • various
Verapamil • Calan, Isoptin

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Patients with anxiety disorders often take medications for comorbid medical or psychiatric problems. To prevent drug-drug interactions with anxiolytics, consider the pharmacodynamic and pharmacokinetic properties of everything a patient may be ingesting. This includes concomitant drugs, over-the-counter products, herbals, illicit drugs, and dietary substances.

Bottom Line