Avoiding common drug–drug interactions

Kristen Wiese, PharmD, and Vicki L. Ellingrod, PharmD, FCCP

Mr. T, age 23, was given a diagnosis of bipolar disorder 1 year ago. After he experienced inadequate symptom relief with valproate, you switched him to extended-release lithium, 1,200 mg/d. Mr. T reported improved mood and stability with this medication adjustment. These positive changes led him to resume activities he enjoyed before onset of bipolar disorder, such as running, reading, and going out to dinner with friends.

Now, Mr. T's mother calls your office to express concern about her son's slight hand tremor, which appeared after 2 days of gastrointestinal distress. She tells you that Mr. T sprained his ankle while running 1 week ago and has been taking over-the-counter ibuprofen for pain relief, which he did often in the past.

You suspect that Mr. T is experiencing lithium toxicity as a result of ibuprofen use.

Although mental health providers can easily recognize the drug–drug interaction between lithium and nonsteroidal anti-inflammatory drugs (NSAIDs) that Mr. T experienced, interpreting the safety of a medication regimen with respect to drug–drug interactions before prescribing often is more daunting. This article reviews the basics of drug–drug interactions, while briefly highlighting common examples in psychiatric medicine (***Table 1,***[1-5] ***page 22***). We also provide an outline of additional points to consider when reviewing your patients' medication regimens and encountering unfamiliar drug–drug interactions.

Types of drug–drug interactions

Drug–drug interactions fall into 2 categories: *pharmacodynamic* (PD) and *pharmacokinetic* (PK):

- PD interactions are a result of the combined impact of medications on the body when there is no direct effect on absorption, distribution, metabolism, or excretion characteristics, such as 2 medications that act at the same receptor or lead to similar or opposing pharmacologic effects.
- PK interactions occur when a drug affects the absorption, distribution, metabolism, or excretion characteristics of another drug.

continued

Practice Points

- Pharmacodynamic interactions are the result of the **combined impact of 2 or more medications on the body.**
- Pharmacokinetic interactions occur when the **drug affects absorption, distribution, metabolism, or excretion of another drug.**
- Before changing a patient's medication regimen, **check online databases for possible drug–drug interactions.**
- Drug–drug interaction consequences **can persist if the drugs have a long half-life.**

Vicki L. Ellingrod, PharmD, FCCP
Department Editor

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists
cpnp.org
mhc.cpnp.org (journal)

Dr. Wiese is a Research Fellow, University of Michigan College of Pharmacy, Ann Arbor, Michigan, and Dr. Ellingrod is the John Gideon Searle Professor of Clinical and Translational Pharmacy, University of Michigan College of Pharmacy and School of Medicine, Ann Arbor, Michigan.

Disclosure

The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

It is possible that a drug–drug interaction will have no clinical effect

Table 1

Common drug–drug interactions in psychiatry

Outcome	Interacting medications	Mechanism of interaction
Serotonin syndrome	Medications that increase serotonin release, inhibit reuptake, or inhibit metabolism (selective serotonin reuptake inhibitors, TCAs, monoamine oxidase inhibitors, trazodone, etc.)	**Pharmacodynamic:** Increased serotoninergic receptor activation. 5-HT2 receptors have been implicated in the more severe manifestations of serotonin syndrome[1]
Anticholinergic toxicity	Any medication that inhibits acetylcholine or blocks muscarinic receptors, such as TCAs, benztropine, diphenhydramine, clozapine, quetiapine	**Pharmacodynamic:** Additive effect of decreased acetylcholine
QT interval prolongation	Medications that increase QT interval, such as haloperidol, ziprasidone, TCAs, antiarrhythmic agents, macrolide antibiotics	**Pharmacodynamic:** Additive QT prolongation
Increased risk for seizures	Bupropion and drugs that lower the seizure threshold, alcohol or benzodiazepine withdrawal, and traumatic brain injury	**Pharmacodynamic:** Additive lowering of the seizure threshold
Increased risk of bleeding	Serotonin reuptake inhibitors combined with NSAIDs or oral anticoagulants	**Pharmacodynamic:** Blocked serotonin reuptake on platelets, leading to reduced platelet aggregation and increased risk for bleeding
Decreased efficacy of oncology medication	Tamoxifen and moderate to strong inhibitors of CYP2D6, such as fluoxetine, bupropion, paroxetine, duloxetine, and sertraline	**Pharmacokinetic:** Tamoxifen is a prodrug that is converted to an active metabolite by CYP2D6. Inhibiting this enzyme leads to decreased tamoxifen activity
Decreased antipsychotic plasma concentrations	Cigarette smoking and CYP1A2 substrates, such as clozapine and olanzapine	**Pharmacokinetic:** Polycyclic aromatic hydrocarbons in cigarette smoke induce activity of CYP1A2, leading to decreased concentrations of medications metabolized by this enzyme
Decreased efficacy of oral contraceptives	Carbamazepine (inducers of CYP450 metabolizing enzymes)	**Pharmacokinetic:** Carbamazepine increases metabolism of oral contraceptives by inducing the activity of several CYP450 metabolizing enzymes
Decreased analgesic efficacy	CYP2D6 inhibitors (such as paroxetine, fluoxetine, bupropion, and duloxetine); prodrug analgesics (codeine, oxycodone, hydrocodone)	**Pharmacokinetic:** Decreased activity of the CYP2D6 metabolizing enzyme will lead to decreased production of the active analgesic metabolites with some opioids
Lithium toxicity[2-5]	Lithium, NSAIDs, thiazide diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers	**Pharmacokinetic:** Increased serum lithium concentration through decreased renal excretion or increased renal re-absorption (thiazide diuretics)

CYP: cytochrome P450; NSAIDs: non-steroidal anti-inflammatory drugs; TCAs: tricyclic antidepressants

Discuss this article at www.facebook.com/CurrentPsychiatry

Although it is possible that drug–drug interactions will have no clinical effect, when the impact of a PD or PK drug–drug interaction is evident, it likely is the result of additive, synergistic, or antagonistic consequences on the medications' intended impact or side-effect profile.

Pharmacodynamic interactions

Serotonin syndrome. The potential for serotonin syndrome occurs when medications that increase synaptic serotonin concentration are used concomitantly.[1] This can occur through several mechanisms, including increased serotonin release,

	Comments
	Potentially fatal, quick onset (hours) after medication addition or dosage increase; warn patients of signs and symptoms
	This is of concern in geriatric patients who may be at higher risk for falls and increased confusion due to an adverse effect; could be mistaken for dementia
	Increased QT interval can lead to torsades de pointes, which is a potentially fatal arrhythmia. Monitor with electrocardiography and electrolytes before and after addition of medications known to increase QT interval
	Avoid in patients with epilepsy, electrolyte disorders, and others at increased risk of seizures
	In observational studies, the most common bleeding site was the upper gastrointestinal tract. Reports vary on the severity and clinical relevance of this interaction
	Antidepressants often are prescribed to breast cancer patients. Avoid these antidepressants and other CYP2D6 inhibitors in patients taking tamoxifen
	Changes in smoking status are likely to require a clozapine dosage adjustment. Olanzapine concentrations also will decrease but this medication has a wider therapeutic window than clozapine. Monitor patients for effect
	Consider contraceptive options such as an intrauterine device or progestin implants, or mood stabilizers that do not induce metabolizing enzymes, to avoid unplanned pregnancies
	May see a less-than-expected response to these opioids in patients taking CYP2D6 inhibitors. Genetic polymorphisms in the CYP2D6 could complicate the picture (decreased or increased CYP2D6 activity)
	Avoid these medications in patients taking lithium but, if necessary to use them, monitor closely and adjust lithium dosage as needed

decreased reuptake, or decreased serotonin metabolism. A high serotonin concentration in the CNS and in the periphery overstimulates serotonin receptors, leading to signs and symptoms that can include diarrhea, fever, delirium, coma, and potentially death.

QT prolongation and anticholinergic toxicity are further examples of additive PD drug–drug interactions. Anticholinergic toxicity is possible when multiple medications contribute to inhibition of the neurotransmitter acetylcholine at muscarinic receptors. This leads to adverse effects such as dry mouth, constipation, confusion, and urinary retention.

QT prolongation, which can lead to arrhythmia, occurs when a patient is taking several medications that can increase the QT interval. Consider close monitoring and using alternative agents with less potential to increase the QT interval in patients at risk of arrhythmias (geriatric patients, those with an increased QT interval at baseline, etc.).

Decreased seizure threshold. The increased risk of seizures with bupropion and other medications that lower the seizure threshold is another example of an additive PD drug interaction. Bupropion can increase the risk of seizures in a dose-dependent manner, which increases when bupropion is taken with other drugs that lower the seizure threshold.[6] Seizure risk associated with alcohol or benzodiazepine withdrawal also may increase the risk for this interaction.

Of note, the increased risk of seizures with the combination of bupropion and alcohol in the absence of withdrawal is not well studied in humans, but positive correlation has been seen in an animal study.[6]

Decreased platelet function. Another example of a PD drug–drug interaction is increased risk of bleeding when a selective serotonin reuptake inhibitor is used with a NSAID or oral anticoagulant. The proposed mechanism for this interaction is that blocking serotonin reuptake on platelets leads to decreased platelet function and an increased risk for prolonged bleeding.[7] This is somewhat controversial because, first, it has been noted that drugs with the highest degree of serotonin reup-

continued on page 31

Clinical Point

Bupropion can increase the risk of seizures in a dose-dependent manner, which increases with other drugs that lower the seizure threshold

continued from page 23

Table 2

Considerations when reviewing a patient's drug regimen for possible drug–drug interactions

Assess for drug interactions with reliable resources:

- If the patient has a complex drug regimen or medical history (transplant, epilepsy, etc.) consult several drug interaction references (Lexicomp, Micromedex, Medscape, etc.). Predicted interactions and their severity will vary by source
- Include over-the-counter drugs when assessing possible interactions

Determine the potential severity of listed interactions:

Clinical significance is greater when…	Clinical significance decreases when…
The involved medication has a narrow therapeutic index • Difference between effective and harmful dosage is small	The medication has a wide therapeutic index
The medications is a "strong" inducer or inhibitor of metabolism	The medication is a "weak" inducer or inhibitor of metabolism
Patient has baseline difficulty metabolizing or excreting interacting medications • Renal or hepatic dysfunction	Patient has normal renal and hepatic function

Further considerations when changing medication regimens:

- Active metabolites can contribute to adverse effects or be essential for the drug's mechanism of action (prodrugs that must be metabolized to be active)
- Adverse effects of drug–drug interactions could remain for an extended time if the involved drugs have a long half-life
- Discontinuing an enzyme-inhibiting medication could require increasing the dosage of impacted medications to have the same effect
- Discontinuing an enzyme-inducing medication requires decreasing the dosage of impacted medications to avoid toxicity

take inhibition do not always cause the highest risk of bleeding and, second, most of the evidence for this interaction is from observational studies.[7]

This potential interaction could be most important for patients who need an antidepressant, are on chronic NSAID or anticoagulant therapy, and are at high risk of bleeding.

Pharmacokinetic interactions

PK interactions in psychiatry often are caused by interference of drug metabolizing enzymes. The cytochrome P450 (CYP450) family of metabolizing enzymes in particular is important to the breakdown of medications in the body. Many drug–drug interactions involve medications that can inhibit or induce metabolism of other drugs through their effect on the CYP450 system.

Inhibition interactions. When a drug's metabolism is inhibited, the result is usually increased serum concentration of that medication (because of less breakdown) and a more potent impact on the primary mechanism of action or adverse effects. Sometimes, inhibiting metabolism can lead to decreased clinical effect. Tamoxifen (an oral agent used to treat breast cancer) and certain analgesics when used in combination with moderate or strong inhibitors of the CYP2D6 subfamily of CYP450 metabolizing enzymes are 2 examples of metabolism inhibition leading to decreased efficacy.[8] Both tamoxifen and the analgesics listed in ***Table 1***[1-5] (***page 22***) are prodrugs; that is, they must be metabolized to be active. When the enzymes that metabolize these drugs into their active form are inhibited, the concentration of active drug decreases.

continued

Clinical Point

Many drug–drug interactions involve agents that can inhibit or induce metabolism of other drugs through their effect on the CYP450 system

Clinical Point

Patients who smoke and use medications metabolized by CYP1A2, such as clozapine and olanzapine, may need a higher dosage

Related Resources

- CredibleMeds. Online resource on QT prolonging drugs. http://crediblemeds.org.
- Madhusoodanan S, Velama U, Parmar J, et al. A current review of cytochrome P450 interactions of psychotropic drugs. Ann Clin Psychiatry. 2014;26(2):120-138.

Drug Brand Names

Benztropine • Cogentin
Bupropion • Wellbutrin
Carbamazepine • Tegretol
Clozapine • Clozaril
Diphenhydramine • Benadryl
Duloxetine • Cymbalta
Fluoxetine • Prozac
Lithium • Eskalith, Lithobid
Haloperidol • Haldol
Hydrocodone • Vicodin
Olanzapine • Zyprexa
Oxycodone • Oxycontin
Paroxetine • Paxil
Quetiapine • Seroquel
Sertraline • Zoloft
Tamoxifen • Soltamox
Trazodone • Desyrel
Valproate • Divalproex
Ziprasidone • Geodon

Induction interactions. Alternatively, there is an increased rate of drug breakdown and resulting decrease in effect when drugs that induce the activity of metabolizing enzymes are used with medications that are substrates of the same enzyme. Carbamazepine is commonly involved in this type of drug interaction because it is a strong inducer of CYP 1A2, 2B6, 2C19, 2C9, and 3A4, and the p-glycoprotein drug efflux pump.[9] As a result of this rampant induction, carbamazepine can decrease the serum concentration of oral contraceptives below a reliably effective level. Therefore, it is recommended that women of childbearing potential use other contraceptive methods, such as a progestin implant or an intrauterine device.[10]

In addition, the polycyclic aromatic hydrocarbons found in cigarettes induce activity of CYP1A2. Patients who smoke and use medications metabolized by this enzyme, such as clozapine and olanzapine, may need a higher dosage.

Drug elimination interactions

The last drug–drug interaction discussed here returns the discussion to Mr. T and involves drug elimination.[2] The NSAIDs Mr. T was using for pain likely caused decreased renal excretion of lithium. Because lithium is primarily excreted through the kidneys, Mr. T's NSAID use, possibly in combination with dehydration caused by gastrointestinal distress, resulted in lithium toxicity. This class of analgesics should be avoided or used cautiously in patients taking lithium.

Clinical applications

The relatively common drug–drug interactions discussed here are just a fraction of the potential interactions mental health practitioners see on a daily basis. Understanding the basics of PD and PK interactions in the setting of patient-specific factors can help to clarify the information found in drug–drug interaction databases, such as Micromedex, Lexicomp, Facts and Comparisons, and Epocrates. ***Table 2*** (***page 31***) lists additional insights into drug interactions.

References

1. Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. BMJ. 2014;348:g1626. doi: 10.1136/bmj.g1626.
2. Eskalith [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2003.
3. Handler J. Lithium and antihypertensive medication: a potentially dangerous interaction. J Clin Hypertens (Greenwich). 2009;11(12):738-742.
4. Blanche P, Raynaud E, Kerob D, et al. Lithium intoxication in an elderly patient after combined treatment with losartan. Eur J Clin Pharmacol. 1997;52(6):501.
5. Atacand [package insert]. Wilmington, DE: AstraZeneca LP; 2013.
6. Silverstone PH, Williams R, McMahon L, et al. Alcohol significantly lowers the seizure threshold in mice when co-administered with bupropion hydrochloride. Ann Gen Psychiatry. 2008;7:11.
7. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. CNS Drugs. 2012; 26(1):39-67.
8. Ereshefsky L, Sloan DM. Drug-drug interactions with the use of psychotropic medications. CNS Spectr. 2009;14(suppl Q and A forum 8):1-8.
9. Carbamazepine. Drug facts and comparisons database. St. Louis, MO: Wolters Kluwer Health Inc; November 2014.
10. Pennell PB. Pregnancy, epilepsy, and women's issues. Continuum (Minneap Minn). 2013;19(3 Epilepsy):697-714.