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The authors reported no potential conflict of interest relevant to this article.

# 5 drug interactions you don't want to miss

These interactions can affect contraceptive efficacy, increase bleeding risk, or lead to rhabdomyolysis. This practical guide can help you avoid trouble.

## PRACTICE RECOMMENDATIONS

- › Recommend progesterone-containing intrauterine devices or long-acting progesterone injections for women using antiepileptic drugs. **(B)**
- › Be aware that there is an increased risk of gastrointestinal bleeding when nonsteroidal anti-inflammatory drugs are used with selective serotonin reuptake inhibitors. **(A)**
- › Do not prescribe novel oral anticoagulants for patients taking carbamazepine, phenytoin, or phenobarbital. **(B)**
- › Choose fenofibrate over gemfibrozil when combining a fibrate and a statin. **(B)**

### Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

There is a strong relationship between the number of medications taken and the likelihood of a potentially serious drug-drug interaction.<sup>1,2</sup> Drug interaction software programs can help alert prescribers to potential problems, but these programs sometimes fail to detect important interactions or generate so many clinically insignificant alerts that they become a nuisance.<sup>3</sup> This review provides guidance about 5 clinically relevant drug interactions, including those that are common (TABLE 1<sup>4-6</sup>)—and those that are less common, but no less important (TABLE 2<sup>6-10</sup>).

## 1. Antiepileptics & contraceptives

### Many antiepileptic medications decrease the efficacy of certain contraceptives

Contraception management in women with epilepsy is critical due to potential maternal and fetal complications. Many antiepileptic drugs (AEDs), including carbamazepine, ethosuximide, fosphenytoin, phenobarbital, phenytoin, primidone, topiramate, and valproate, are potentially teratogenic.<sup>11</sup> A retrospective, observational study of 115 women of childbearing age who had epilepsy and were seen at a neurology clinic found that 74% were not using documented contraception.<sup>11</sup> Of the minority of study participants using contraception, most were using oral contraceptives (OCs) that could potentially interact with AEDs.

**CYP inducers.** Estrogen and progesterone are metabolized by the cytochrome P450 3A4 enzyme. Some AEDs induce this enzyme, which can enhance the metabolism of OCs, thus reducing their efficacy.<sup>12</sup> It is not known, however, if this interaction results in increased pregnancy rates.<sup>13</sup> Most newer AEDs (TABLE 3<sup>6</sup>) do not induce cytochrome P450 3A4 and, thus, do not appear to affect OC efficacy, and may be safer for women with seizure disorders.<sup>12</sup> While enzyme-inducing AEDs may decrease the efficacy of progesterone-only OCs and

TABLE 1

Common and clinically relevant drug interactions<sup>4-6</sup>

Drug interaction	Mechanism of interaction	Clinical relevance	Recommendation
Nitrates PLUS phosphodiesterase type-5 inhibitors (eg, tadalafil, sildenafil citrate)	Increases cyclic GMP in smooth muscle, causing vasodilation	Severe hypotension, syncope, myocardial infarction, death	Contraindicated for concomitant use. Do not prescribe together.
Calcium/iron/magnesium/aluminum supplements OR sucralfate PLUS fluoroquinolone or tetracycline antibiotics or levothyroxine	Chelation of metal ions to medication causes reduced absorption	Subtherapeutic antibiotic or thyroid medication levels in the body	Separate drug and supplement administration by 2 hours.
Simvastatin PLUS amiodarone	Amiodarone is a CYP3A4 inhibitor; simvastatin is a CYP3A4 substrate.  Co-administration can result in increased systemic exposure to simvastatin.	Increased risk of myopathy or rhabdomyolysis	Avoid concomitant use and switch to a different statin with less interaction risk or limit simvastatin dose to 20 mg/d.
Lithium PLUS NSAID or diuretic	It is theorized that prostaglandins involved in renal clearance of lithium are inhibited by NSAIDs, causing lithium accumulation from reduced clearance.	Lithium toxicity presents with diarrhea, vomiting, drowsiness, muscle weakness, impaired vision, and impaired coordination.	Avoid concomitant use of lithium and NSAIDs; if both are necessary, obtain lithium levels and assess for symptoms of toxicity.
Potassium chloride tablets PLUS anticholinergics	Potassium chloride is acidic. Any medication that could slow gastric emptying or dry oral and gastric secretions could increase the risk of potassium tablets getting caught in the gut and causing mucosal damage.	Extended release and wax matrix tablets have been associated with severe esophageal damage and death; however, there are no clear data that combining these medications increases this risk. <sup>4</sup>	Potassium and anticholinergics can be taken together. Advise patients to take them with a full glass of water and remain upright for at least 10 minutes after swallowing the potassium.  Microencapsulated potassium formulations (eg, Micro-K, Klor-Con M) should cause less upper GI irritation than wax matrix formulations (eg, K-Tab, Klor-Con).

GI, gastrointestinal; GMP, guanosine 3'5' monophosphate; NSAID, nonsteroidal anti-inflammatory drug.

the morning-after pill,<sup>12,14,15</sup> progesterone-containing intrauterine devices (IUDs), long-acting progesterone injections, and non-hormonal contraceptive methods appear to be unaffected.<sup>14-17</sup>

■ **OCs and seizure frequency.** There is no strong evidence that OCs affect seizure frequency in epileptic women, although changes in hormone levels during the menstrual cycle do affect seizure susceptibility.<sup>12</sup> Combination OCs decrease lamotrigine lev-

els and, therefore, may increase the risk of seizures, but progesterone-only pills do not produce this effect.<sup>12,16</sup>

■ **Do guidelines exist?** There are no specific evidence-based guidelines that pertain to the use of AEDs and contraception together, but some organizations have issued recommendations.

■ **The American College of Obstetricians and Gynecologists** recommends using a 30- to 35-mcg estrogen-containing OC

TABLE 2

## Medications with multiple interactions

Medication	Mechanism of interaction <sup>6</sup>	Clinical relevance	Recommendation
Amiodarone	A substrate and inhibitor of many CYP enzymes. Also inhibits OCT2 and P-glycoprotein	Bleeding has been reported when used with warfarin; Torsades de pointes has occurred when given with some antiarrhythmics; bradycardia may occur when used with beta-blockers and calcium channel blockers. <sup>7</sup>	Use extreme caution with narrow therapeutic index or high-risk medications.
Digoxin	Substrate for CYP3A4 and P-glycoprotein	With a narrow therapeutic index, potentially life-threatening cardiac adverse effects can occur when combined with medications such as macrolide antibiotics or amiodarone. <sup>8</sup>	Close monitoring in elderly patients or those with renal disease is recommended.
Methadone	A substrate and inhibitor of many CYP enzymes; a significant CNS depressant; may increase serotonin syndrome risk	Fatalities have been associated with benzodiazepines and alcohol. Opiate withdrawal may occur when given with rifampin. <sup>9</sup>	Only prescribers with extensive experience with methadone should prescribe it.
Hepatitis C treatments (ledipasvir/sofosbuvir; elbasvir/grazoprevir)	P-glycoprotein/ABCB1 inhibitor, CYP3A4 substrate	P-glycoprotein/ABCB1 inducers may decrease serum concentration of ledipasvir/sofosbuvir; antacids may decrease serum concentration of ledipasvir. <sup>6</sup>	Avoid the use of PPIs at doses greater than the equivalent of omeprazole 20 mg; avoid CYP3A4 inducers. <sup>6</sup>
Rifampin	Induces many CYP enzymes; substrate and inducer of P-glycoprotein	Decreases the concentration of many medications such as warfarin or oral contraceptives <sup>6</sup>	Use extreme caution with narrow therapeutic index or high-risk medications.
Theophylline	Substrate and inhibitor of CYP1A2, CYP2E1, CYP3A4	Has been reported to reduce the effect of benzodiazepines; macrolides may decrease theophylline concentrations. <sup>6</sup>	375 drugs are known to interact with theophylline, which supports its decline in popularity. <sup>10</sup> Avoid using this agent unless all other options have failed.

ABCB1, ATP-binding cassette sub-family B member 1; TP, adenosine triphosphate; CNS, central nervous system; CYP, cytochrome P450 enzyme; OCT2, organic cation transporter 2; PPIs, proton pump inhibitors.

rather than a lower dose in women taking an enzyme-inducing AED. The group also recommends using condoms with OCs or using IUDs.<sup>18</sup>

■ **The American Academy of Neurology** suggests that women taking OCs and enzyme-inducing AEDs use an OC containing at least 50 mcg estrogen.<sup>19</sup>

■ **The National Institute for Health and Care Excellence** recommends that women taking enzyme-inducing AEDs avoid progestin-only pills.<sup>20</sup>

■ **The Faculty of Sexual and Reproductive Healthcare** agrees that enzyme-inducing drugs may decrease efficacy and recommend

considering IUDs and injectable contraceptive methods.<sup>21</sup>

## 2. SSRIs & NSAIDs

### SSRIs increase the GI bleeding risk associated with NSAIDs alone

Nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed worldwide.<sup>22,23</sup> A well-established adverse effect of NSAIDs is gastrointestinal (GI) bleeding, and there is increasing evidence that concomitant use of an SSRI can further increase that risk through a variety of mechanisms.<sup>23</sup>

SSRIs decrease platelet serotonin levels resulting in defective platelet aggregation and impaired hemostasis. Studies have also shown that SSRIs increase gastric acidity, which leads to increased risk of peptic ulcer disease and GI bleeding.<sup>23</sup> These mechanisms, combined with the inhibition of gastroprotective prostaglandin cyclooxygenase-1 and platelets by NSAIDs, further potentiate GI bleeding risk.<sup>24</sup>

Patients at high risk for bleeding with concomitant SSRIs and NSAIDs include older patients, patients with other risk factors for GI bleeding (eg, chronic steroid use), and patients with a history of GI bleeding.<sup>23</sup>

**■ The evidence.** A 2014 meta-analysis found that when SSRIs were used in combination with NSAIDs, the risk of GI bleeding was significantly increased, compared with SSRI monotherapy.<sup>23</sup>

Case control studies found the risk of upper GI bleeding with SSRIs had a number needed to harm (NNH) of 3177 for a low-risk population and 881 for a high-risk population with an odds ratio (OR) of 1.66 (95% confidence interval [CI], 1.44-1.92;  $P < .00001$ ).<sup>23</sup> When SSRIs were used in combination with NSAIDs, the NNH decreased to 645 for a low-risk population and 179 for a high-risk population (OR=4.25; 95% CI, 2.82-6.42;  $P < .0001$ ).<sup>23</sup>

Another meta-analysis found that the OR for bleeding risk increased to 6.33 (95% CI, 3.40-11.8;  $P < .00001$ ; NNH=106) with concomitant use of NSAIDs and SSRIs, compared with 2.36 (95% CI, 1.44-3.85;  $P = .0006$ ; NNH=411) for SSRI use alone.<sup>25</sup>

The studies did not evaluate results based on the indication, dose, or duration of SSRI or NSAID treatment. If both an SSRI and an NSAID must be used, select a cyclooxygenase-2 selective NSAID at the lowest effective dose and consider the addition of a proton pump inhibitor to decrease the risk of a GI bleed.<sup>23,26</sup>

### 3. Direct oral anticoagulants and antiepileptics

#### Don't use DOACs in patients taking certain antiepileptic medications

Drug interactions with anticoagulants, such as warfarin, are well documented and have been publicized for years, but physicians

TABLE 3

### Antiepileptic drugs to avoid—and consider—when the patient is taking certain OCs<sup>6</sup>

We recommend that patients taking enzyme-inducing antiepileptics avoid all oral contraceptives.

Avoid these enzyme-inducing antiepileptic drugs	Consider these non-enzyme-inducing antiepileptic drugs
<ul style="list-style-type: none"> <li>• Carbamazepine (Tegretol)</li> <li>• Felbamate (Felbatol)</li> <li>• Lamotrigine (Lamictal)</li> <li>• Oxcarbazepine (Trileptal)</li> <li>• Phenobarbital (Luminal)</li> <li>• Phenytoin (Dilantin)</li> <li>• Primidone (Mysoline)</li> <li>• Topiramate (Topamax)</li> </ul>	<ul style="list-style-type: none"> <li>• Ethosuximide (Zarontin)</li> <li>• Gabapentin (Neurontin)</li> <li>• Levetiracetam (Keppra)</li> <li>• Pregabalin (Lyrica)</li> <li>• Tiagabine (Gabitril)</li> <li>• Valproate (Depakote)</li> <li>• Vigabatrin (Sabril)</li> <li>• Zonisamide (Zonegran)</li> <li>• Benzodiazepines</li> </ul>

OCs, oral contraceptives.

must also be aware of the potential for interaction between the direct oral anticoagulants (DOACs) and AEDs.

Apixaban, rivaroxaban, and dabigatran appear to interact with the AEDs carbamazepine, phenytoin, and phenobarbital.<sup>27,28</sup> These interactions occur due to AED induction of the CYP3A4 enzyme and effects on the P-glycoprotein (P-gp) efflux pump.<sup>27,29</sup> When taken together, the AED induces metabolism and elimination of the DOAC medication to occur more quickly than it would normally, resulting in subtherapeutic concentrations of the DOAC. This could theoretically result in a venous thromboembolic event or stroke.

**■ A caveat.** One thing to consider is that studies demonstrating interaction between the DOAC and AED drug classes have been performed in healthy volunteers, making it difficult to extrapolate how this interaction may increase the risk for thrombotic events in other patients.

Some studies demonstrated reductions in drug levels of up to 50% with strong CYP3A4 and P-glycoprotein inducers.<sup>30</sup> Common inducers include carbamazepine, rifampin, and St. John's Wort.<sup>6</sup> Patients taking such agents could theoretically have decreased exposure to the DOAC, resulting in an increase in thromboembolic risk.<sup>31</sup>

CONTINUED

➤ **Enzyme-inducing antiepileptic drugs can enhance the metabolism of oral contraceptives, thus reducing their efficacy.**

#### 4. Statins & certain CYP inhibitors

##### Combining simvastatin with fibrates warrants extra attention

The efficacy of statin medications in the prevention of atherosclerotic cardiovascular disease (ASCVD) is clear. However, the clinical significance of many identified drug interactions involving statins is difficult to interpret. Interactions that cause increased serum concentrations of statins can increase the risk for liver enzyme elevations and skeletal muscle abnormalities (myalgias to rhabdomyolysis).<sup>32</sup> Strong inhibitors of CYP3A4 (amiodarone, cyclosporine, ketoconazole, etc.) significantly increase concentrations of lovastatin, simvastatin, and atorvastatin. Pitavastatin, pravastatin, and rosuvastatin are not susceptible to any CYP-mediated drug interactions;<sup>33</sup> therefore, rosuvastatin (a high-intensity statin) is usually recommended over other statins for patients taking strong inhibitors of CYP3A4.

■ **When to limit simvastatin.** Doses of simvastatin should not exceed 10 mg/d when combined with diltiazem, dronedarone, or verapamil, and doses should not exceed 20 mg/d when used with amiodarone, amlodipine, or ranolazine.<sup>6</sup> These recommendations are in response to results from the SEARCH (Study of the Effectiveness of Additional Reductions in cholesterol and homocysteine) trial, which found a higher incidence of myopathies and rhabdomyolysis in patients taking 80 mg of simvastatin compared with those taking 20-mg doses.<sup>34</sup> CYP3A4-inducing medications, especially diltiazem, were thought to also contribute to an increased risk.<sup>34</sup>

■ **Avoid gemfibrozil with statins.** Using fibrates with statins is beneficial for some patients; however, gemfibrozil significantly interacts with statins by inhibiting CYP2C8 and organic anion transporting polypeptide 1B1 (OATP1B1).<sup>33</sup> The safer choice is fenofibrate because it does not interfere with statin metabolism and can be safely used in combination with statins.<sup>6</sup>

A retrospective review of the FDA Adverse Event Reporting System (AERS) database found that 88% of fibrate and statin combinations that resulted in rhabdomyolysis were associated with gemfibrozil/cerivas-

tatin (cerivastatin is no longer available in the United States).<sup>35</sup>

#### 5. One serotonergic drug & another

##### Serotonin syndrome is associated with more than just SSRIs

Serotonin syndrome is a constellation of symptoms (hyperthermia, hyperreflexia, muscle clonus, tremor and altered mental status) caused by increases in serotonin levels in the central and peripheral nervous systems that can lead to mild or life-threatening complications such as seizures, muscle breakdown, or hyperthermia. Serotonin syndrome is most likely to occur within 24 hours after a dose increase, after starting a new medication that increases serotonin levels, or after a drug overdose.<sup>36</sup>

SSRIs are the most commonly reported drug associated with serotonin syndrome; however, other medications (TABLE 4<sup>37</sup>) may be responsible, especially when used in combination with agents that act on serotonin receptors or in patients with impaired metabolism of the drugs being used.<sup>37</sup>

■ **Other culprits.** Serotonergic effects can also be associated with illicit drugs, some nonprescription medications, and supplements. And in March 2016, the FDA issued a warning about the risks of taking opioids with serotonergic medications.<sup>38</sup> Although labeling changes have been recommended for all opioids, the cases of serotonin syndrome were reported more often with normal doses of fentanyl and methadone.

■ **There are 2 mechanisms** by which drugs may increase a patient's risk for serotonin syndrome. The first is a pharmacodynamic interaction, which can occur when 2 or more medications act at the same receptor site (serotonin receptors in this example), which may result in an additive or synergistic effect.<sup>39</sup>

The second mechanism is a pharmacokinetic alteration (an agent alters absorption, distribution, metabolism, or excretion) of CYP enzymes.<sup>40</sup> Of the more commonly used antidepressants, citalopram, escitalopram, venlafaxine, and mirtazapine seem to have the least potential for clinically significant pharmacokinetic interactions.<sup>41</sup>

TABLE 4

## Drugs/supplements that can affect serotonin levels and cause serotonin syndrome<sup>\*37</sup>

Avoid these substances in patients taking other agents that act on serotonin receptors, and monitor patients closely during dose increases.

Analgesics/-muscle relaxants	Cyclobenzaprine
	Fentanyl
	Methadone
	Tramadol
Antibiotic	Linezolid
Anticonvulsants	Carbamazepine
	Valproic acid
Antidepressants	Bupropion
	Buspirone
	Lithium
	MAOIs
	SSRIs/SNRIs
	St. John's Wort
	TCA's
Antimigraine	Ergotamine
	Triptans
Anti-nausea	Metoclopramide
	Ondansetron
Other	Illicit drugs (amphetamines, cocaine, MDMA [ecstasy], LSD)
	Dextromethorphan
	Phentermine

LSD, lysergic acid diethylamide; MAOIs, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

\*This is not an all-inclusive list.

**Guidelines?** Currently there are no guidelines for preventing serotonin syndrome. Clinicians should exercise caution in patients at high risk for drug adverse events, such as the elderly, patients taking multiple medications, and patients with comorbidities. Healthy low-risk patients can generally take 2 or 3 serotonergic medications at therapeutic doses without a major risk of harm.

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### CORRESPONDENCE

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