

Grapefruit juice and psychotropics: How to avoid potential interactions

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Ms. H, age 42, was given a diagnosis of bipolar disorder 10 years ago and has been taking carbamazepine, 1,200 mg/d, and olanzapine, 10 mg/d, for the past 2 years. She has not experienced a mood episode while on this regimen, and her carbamazepine level was 9.2 µg/mL 6 months ago. The only adverse effect she experienced was weight gain of approximately 10 lb. Ms. H takes a calcium supplement, but no other medications.

Ms. H reports to her psychiatrist that, for the past few days, she has been feeling nauseated, fatigued, and dizzy, but has continued taking her medications as prescribed. Her carbamazepine level is found to be 13.1 µg/mL. Ms. H states she has not started any new medications or supplements; her serum creatinine and liver function test results are within normal limits.

Upon further questioning, Ms. H says that an upper respiratory infection has been “going around her office,” so she increased her vitamin C intake by drinking 2 glasses of grapefruit juice a day (she doesn’t like orange juice). She has heard grapefruit juice can cause problems with some drugs so she is careful not to drink it at the same time she takes her medications. Her psychiatrist recognizes there may be a drug interaction involved, and recommends Ms. H hold her carbamazepine for 1 day and not consume any more grapefruit juice. A few days later,

she reports feeling much better during a follow-up call and she makes an appointment to have her carbamazepine level rechecked in a week.

Although grapefruit products are high in vitamins and low in calories, they can be associated with potentially serious drug interactions. The interaction between grapefruit juice and the calcium channel blocker felodipine was discovered inadvertently >20 years ago; since that time, possible interactions with >85 medications have been identified.¹ Interactions with grapefruit products are complicated

Practice Points

- In general, **an entire grapefruit or 8 oz of juice is enough** to alter a susceptible drug’s pharmacokinetics.
- Several **drug-specific characteristics can help identify risk** of a clinically relevant interaction with grapefruit, including low bioavailability, metabolism through CYP3A4, oral administration, and a narrow therapeutic index.
- Grapefruit most commonly causes an **increase in concentration of certain oral medications** through inhibition of intestinal cytochrome 3A4 enzymes; however, grapefruit also has been shown to decrease the concentration of specific drugs through inhibition of organic anion-transporting polypeptides.
- Interactions with grapefruit-containing products **may apply only to specific medications within a therapeutic category** and are not necessarily a “class effect.”

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because, although most result in increased drug exposure, reduced exposure of the medication also can occur. Additionally, the degree and clinical significance of the interaction varies among individuals and from one drug to another.

Mechanism of action

Most interactions with grapefruit products are thought to result from the inhibition of intestinal cytochrome P450 3A4 (CYP3A4). CYP3A4 is involved in the metabolism of numerous drugs, and is the most abundant cytochrome P450 enzyme in the liver and epithelial cells lining the intestine.² Although hepatic CYP3A4 is thought to be minimally affected by grapefruit, inhibition of intestinal CYP3A4 can result in an overall increase in bioavailability of medications that are substrates and raise the risk of potential toxicity.³ Grapefruit contains various chemicals collectively known as furanocoumarins, which are largely responsible for inhibition of intestinal CYP3A4.⁴ Additionally, Seville oranges and the pomelo (a large, sweet grapefruit-like citrus fruit) also contain furanocoumarins and could have a similar effect, warranting caution with certain medications.⁵

Inhibition of CYP3A4 by furanocoumarins cannot be reversed, and new enzymes must be synthesized to return to the previous level of function.⁶ Therefore, drug interactions resulting from CYP3A4 inhibition can last for as long as 72 hours after ingesting grapefruit products.⁷ Separating consumption of grapefruit products and medication administration will not help manage this interaction.

Grapefruit products also could affect drug disposition through effects on various drug transporters. Decreased systemic exposure to certain medications could occur through grapefruit's inhibition of organic anion-transporting polypeptides (OATPs). OATPs form a family of drug uptake transporters found in the intestine, liver, kidney, and brain.⁸ For drugs that are

substrates of OATPs, grapefruit's inhibition of this transporter can result in decreased absorption and a resulting decrease in efficacy. Flavanoids in grapefruit, such as naringin, inhibit OATPs, which is competitive in nature.⁹ Unlike the irreversible inhibition of CYP3A4 by furanocoumarins, flavanoids effects on OATPs have been shown to decrease within 4 hours.¹⁰

No psychotropic medications have been identified as being susceptible to this interaction, but for those medications affected—including fexofenadine and levothyroxine—separating consumption of grapefruit and medication administration by 4 hours could avoid this interaction.¹¹ Additional data indicate that orange juice and apple juice could have similar effects on OATPs.¹²

Perhaps the most well-known drug transporter, P-glycoprotein is part of the multidrug-resistant subfamily of transporters. It is located throughout the body, including in the intestine, kidneys, liver, and blood-brain barrier. P-glycoprotein acts as an export pump to decrease the cellular concentration of many different drug substrates, and many agents can alter P-glycoprotein's expression or function.

Small changes in P-glycoprotein's activity can result in substantial changes in the disposition of substrates, which can include certain antineoplastics and antiretrovirals. Most reports have found grapefruit juice inhibits P-glycoprotein-mediated efflux; however, there also are reports of transporter activation.⁶ Additionally, P-glycoprotein and CYP3A4 share many substrates, so it can be difficult to isolate the contribution of P-glycoprotein to grapefruit–drug interactions.¹³ The effect of grapefruit on P-glycoprotein activity has been difficult to fully elucidate; more studies are needed.

Grapefruit consumption and its effect

Drug interactions can occur by consuming commercially produced grapefruit

Clinical Point

Drug interactions resulting from CYP3A4 inhibition can last for as long as 72 hours after ingesting grapefruit products



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Clinical Point

The effect of grapefruit on P-glycoprotein activity has been difficult to fully elucidate; more studies are needed

juice and juice from concentrate, as well as freshly squeezed juice and grapefruit segments.¹⁴ CYP3A4-inhibiting furanocoumarins also have been isolated in grapefruit peel; it is not known, however, whether items made from peel (marmalade, candied peel) contain concentrations high enough to pose a risk of a drug interaction.¹⁴ Contributing to the unpredictability of grapefruit-drug interactions, the amount or concentration of furanocoumarins can vary among grapefruit products and brands.¹⁵ This variability can be influenced by the variety or maturity of the fruit and the fruit's exposure to environmental stress.⁴

The frequency of consuming a grapefruit product can influence the degree of a drug interaction. In general, consuming one 8-oz glass of grapefruit juice or the segments from a whole grapefruit is enough to alter a susceptible drug's pharmacokinetics.¹⁴ Regular grapefruit product consumption, however, can result in an overall greater effect.^{16,17}

Lilja et al¹⁶ conducted a randomized, 4-phase, crossover study to look at the effect of grapefruit juice dose on kinetics of triazolam. Grapefruit juice was found to increase the mean area under the concentration-time curve (AUC) of triazolam compared with water, but no difference was found between single glasses of normal-strength and double-strength grapefruit juice. However, repeated consumption of double-strength grapefruit juice (200 mL, 3 times/d for 3 days) increased triazolam's mean AUC by 143%, compared with an increase of 49% with just a single 200-mL glass of double-strength juice.¹⁶ Recurrent consumption of grapefruit juice (8 oz, 3 times/d for 6 days) also was found to increase the kinetics of the antihypertensive felodipine more than a single glass of grapefruit juice.¹⁷

Clinical consequences of an interaction between a drug and grapefruit can be difficult to predict. Drug concentration

changes caused by a grapefruit interaction could vary based on interindividual differences. The amount and activity of intestinal CYP3A4 can vary from person to person, and can be influenced by genetic polymorphisms in addition to race, age, and environmental variables.¹⁸ Interindividual sensitivity to a change in a drug's concentration also will differ, and patient-specific factors, such as concomitant drugs or diseases, could influence the likelihood of harm.

Interactions with grapefruit products are not necessarily a "class effect," and specific drugs within a therapeutic category can be affected (although others might not). Several drug-specific characteristics can help gauge the risk of a clinically relevant interaction with grapefruit, including:

- metabolism through CYP3A4
- low bioavailability
- oral administration
- a narrow therapeutic index.¹

For drugs with low bioavailability because of first-pass metabolism, grapefruit's inhibition of intestinal CYP3A4 can result in a greater relative increase in plasma concentrations compared with a drug with high bioavailability.¹⁹

For example, an increase in bioavailability from 5% to 10% will result in a much larger increase in AUC and overall clinical exposure compared with an increase from 85% to 90% even though both represent an absolute increase of 5%. Although a drug does not have to have low oral bioavailability for an interaction to occur, lower bioavailability means that a drug has a higher likelihood of causing a significant interaction because of altered pharmacokinetics. Of note, injectable medications will not interact with grapefruit because metabolism through intestinal CYP3A4 is bypassed and grapefruit does not significantly inhibit hepatic CYP3A4.

Although grapefruit products could alter the pharmacokinetics of susceptible drugs, those changes might not be associated with

Table

Potential grapefruit interactions with psychotropic medications metabolized by CYP3A4

Drug	Interaction included in product labeling? ²⁰	Comments
Alprazolam	Yes ^a	Pharmacokinetics and clinical effects of alprazolam were not found to be altered by grapefruit juice ²¹
Buspirone	Yes	AUC increased \times 9.2, Cmax increased \times 4.3. ²² Undergoes extensive first-pass metabolism with resulting low oral bioavailability of 5% ²²
Carbamazepine	Yes	AUC increased 41%, Cmax increased 40%, Cmin increased 39% ²³
Clomipramine	No	Case report of increased ratio of clomipramine: desmethylclomipramine in 2 pediatric patients ²⁴
Clozapine	No	No interaction found ²⁵
Diazepam	No	AUC increased \times 3.2, Cmax increased \times 1.5 ²⁶
Fluoxetine	No	Mild serotonin syndrome suggested by a case report ²⁷
Fluvoxamine	No	AUC increased \times 1.6, Cmax increased \times 1.3 ²⁸
Haloperidol	No	No interaction found ²⁹
Lurasidone	Yes	No data on effect of grapefruit on lurasidone disposition. Low oral bioavailability of 9% to 19%. ²⁰ Product labeling recommends avoiding grapefruit and grapefruit juice because they could alter lurasidone concentration ²⁰
Midazolam (oral)	Yes	AUC increased 52%, Cmax increased 56%. IV midazolam is not affected by grapefruit juice ³⁰
Methadone	No	AUC increased 17%, Cmax increased 17% ³¹
Nefazodone	No	Theoretical. Undergoes extensive first-pass metabolism; low oral bioavailability of 20% ²⁰
Pimozide	Yes	Product labeling recommends avoiding grapefruit juice because it could inhibit metabolism of pimozide. Pimozide undergoes significant first-pass metabolism and is primarily metabolized by CYP3A4 ²⁰
Quetiapine	No	Theoretical. Absolute bioavailability has not been determined, but primarily metabolized by CYP3A4 ³²
Sertraline	No	Increases in sertraline concentration noted in 2 studies ^{33,34}
Trazodone	No	Theoretical. Extensively metabolized by CYP3A4 ²⁰
Triazolam	Yes	AUC increased 48%, Cmax increased 25%. ²⁰ Several studies have confirmed the impact of grapefruit juice on triazolam disposition ^{16,35}
Ziprasidone	No	Theoretical. Primarily metabolized by CYP3A4 ²⁰

^aPossible interaction between grapefruit juice and alprazolam suggested by data from clinical studies of other benzodiazepines

AUC: area under the plasma concentration-time curve; Cmax: maximum plasma concentration; Cmin: minimum plasma concentration; CYP: cytochrome P450

adverse effects. Therefore, a factor to consider in evaluating a potential interaction with grapefruit is the drug's therapeutic index and its risk of serious adverse effects. Drugs with a narrow therapeutic index are of particular concern because a significant increase in therapeutic or adverse effects

could result from a relatively small increase in the drug's concentration.⁷

Which medications are affected?

Among medications identified as interacting with grapefruit, some cardiovascular agents and several of the HMG-CoA reduc-

Clinical Point

Although grapefruit could alter the pharmacokinetics of drugs, those changes might not be associated with adverse effects

Clinical Point

If you are concerned about a possible interaction and avoiding grapefruit is not feasible, consider a different medication in the same class

tase inhibitors (statins) have garnered the most attention. However, grapefruit also can affect the metabolism of several psychotropic medications through inhibition of intestinal CYP3A4 (*Table, page 63*).^{16,20-35} Prescribing information for some drugs warns against consuming grapefruit while using the medication. Among CNS agents, buspirone, carbamazepine, lurasidone, pimozide, triazolam, and oral midazolam all have such warnings in their product labeling.

Buspirone currently is not recommended with “large quantities of grapefruit juice.”²⁰ A randomized, 2-phase crossover study looking at the effects of grapefruit juice on buspirone’s pharmacokinetics found that double-strength grapefruit juice (200 mL, administered 3 times/d for 3 days) resulted in a 9.2-fold increase in mean AUC and a 4.3-fold increase in mean Cmax after a single 10-mg buspirone dose.²² Highlighting the wide interindividual variability seen with drug-grapefruit interactions, the increase found in buspirone’s AUC ranged from 3-fold to 20-fold among study participants.²²

Carbamazepine product labeling lists grapefruit juice as a CYP3A4 inhibitor that is expected to or has been found to increase plasma levels of the drug.²⁰ Carbamazepine’s bioavailability is influenced by intestinal CYP3A4 activity; in a randomized, 2-phase crossover study of 10 patients with epilepsy, grapefruit juice was found to increase AUC of carbamazepine by 41% and Cmax by 40%.^{23,36}

Lurasidone and pimozide, although not specifically studied, have product labels that recommend avoiding grapefruit juice because it could inhibit metabolism of these agents by CYP3A4.²⁰ Of particular concern is the potential for elevated levels of pimozide to increase the risk of adverse cardiovascular effects including QT interval prolongation.¹⁹

Midazolam. Although grapefruit juice does not affect the disposition of IV midazolam, pretreatment with grapefruit juice was found to increase the AUC and Cmax of oral midazolam by 52% and 56%, respectively.³⁰

Other considerations in drug-grapefruit interactions

Cautionary statements about a possible interaction with grapefruit juice for many other psychotropics can be found in commonly used drug information references or online sources. If you are concerned about a possible interaction and avoiding grapefruit products is not feasible, consider a different medication in the same class.

However, you also should consider the level of evidence supporting any purported interaction. Several psychotropic agents do have studies or case reports supporting an interaction with grapefruit, but cautionary statements could be based on theoretical concerns because of a medication’s bioavailability, metabolic pathway, and concern for increased adverse events related to higher drug concentrations. Adding to the confusion, cautionary statements can be found about medications, such as clozapine, that have not been shown to have an interaction with grapefruit juice when studied.

With many of the drugs that have a reported or theoretical interaction with grapefruit, data are inconsistent as to whether the resulting interaction will be clinically relevant. A number of variables relating to the individual patient, grapefruit product, or particular drug can play a role in the significance of an interaction. Additionally, effects on drug disposition can last for a few days after consuming a grapefruit product.

Keep alert to situations of increased risk

Recall that the case patient, Ms. H, presented with an elevated carbamazepine level and suffered resulting adverse effects

because of an interaction between the drug and grapefruit juice. Although Ms. H was careful to separate intake of grapefruit juice from carbamazepine administration, grapefruit's inhibition of intestinal CYP3A4 still was present, leading to the interaction.

It is important for health care professionals to recognize this potential risk and to advise patients regarding possible interactions between medications and grapefruit products.

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Related Resources

- U.S. Food and Drug Administration. Grapefruit juice and medicine may not mix. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm292276.htm>.
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Drug Brand Names

Alprazolam • Xanax	Lurasidone • Latuda
Buspirone • BuSpar	Midazolam • Versed
Carbamazepine • Tegretol	Methadone • Dolophine
Clomipramine • Anafranil	Nefazodone • Serzone
Clozapine • Clozaril	Olanzapine • Zyprexa
Diazepam • Valium	Pimozide • Orap
Felodipine • Plendil	Quetiapine • Seroquel
Fexofenadine • Allegra	Sertraline • Zoloft
Fluoxetine • Prozac	Trazodone • Desyrel
Fluvoxamine • Luvox	Triazolam • Halcion
Haloperidol • Haldol	Ziprasidone • Geodon
Levothyroxine • Levoxyol, Synthroid	

Clinical Point

Variables related to the individual patient, grapefruit product, or particular drug can play a role in the significance of an interaction

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continued

This month's instantpoll%

Ms. H, age 33, has completed a course of cognitive-behavioral therapy (CBT) for major depressive disorder (MDD) and is continuing to take sertraline, 50 mg/d. During treatment, Ms. H reported improved mood and quality of life and increased productivity at work. Two months later, Ms. H reports that she is exhausted and unmotivated to go to work, and has started to withdraw socially. Ms. H says that no matter how much sleep she gets, she does not want to get out of bed in the morning and has called in sick to work for several days in a row. She scores high on the Fatigue Associated with Depression Questionnaire. **What treatment would you choose for Ms. H?**

- Stop sertraline and start bupropion, titrated to 450 mg/d
- Continue sertraline, begin another course of CBT, and encourage Ms. H to exercise
- Stop sertraline, and switch to escitalopram, 20 mg/d
- Stop sertraline and start modafinil, 200 mg/d, and encourage Ms. H to start exercising for 30 minutes daily

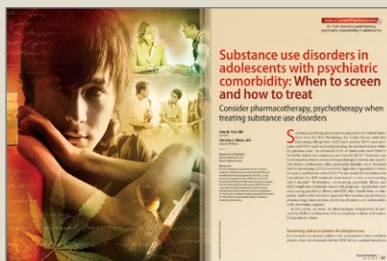
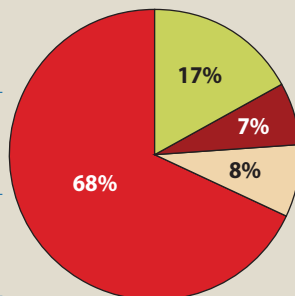
See **'Fatigue after depression responds to therapy. What are the next steps?'** pages 32-40,42

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APRIL POLL RESULTS

You've been treating J, age 12, for attention-deficit/hyperactivity disorder (ADHD), with methylphenidate, 30 mg/d, but his parents are now concerned that he hasn't been acting like himself. He has been caught lying and sneaking around, and they found several empty vodka bottles hidden in his room. J says he has "just a few" shots before, during, and after school to get through the day. Using the Screening to Brief Intervention, you assess that J is at risk for a substance use disorder. **How would you treat J?**

- 17%** Prescribe naltrexone, 50 mg/d, to decrease until alcohol use is stabilized, then titrate atomoxetine to 80 mg/d for ADHD symptoms
- 7%** Prescribe naltrexone, 50 mg/d, and encourage J and his parents to attend 12-step meetings
- 8%** Prescribe disulfiram, 500 mg/d, for 1 to 2 weeks, then reduce to 250 mg/d, and start cognitive-behavioral therapy
- 68%** Educate J on the dangers of abusing alcohol, and start regular screenings for substance use



SUGGESTED READING:
Yule AM, Wilens TE.
CURRENT PSYCHIATRY.
2015;14(4):36-39,47-51.

Savvy Psychopharmacology

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