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Your expert, independent second opinion for prescription drug information

MICHAEL CAROME, M.D., EDITOR

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Routine Monthly High-Dose Vitamin D Supplementation Does Not Reduce Mortality in the Elderly, Trial Shows

Vitamin D is an essential nutrient whose role in bone growth and health, including preventing bone softening in children (rickets) and adults (osteomalacia), is well-documented.

However, the benefits of this vitamin for improving longevity are uncertain. Although evidence from observational studies suggests an association between low vitamin D levels in the blood and acute or chronic adverse health outcomes, no previous large, randomized clinical trial of high-dose vitamin D supplementation has studied death as a primary outcome.

To address this evidence gap, a well-designed, Australian government-funded, placebo-controlled clinical trial called the D-Health Trial assessed the effect of monthly high-dose oral vitamin D supplementation for five years on mortality as a primary outcome in the elderly. The trial, which is the largest that has examined this issue to date, showed that long-term supplementation with monthly high-dose vitamin D was not useful for decreasing all-cause (overall) mortality in elderly adults who were not screened for vitamin D deficiency.

The results of the D-Health trial were published in the February 2022 issue of *The Lancet Diabetes and Endocrinology.*

Vitamin D sources and daily requirements

Vitamin D is available in several foods. It is found naturally in some fatty fishes, fish-liver oils, egg yolks and chicken livers. Food producers in the U.S. also fortify many foods with vitamin D, including milk, orange juice and breakfast cereals. In addition, vitamin D is produced naturally in the skin during direct exposure to sunlight. Some experts suggest that up to 30 minutes of sun exposure, particularly between 10 a.m. and 4 p.m., at least twice weekly to the face, arms, hands and legs without sunscreen leads to sufficient vitamin D synthesis. People with dark skin and the elderly are less able to produce vitamin D from sunlight.

Several forms of vitamin D supplements are available for people who clearly have inadequate vitamin D dietary intake and skin production from sun exposure. The most commonly used forms are cholecalciferol, also known as vitamin D_3, and ergocalciferol, or vitamin D_2.

Overall, U.S. nutritional guidelines recommend that healthy adults up to age 70 consume 600 international units (IU) of vitamin D daily. After age 70, the recommended daily allowance increases to 800 IU.

There is no consensus about the threshold for vitamin D sufficiency; however, vitamin D_3 blood levels of 50 nanomoles per liter (nmol/L) or more are generally considered adequate for most people.

The D-Health Trial

A total of 21,310 Australian subjects whose ages ranged from 60 to 84 years enrolled in the trial until its completion and were randomized to one of the two trial groups: 10,661 received a monthly gel capsule with 60,000 IU of vitamin D and the remaining 10,649 received monthly placebo gel capsules.

Subjects in both groups took their assigned capsules for five years and the researchers evaluated the trial outcomes one year later to capture any prolonged effects of vitamin D supplementation.

Of the total sample, 54% were men and the mean age was 69 years. The trial excluded subjects with self-reported history of certain conditions including kidney stones, hypercalce-

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FROM THE EDITOR Michael Carome, M.D. • Director, Health Research Group

FDA Increasingly Reluctant to Seek Input From External Experts Before Approving New Drugs

Historically, the Food and Drug Administration (FDA) in a large proportion of cases has convened an advisory committee to obtain advice and recommendations from independent, external experts before deciding whether to approve new drugs that contain any active ingredient not previously marketed in the U.S. Such consultation with advisory committees — which are composed of physicians, epidemiologists, statisticians and consumer representatives, among other experts — fosters transparency in FDA decision-making and promotes public confidence in the agency's review and approval process for new drugs.

Indeed, Congress many years ago passed a law requiring that the FDA either refer applications for new drugs containing any active ingredients not previously marketed to an advisory committee for review prior to approval or provide a written summary of the reasons why the drug was not referred to an advisory committee prior to approval.

However, a study published in the May 2022 issue of *Health Affairs* by researchers at Brigham and Women's Hospital and Harvard University revealed a stunning drop over the past decade in the proportion of new drugs approved by the FDA each year that were referred to an advisory committee. Specifically, of all new drugs approved by the FDA in 2010 and 2011, the agency referred the majority — 55% and 59%, respectively — to an advisory committee prior to approval. In stark contrast, in 2020 and 2021, the FDA referred a small minority of the new drugs that it approved — only 8% and 6%, respectively — to an advisory committee before granting approval.

The *Health Affairs* study researchers also examined the specific voting questions that were posed by the FDA to the advisory committees that were convened prior to drug approval from 2010 to 2021. They found wide variation in the substance and wording of key voting questions posed to the committee that ultimately framed the committees' advice to the agency. In some cases, the voting questions posed to the committee failed to directly address whether the drug under review should be approved.

The researchers noted that the "decade-long decrease in referrals of approved drugs to advisory committees suggests that the FDA needs specific criteria for how it chooses to subject new drugs to external scrutiny."

The FDA in recent years clearly has abused the discretion that was granted to it by Congress regarding whether the agency should seek recommendations from its advisory committees before deciding whether to approve new drugs. Congress must pass new legislation that would sharply limit such discretion and direct the FDA to convene its advisory committee far more often before new drugs are approved. Without such action, public confidence in the agency's drug-approval process will continue to dwindle.

Important Drug Interactions for the Combination Antiviral COVID-19 Drug PAXLOVID

Patients taking the oral combination antiviral drug PAXLOVID (nirmatrelvir and ritonavir) should be aware that it has clinically important and potentially dangerous interactions with many other prescription medications.

In December 2021, the Food and Drug Administration (FDA) issued an emergency use authorization for Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and children (age 12 years or older and weighing at least 88 pounds) who test positive for the COVID-19 virus and are at high risk of progression to severe COVID-19, including hospitalization and death. The drug is available by prescription only and must be started within five days of onset of COVID-19 symptoms.

Paxlovid consists of two active ingredients that are dispensed in separate tablets. The first is nirmatrelvir, which prevents the COVID-19 virus from making copies of itself after it infects a person's cells. The second is ritonavir — a drug that was originally approved by the FDA in 1996 for use in combination with other drugs to treat HIV infection.

Notably, ritonavir does not have any antiviral activity against the COVID-19 virus. Instead, it slows the breakdown of nirmatrelvir by enzymes in the liver and thus helps nirmatrelvir to remain in the body for a longer period at higher concentrations.

Paxlovid is administered as three tablets (two nirmatrelvir tablets and one ritonavir tablet packaged together) taken twice daily for five days.

Contraindicated interacting drugs

The FDA issued a patient eligibility screening checklist for patients being considered for Paxlovid treatment.

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Table 1: Drugs That Are Contraindicated in Patients Taking Paxlovid

Generic Name	Brand Name(s)	Drug Class
Concomitant use of Paxlovid with the following drugs can cause dangerously high levels of the interacting drug		
alfuzosin*	UROXATRAL	Alpha blocker for benign prostate enlargement
amiodarone*	PACERONE	Heart-rhythm disorder drug
clozapine*	CLOZARIL, VERSACLOZ	Antipsychotic
colchicine	COLCRYS, GLOPERBA, MITIGARE	Gout drug
dihydroergotamine	D.H.E. 45, MIGRANAL, TRUDHESA	Migraine headache drug
dronedarone**	MULTAQ	Heart-rhythm disorder drug
ergotamine	CAFERGOT,† ERGOMAR, MIGERGOT,† WIGRAINE†	Migraine headache drug
flecainide	generic only	Heart-rhythm disorder drug
lovastatin	ALTOPREV	Cholesterol-lowering statin
lurasidone	LATUDA	Antipsychotic
meperidine*	DEMEROL	Opioid analgesic
methylergonovine	METHERGINE	Drug for uterine bleeding
midazolam (oral)	generic only	Benzodiazepine sedative
pimozide	generic only	Tourette's syndrome drug
propafenone	RYTHMOL SR	Heart-rhythm disorder drug
quinidine*	NUEDEXTA†	Heart-rhythm disorder/malaria/ pseudobulbar affect drug
ranolazine	RANEXA, ASPRUZYO SPRINKLE	Angina drug
sildenafil (only products used for pulmonary arterial hypertension)	REVATIO	Drug for pulmonary hypertension
simvastatin	FLOLIPID, VYTORIN,† ZOCOR	Cholesterol-lowering statin
triazolam**	HALCION	Benzodiazepine sedative
Concomitant use of Paxlovid with the following drugs can cause reduced Paxlovid levels		
apalutamide	ERLEADA	Prostate cancer drug
carbamazepine	CARBATROL, EPITOL, EQUETRO, TEGRETOL, TERIL	Seizure drug
phenobarbital*	LUMINAL, SOLFOTON	Seizure drug
phenytoin	DILANTIN, PHENYTEK	Seizure drug
rifampin	RIFADIN, RIMACTANE	Antibiotic

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†Brand-name combination product that contains one or more additional active ingredients not listed

Medications May Be Carefully Discontinued If Obsessive-Compulsive Disorder Remits

Obsessive-compulsive disorder (OCD) is a chronic condition that is often treated with both behavioral therapy and selective serotonin reuptake inhibitors (SSRIs). Because SSRIs cause numerous adverse effects, patients often seek to stop using their medication once their OCD symptoms remit; however, there is little data available about the outcomes associated with such drug discontinuance.

A recent clinical trial indicates that many persons with OCD who respond favorably to joint behavioral and SSRI treatment may then safely taper their SSRI use very slowly to elimination, though careful follow-up clinical monitoring is still essential.

Background on OCD

OCD is an often severe and persistent illness characterized by uncontrollable obsessions (repeated thoughts, urges or mental images that cause anxiety) and corresponding compulsions (repetitive behaviors in response to those obsessions) that greatly interfere with day-to-day living. In any year, just over 1% of U.S. adults suffer from OCD, and over half of those sufferers experience serious impairment.

Several SSRIs are approved by the Food and Drug Administration for the treatment of OCD, though they also cause the following common adverse reactions: sexual dysfunction, reduced appetite, diarrhea, tremor, sweating and nausea. Clomipramine (ANAFRANIL), which is chemically similar to tricyclic antidepressants, is also FDA-approved for treating OCD.

The new clinical trial

The new clinical trial, which was published in the March 2022 issue of the *Journal of the American Medical Association, Psychiatry*, was a randomized, double-blind study of 101 adults with OCD who either continued using SSRI or clomipramine therapy or discontinued that therapy after four weeks of tapering their dose to zero. Those in the taper group received placebo pills after discontinuing the drug so they and the study researchers would not know their medication was being gradually eliminated.

This trial was conducted from 2013 to 2018 at two academically affiliated treatment centers, one in New York at Columbia University and the other in Philadelphia at University of Pennsylvania.

Adults age 18 to 75 years old were eligible for participation if they had 1) an OCD diagnosis for at least one year with moderate symptoms; 2) been on an "adequate" dose of an SSRI or clomipramine (see Table, below) for at least 12 weeks; and 3) attained wellness following up to 25 sessions of a specific behavioral therapy known as exposure/response prevention (EX/RP), which involves safe but challenging exposures to objects or situations that trigger debilitating feelings while discouraging corresponding compulsions. For example, a person with an irrational fear of germs may be coached by their therapist to touch floors or other seemingly contaminated surfaces without immediate hand-cleansing afterwards and work towards comfortably doing so at least three times a day.

Participants were said to achieve wellness after medication and EX/RP treatments if their OCD symptoms

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Oral Drugs Used to Treat OCD by "Adequate"† Daily Dose

Generic Name	Brand Name(s)††	"Adequate" Daily Dose (mg)	Recommended Maximum Daily Adult Dose (mg)	FDA-Approved for OCD?
citalopram	CELEXA	40	40	No
clomipramine	ANAFRANIL	225	250	Yes
escitalopram	LEXAPRO	30	20	No
fluoxetine	PROZAC	60	80	Yes
fluvoxamine	LUVOX	250	300	Yes
paroxetine	PAXIL, PEXEVA	60	60	Yes
sertraline	ZOLOFT	200	200	Yes

†*Per Foa et al, JAMA Psychiatry. 2022;79(3):193-200.*
††*Brand-name combination products that contain one or more additional active ingredients not listed.*
All drugs in this Table are classified as Limited Use by Worst Pills Best Pills News.

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The checklist identified 25 drugs currently marketed in the U.S. that are contraindicated in patients taking Paxlovid, meaning the interacting drugs should never be used concomitantly (at the same time) with Paxlovid (see Table 1, page 3). The list includes certain drugs for gout, heart-rhythm disorders, high blood cholesterol, infections, migraine headaches, prostate disease, psychosis and seizures.

For some of these drugs, Paxlovid inhibits the liver enzymes that break down the interacting drug. Thus, concomitant use of Paxlovid with these interacting drugs can increase blood concentrations of the interacting drugs to toxic levels, potentially resulting in serious or life-threatening adverse effects. To avoid such toxicity, the interacting drug should be discontinued prior to Paxlovid treatment and not restarted until the effect of the antiviral drug on liver enzymes has subsided. For example, patients who are taking either lovastatin (ALTOPREV) or simvastatin (FLOLIPID, VYTORIN, ZOCOR) should stop the cholesterol-lowering statin drug 12 hours prior to the first dose of Paxlovid and wait until five days after Paxlovid treatment has ended before restarting the statin.

Other drugs can accelerate the breakdown of Paxlovid by liver enzymes. Thus, their concomitant use with Paxlovid can lead to reduced blood levels of Paxlovid, which may result in COVID-19 treatment failure and potentially promote the development of COVID-19 virus variants that are resistant to Paxlovid. For the same reason, use of the herbal supplement St. John's wort also is contraindicated in patients taking Paxlovid. Importantly, Paxlovid cannot be initiated immediately after discontinuation of any of these interacting drugs (or St. John's wort) because it takes time for their effect on liver enzymes to resolve.

Other interacting drugs

The FDA's patient eligibility screen-

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Table 2: Examples of Other Drugs That Interact With Paxlovid

Generic Name	Brand Name(s)	Drug Class
amlodipine*	AZOR,† CADUET,† EXFORGE,† EXFORGE HCT,† KATERZIA, LOTREL,† NORLIQVA, NORVASC, PRESTALIA,† TRIBENZOR†	Calcium channel blocker, hypertension drug
bupropion**	APLENZIN, CONTRAVE,† FORFIVO XL, WELLBUTRIN	Antidepressant, weight-loss drug
ceritinib	ZYKADIA	Cancer drug
clarithromycin*	generic only	Antibiotic
cyclosporine	GENGRAF, NEORAL, SANDIMMUNE	Immunosuppressant/ organ-transplant drug
dabigatran**	PRADAXA	Anticoagulant
dexamethasone	HEMADY	Glucocorticoid
digoxin	LANOXIN	Heart disease drug
diltiazem*	CARDIZEM, CARTIA XT, TAZTIA XT, TIAZAC	Calcium channel blocker, hypertension drug
erythromycin	E.E.S., E.E.S. 400, ERYC, ERYPED, ERY-TAB, ERYTHROCIN	Antibiotic
felodipine	generic only	Calcium channel blocker, hypertension drug
fentanyl*	ACTIQ, FENTORA, LAZANDA, SUBSYS	Opioid analgesic
ibrutinib	IMBRUVICA	Cancer drug
itraconazole***	SPORANOX, TOLSURA	Antifungal drug
ketoconazole (oral)**	generic only	Antifungal drug
methadone*	METHADOSE	Opioid for pain, opioid-use disorder
methylprednisolone	DEPO-MEDROL, MEDROL, SOLU-MEDROL	Glucocorticoid
nicardipine*	generic only	Calcium channel blocker, hypertension drug
prednisone	RAYOS	Glucocorticoid
quetiapine*	SEROQUEL	Antipsychotic
rifabutin	MYCOBUTIN, TALICIA†	Antibiotic
rivaroxaban**	XARELTO	Anticoagulant
sirolimus	FYARRO, RAPAMUNE	Immunosuppressant/ organ-transplant drug
tacrolimus	ASTAGRAF XL, ENVARSUS XR, PROGRAF	Immunosuppressant/ organ-transplant drug
trazodone**	generic only	Antidepressant
vincristine	generic only	Cancer drug
voriconazole	VFEND	Antifungal drug
warfarin	JANTOVEN	Anticoagulant

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****Designated as Do Not Use except for serious fungal infection by* Worst Pills, Best Pills News
†Brand-name combination product that contains one or more additional active ingredients not listed

Trial Compares Titrated Treatment With Two Gout Drugs: Allopurinol and Febuxostat

Gout is a chronic condition that affects approximately 4% of American adults. It is a painful type of inflammatory arthritis characterized by excessive amounts of uric acid in the blood (hyperuricemia), which can cause sudden gout flares (attacks) due to needle-like deposits of uric-acid crystals in the joints causing redness, swelling and pain.

Two main uric-acid–lowering medications are available. The first is allopurinol (LOPURIN, ZYLOPRIM), which has been the first-line medication for preventing gout attacks since the Food and Drug Administration (FDA) approved it in 1966. Allopurinol is particularly effective in reducing uric acid in patients with kidney disease. The second is febuxostat (ULORIC), which the FDA approved in 2009 and is almost 20 times more expensive than allopurinol.

Public Citizen's Health Research Group has long recommended the use of allopurinol for most patients with gout and designated febuxostat as a **Do Not Use** drug.

A weakness of the earlier major clinical trials supporting the approval of febuxostat is that they compared subjects who received fixed doses of febuxostat with those who received a maximal dose of allopurinol, rather than comparing titrated doses of these drugs as necessary to achieve adequate reduction of blood uric-acid levels, which should be done in the management of gout patients. A new randomized clinical trial that addressed this limitation and hypothesized that allopurinol is inferior to febuxostat showed that allopurinol actually did better than febuxostat in controlling gout flares, including in patients with moderate chronic kidney disease.

Funded by the Department of Veterans Affairs, the new trial was initiated before the FDA warned about the risks of febuxostat and limited its use (see next section). The findings of the trial were published in the March 2022 issue of the *New England Journal of Medicine (NEJM) Evidence*, a new online journal.

Grounds for our position regarding febuxostat

We based our **Do Not Use** designation of febuxostat on evidence from the clinical trials that supported its approval, which showed that even though the drug lowered blood uric-acid levels more than allopurinol, it was not more effective than allopurinol in preventing gout attacks, which is the main goal of treatment. Additionally, there was early troubling evidence suggesting that febuxostat increased the risk of serious cardiovascular adverse effects and related mortality.

In June 2018, we petitioned the FDA to ban febuxostat following the release of findings from a postmarketing safety trial (called CARES) that was required by the agency. These findings provided stronger evidence that febuxostat increases cardiovascular and all-cause mortality compared with allopurinol.

In February 2019, the FDA mandated the addition of a black-box warning, the agency's most prominent warning, to febuxostat's labeling indicating that patients with established cardiovascular disease who were treated with the drug had an increased risk of death compared with similar patients treated with allopurinol. The agency also limited the approved use of febuxostat to certain patients who have an inadequate response to a maximally titrated dose of allopurinol, who cannot tolerate allopurinol or for whom treatment with allopurinol is not recommended.

The new clinical trial

Trial researchers enrolled 940 subjects with gout and hyperuricemia. As designed by the researchers, one-third of these subjects had moderate chronic kidney disease in order to approximate the prevalence of this condition among gout patients in the real world. The trial subjects were randomized to receive either allopurinol or febuxostat for 72 weeks.

The trial had three phases: weeks 0 to 24 (during which allopurinol and febuxostat dosages were titrated gradually for each subject to achieve adequate reduction of blood uric-acid levels), weeks 25 to 48 (during which further dosage adjustments of both drugs was permitted until week 33) and weeks 49 to 72 (during which no dosage adjustments of the drugs were permitted).

Subjects received first doses of either 100 milligram (mg) of allopurinol, which were maximally titrated to 800 mg, or 40 mg of febuxostat, which were maximally titrated to 120 mg initially and to 80 mg later at the request of the FDA. All subjects also received anti-inflammatory treatment (mostly with colchicine [COLCRYS, GLOPERBA, MITIGARE]) in the first two phases of the trial, which is recommended as prophylaxis for gout attacks during initial treatment with allopurinol or febuxostat.

In the third phase, the researchers found that 37% of the subjects in the allopurinol-treated group had one or more gout flares (the primary efficacy outcome of the trial), compared with 44% of those in the febuxostat-treated group. This finding negated the hypothesis that allopurinol is inferior to febuxostat. However, 80% of the subjects in both groups reached their target uric-acid levels in the blood.

Among gout subjects with moderate chronic kidney disease, 32% and

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mia (high blood calcium levels), hyperparathyroidism (overactivity of the parathyroid gland) and osteomalacia. Retention in the trial and compliance with assigned capsules among subjects of both groups were high.

Because the researchers were interested in routine administration of vitamin D in the elderly, they did not screen the subjects for vitamin D deficiency before enrolling them in the trial. However, subjects in both groups were vitamin D-replete; average D_3 blood levels in randomly sampled vitamin D and placebo subjects during the trial follow-up were 115 and 77 nmol/L, respectively.

Using six-year follow-up data, the researchers found that all-cause mortality and mortality from cancer and cardiovascular disease were similar among subjects in the two groups. In fact, an exploratory analysis that excluded data from the first two years of follow-up found a mild increase in cancer mortality among subjects in the vitamin D group.

Therefore, the researchers concluded that routine supplementation of older adults with vitamin D in populations that are largely vitamin D-replete is unlikely to reduce overall or cardiovascular mortality. They also cautioned against long-term use of the trial's high vitamin D dosing regimen in the real world.

An important shortcoming of the trial is that it was not focused on subjects with low vitamin D blood levels, who may be more likely to benefit from vitamin D supplementation.

What You Can Do

You should not take high-dose vitamin D supplements to reduce your risk of death. You generally do not need to take any vitamin D supplements unless you do not consume enough vitamin D from dietary sources, do not get enough direct exposure to sunlight or have a medical condition that predisposes you to vitamin D deficiency. Talk to your doctor before taking vitamin D or any other supplement to avoid overdosing and related adverse effects. ✦

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ing checklist for patients being considered for Paxlovid treatment identifies 56 other drugs that have potentially dangerous interactions with Paxlovid (see Table 2, page 5, for a list of examples; the complete list is available at https://www.fda.gov/media/158165/download). The list includes certain antibiotics, anticoagulants (blood thinners), antidepressants, antifungal drugs, calcium channel blockers for treating hypertension, cancer drugs, glucocorticoids (also called corticosteroids) administered orally or by injection, immunosuppressants used in organ transplant patients and opioids.

For these drugs, the FDA advises that concomitant use of Paxlovid with the interacting drug should be avoided, the dose of the interacting drug should be adjusted or special monitoring of the interacting drug is needed during concomitant use.

For patients taking a hormonal contraceptive containing ethinyl estradiol (AFIRMELLE, BEKYREE, CYCLESSA, GILDAGIA, KURVELO, NORTREL and many others) who need treatment with Paxlovid, an additional nonhormonal method of contraception should be used during the five days of Paxlovid therapy and until one menstrual cycle after stopping Paxlovid.

What You Can Do

If you need treatment with Paxlovid, review all your other medications with your doctor to assess for potentially significant drug interactions. If you are taking a medication that interacts with Paxlovid, you may need to stop or adjust the dosage of the interacting drug, undergo more frequent monitoring of the blood levels of the interacting drug or your doctor may advise you to take a different drug than Paxlovid for treating your COVID-19 infection. Be aware that other drugs not listed in this article also may have dangerous interactions with Paxlovid. ✦

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declined to a score of 14 or lower on the 40-point Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). This score of 14 is notably lower than the pre-EX/RP treatment score required to enter the trial, which was at least 18 on the same scale.

After wellness was achieved using the combination of medication and EX/RP, the four-week tapering phase followed for those assigned to the medication-taper group; all subjects then continued active medication or placebo for an additional 20 weeks. The primary outcome was the Y-BOCS after those 20 weeks. Secondary endpoints included standardized depression and quality-of-life scale scores.

Subjects had an average age of 31 years, 55% were female and 86% were White. The mean Y-BOCS score at the time medication tapering began was 9.

After 24 weeks, among those who completed the trial, the mean scores between the two groups on the Y-BOCS were statistically indistinguishable and still in the wellness range: 10.7 and 10.8, respectively. Depression and quality-of-life scores also were statistically the same between study completers across groups. However, 45% of the medication-taper group demonstrated marked worsening of their OCD, compared with just 24% of the medication-continuation group, a statistically significant difference.

Accordingly, the researchers concluded that those who achieve wellness on medication and EX/RP therapy on average maintained that wellness without continuing medication. However, the fact that medication tapering resulted in significant clinical worsening

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45% of allopurinol- and febuxostat-treated subjects, respectively, experienced one or more gout flares during phase three of the trial. Subjects with moderate chronic kidney disease in both drug groups were similarly successful in achieving their target uric-acid levels in the blood.

For all subjects and for the subgroup of subjects with moderate chronic kidney disease, there were no differences between the two drug groups in the frequency of serious adverse effects, including cardiovascular events. However, unlike the CARES trial, the current trial was not large enough to evaluate cardiovascular safety. Therefore, its safety findings do not override those of the CARES trial.

What You Can Do

You should avoid starting febuxostat if you are not currently taking it. If you are already taking febuxostat, consult with your doctor about switching to the older and safer gout drug, allopurinol. If allopurinol fails to adequately prevent gout attacks, talk to your doctor about adding probenecid (PROBALAN). It is important not to stop taking febuxostat without first talking to your doctor because doing so can exacerbate your condition. Seek emergency medical attention right away if you experience chest pain, dizziness, numbness or weakness on one side of your body, rapid or irregular heartbeat, shortness of breath, sudden severe headache and trouble with your speech while taking febuxostat.

You also should discuss with your doctor lifestyle modifications that can reduce your risk of acute gout attacks, including losing weight, avoiding or reducing alcohol intake and making changes to your diet to lower blood uric acid levels. ✦

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in a substantial proportion of subjects further led to the conclusion that OCD patients who attempt drug tapering after achieving therapeutic wellness on medication and EX/RP therapy must be carefully monitored for OCD-symptom relapse.

An April 2022 commentary from a group of clinician researchers published by *Comprehensive Psychiatry* expressed deep concern that medication discontinuance, even following the achievement of wellness using medication and EX/RP, carries with it a high risk of relapse that may ultimately warrant more gradual or delayed medication tapering.

What You Can Do

If you suffer from OCD and are using an SSRI medication or clomipramine to treat that condition, consider finding a therapist who can additionally treat you with EX/RP. If you achieve wellness with the combination of medication and EX/RP therapy, further consider working closely with your doctors to gradually taper and discontinue your medication, but be careful to maintain regular contact with your therapist and physician during at least the first six months after you begin to taper your medication to monitor for OCD-symptom relapse, which may require resumption of your medication. Never abruptly stop your SSRI or clomipramine. ✦

DRUG INDEX

Drug names in **bold** indicate the drug is the primary subject of an article. Drug names in ALL CAPS are brand names. Numbers refer to the page containing the first reference to the drug or supplement in each article.

In the Next Issue

Learn which drugs can cause urinary incontinence.