Over-the-Counter and Compounded Vitamin D: Is Potency What We Expect?

Because vitamin D insufficiency can be harmful to health,[1-3] supplementation is often prescribed. However, the Food and Drug Administration (FDA) does not regulate vitamin D supplements, so potency may not be well evaluated. In a recent trial examining vitamin D in menopausal women, we found that compounded vitamin D_3 (cholecalciferol) supplements varied significantly in potency. Only one-third of our compounded study pills met US Pharmacopeial (USP) Convention standards, which require that compounded pills contain 90% to 110% of the active ingredient.[4] This variability in compounded cholecalciferol pills led us to additionally investigate over-the-counter (OTC) cholecalciferol pills, in which we also found variability.

Methods. We randomly selected 5 pills from 15 sealed bottles of OTC cholecalciferol dietary supplements (1000 IU, 5000 IU, and 10 000 IU) purchased at 5 stores in Portland, Oregon. We next randomly selected 1 pill from 5 bottles with the same lot number and 1 pill from 5 bottles with different lot numbers. We also analyzed compounded study cholecalciferol pills (1000 IU and 50 000 IU), compounded on 3 occasions over 4 months. Testing was done at variable times (0-6 months) after compounding.

Pill potency was analyzed using high performance liquid chromatography (HPLC) (Rapid Separation LC [RSLC] Ultimate 3000 UHPLC System; Dionex) (see eAppendix; http://www.jamainternalmed.com). To validate our laboratory testing accuracy, we split pills and sent them to a second laboratory. The values from the second laboratory were within 10% of the results of our laboratory.

We describe pill accuracy using the percentage of expected potency. We averaged overall potency of 5 pills from the same bottle and calculated the standard deviation. To standardize variability and compare across doses, we calculated the coefficient of variation (CV)—the ratio of the standard deviation to the mean.

Results. *Analysis of 5 Pills From the Same Bottle*. The OTC pills contained 52% to 135% of expected dose (**Table**). When averaged over 5 pills, two-thirds of bottles met USP Convention standards for OTC cholecalciferol solution,[5] which state that contents should be within 90% to 120% of the stated dose. In approximately one-fourth of bottles, all 5 pills met USP Convention standards. Two-thirds of bottles had less than 10% variability (CV). The one manufacturer that was USP verified (No. 4) was highly accurate (101.7%), and all 5 pills tested were within 10% of expected dose.

Analysis of Pills From 5 Bottles With The Same Lot Number. When we took 1 pill from each of 5 bottles with the same lot number, potency ranged from 57% to 138% of the stated amount (eTable 1). When pills in each lot were averaged, potencies ranged from 99.7% to 107%. Only the 5000 IU dose of the USP-verified manufacturer had pills from the same lot that all tested within 90% to 120% of the expected amount. The 1000 IU pills of that manufacturer were more variable (97% to 135% of the expected dose; CV, 13.0%). Variability of pills from the remaining manufacturers ranged from 7.1% to 27.9%; only 1 had less than 10% variability.

Analysis of Pills From 5 Bottles With Different Lot Numbers. The potency of pills from different lots ranged from 9% to 140% of the stated dose; mean potencies over 5 lots ranged from 89% to 105% (eTable 2). Only the USP-verified manufacturer had pills from different lots that were all within 90% to 120% of the expected dose (CV, 5.5%). The 1000-IU pills from the USP-verified manufacturer were more variable—potency ranged from 70% to 140% (CV, 23.3%). The pills from different lots of the remaining manufacturers were also variable (CVs, 11.3% to 58.2%).

Analysis of Compounded Pills. The compounded 50 000-IU cholecalciferol tablets contained 52% to 105% and the 1000 IU compounded tablets 23% to 146% of the expected dose. Only one-third of pills were within 10% of the expected dose, which is the USP Convention

Table: Vitamin D_3 (Cholecalciferol) Potency of 5 Pills From 1 Bottle

Manufacturer No.	Dosage of Pills, IU	Potency Pill (% of Expected)		Potency of 5 Pills, Mean (SD), %	Coefficient of Variation, %
		Highest	Lowest		
1	10 000	130	123	126.4 (2.7)	2.1
2	10 000	114	85	97.6 (12.7)	13.0
3	5000	121	113	118.0 (3.2)	2.7
4[a]	5000	106	99	101.7 (2.5)	2.4
5	5000	132	129	130.8 (1.1)	0.8
2	1000	97	75	90.5 (8.8)	9.8
3	1000	131	102	115.2(10.7)	9.3
5	1000	124	56	99.6 (25.7)	25.7
6	1000	108	104	105.8 (1.6)	1.5
7	1000	103	95	99.9 (3.9)	3.9
8	1000	122	63	82.2 (23.2)	28.2
9	1000	108	87	97.7 (10.1)	10.4
10	1000	88	52	65.9 (14.0)	21.3
11	1000	110	107	108.6 (1.1)	1.0
12	1000	135	122	128.6 (5.0)	3.9

[a] US Pharmacopeial Convention–verified dietary supplement.

standard for compounded pills.[4] Variation in storage time did not explain potency differences.

Comment. The cholecalciferol content of OTC and compounded vitamins was highly variable; potency ranged from 9% to 146%. In our test, just over one-half of OTC pills and only one-third of compounded pills met USP Convention standards. The manufacturer that was USP verified (No. 4) was generally more accurate and less variable. Lack of accuracy in cholecalciferol dosing may not cause harm in most consumers. However, supplementation may be less effective and dose adjustments inaccurate in inconsistent users,[6] which may harm women with severe vitamin D deficiency. Pill variability may also threaten validity of vitamin D trials that use compounded pills to blind participants. As more people take vitamin D supplements, it is critical that health care providers and patients understand that cholecalciferol potency may vary widely. Products that are USP verified may have better accuracy but may be sparsely distributed. On the basis of our study, we agree with a recent editorial calling for increased regulation of dietary supplements.[7]

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Less Is More

A National Survey of the Treatment of Hyperlipidemia in Primary Prevention

The majority of statin use in the United States is for primary prevention: that is, in patients without established coronary heart disease (CHD). The evidence of mortality benefit in this population is inconclusive.[1,2] The patient's baseline risk is critical in determining the risk-benefit ratio of statins.[3]

Little is known about physician decision making regarding the use of statins in primary prevention. Previous studies investigating treatment of hyperlipidemia focused on adherence to various guidelines.[4,5] We investigated physicians' prescribing strategies in relationship to baseline risk of CHD.

Methods. We sent an anonymous and voluntary written survey to 750 physicians selected randomly from a nationally representative sample of US physicians from the American Medical Association Physician Masterfile. The sample consisted of an equal number of family medicine, cardiology, and general internal medicine physicians. Inclusion criteria were physicians (doctor of medicine or doctor of osteopathic medicine degree) who had seen adult patients with hyperlipidemia in an outpatient clinic within the last 12 months. Three waves of letters were sent with an initial $2 cash incentive.

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The survey contained 6 vignette-style questions involving patients without CHD and different baseline risks, for whom a physician might consider treatment of hyperlipidemia (**Table**). All risk factors were stated, and for all patients, the high-density lipoprotein cholesterol level was 50 mg/dL (to convert cholesterol to millimoles per liter, multiply by 0.0259) and triglyceride level was 150 mg/dL (to convert to millimoles per liter, multiply by 0.0113). Vignettes 3 to 6 describe patients who had attempted lifestyle modifications prior to consideration of medications. Vignettes 3 and 4 queried how many similar patients would need to be treated with a statin to prevent a death at 5 and 20 years and given choices of 1 to 10, 11 to 20, 21 to 50, 51 to 100, 101 to 500, and 501 or more.

All analyses were conducted on fully deidentified data using IBM SPSS Statistics 19 software (SPSS Inc). A logistic regression was run for prescribing vs not prescribing with specialty and sex as independent variables. Inclusion of other physician demographic factors did not substantially affect the model. A linear regression model was fitted for number needed to treat, with specialty and sex as independent variables. We compared prescribing