

The Prudent Prescriber

Phil Mohler, M.D. • pmohler69@gmail.com

2775 Crossroads Blvd • P.O. Box 10600 • Grand Junction, CO 81502-5600

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Pharm Reps ≠ Rational Prescribing

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Calcium and Vitamin D: Still Looking for a Disease to Treat?

I have entered the cohort where

Frailty → Falls → Fracture → Finito
is the frightening cascade. The data in the calcium/vitamin D arena are confusingly conflicted. Here are two recent noteworthy studies.

A randomized, double blind, placebo-controlled trial, the VIDA Study, published in *Lancet, Diabetes and Endocrinology* April 2017 followed 5,108 healthy community dwelling New Zealanders (average age 60, 60% male) for five years. Those in the active group received 100,000 units of vitamin D orally monthly. At baseline both groups had average vitamin levels of 25ng/ml. At the termination of the study, the vitamin D levels of those who received vitamin D had risen to an average of 50ng/ml. This suggests good adherence.

Results: There were no clinical or statistical differences in falls or fractures in the two groups. The authors looked at the outcomes in subgroups of patients who had been more or less active and those who had more or fewer previous falls. Again, there was no evidence that once monthly doses of 100,000 units of vitamin D were protective.

Antibiotics do
NOT

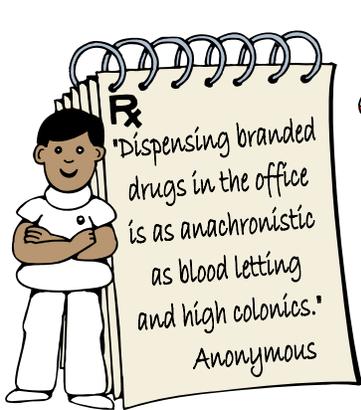


help
acute bronchitis

**β-blockers in
post-MI
save
lives**



Pill splitters save
BIG



R
"Dispensing branded drugs in the office is as anachronistic as blood letting and high colonics."
Anonymous



CHE?

Think:

- Ace**
- Aldactone**
- B-blocker**
- Dig**
- Diuretic**



Avoid these expensive
"me-too" drugs:

- Intermezzo
- Vimovo
- Livalo
- Pristiq
- Viibryd
- Edarbi
- Daliresp



Treat patients
> 60 years to 150/90



NOW AVAILABLE
ON THE
GENERIC MARQUEE

- Frova → frovatriptan
- Voltaren gel → diclofenac Na 1% gel
- Crestor → rosuvastatin
- Nuvigil → armodafinil
- Jalyn → dutasteride/tamsulosin
- Ortho Tri-Cyclen Lo → Tri-Lo-Marzia,
- Tri-Lo-Sprintec, & others

So maybe the monthly high doses in the study above were responsible for the negative results. (Recall the recent trial where a single very high dose of vitamin D resulted in increased fractures early on.) Or maybe the subjects in the New Zealand study were getting too much or not enough calcium.

In a meta-analysis of 33 randomized controlled studies ([JAMA 2017; 318\(24\): 2466-2482](#)) including 51,145 community dwelling participants, Zhao *et al*/ investigated whether calcium, vitamin D or combined calcium and vitamin D supplements are associated with a lower fracture incidence. Hip fracture was defined as the primary outcome. Secondary outcomes were non-vertebral fractures, vertebral fractures, and total fractures.

Results:

There were no significant associations of calcium or vitamin D intake with risk of hip fracture compared with placebo or no treatment. There were no significant associations of combined calcium and vitamin D with hip fracture compared with placebo or no treatment. There were no significant associations found between calcium, vitamin D, or combined calcium and vitamin D supplements in the incidence of non-vertebral, vertebral, or total fractures. Subgroup analyses show that these results were generally consistent regardless of the calcium and vitamin D dose, gender, fracture history, dietary calcium intake, and baseline serum 25-hydroxyvitamin D concentration.

My Take:

So what are you going to say to the next patient who asks you about calcium and vitamin D? In an interview, Dr. Khaw, the first author of the [Lancet](#) high-dose vitamin D study, states “physicians should not be ordering screening serum vitamin D levels.” She waffles regarding oral vitamin D supplementation, saying that it is cheap and probably safe and might help.

Here’s the draft of the October, 2017 USPSTF recommendations regarding calcium and vitamin D supplementation.

Population	Recommendation	Grade (What’s This?)
Men and premenopausal women	The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in men and premenopausal women.	I
Postmenopausal women	The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D and greater than 1,000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.	I
Postmenopausal women	The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1,000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.	D

Other than some minimal risk of kidney stones, calcium and vitamin D are probably safe. Some smaller studies have shown no increased risk of cardiovascular disease with supplementation. Per the USPSTF recommendations, if you are going to recommend supplements, avoid low doses of both vitamin D and calcium. (**D**=do not do it)

Ohhh, for a case of rickets!

Surrogates and Shortcuts: Sloppy FDA Gives Short Shrift to Patients

In the US, the FDA determines whether a new drug is sufficiently safe and effective to be made available to doctors for use by patients. To do this, it must find the difficult balance between requiring sufficient high-quality clinical evidence from premarket evaluation and yet allowing promising new drugs to enter the marketplace quickly.

The FDA maintains a “usual requirement” of “more than one” well-controlled clinical trial that independently proves a drug’s efficacy. However, it also describes several situations in which fewer trials or studies with non-clinical outcomes, such as surrogate markers of disease, might suffice for premarket evaluation.

Over the last decade, the FDA has adopted “lifecycle drug evaluation.” The lifecycle evaluation approach enables regulators to approve drugs based on clinical evidence that is less robust with the understanding that drugs will continue to be evaluated after the approval period.

In an important systematic review published in the British Medical Journal first author Alison Pease {a medical student!} *et al*, (BMJ 2017; 357:j1680) evaluated the post-approval studies of drugs approved by the FDA on the basis of limited evidence.

Here’s what they discovered:

- From 2005-2012, the FDA approved 188 new drugs for 206 indications, more than a third of which were approved on the basis of a single trial. Forty-four percent of the 188 drugs were approved on the basis of trials that used surrogate markers of disease instead of clinical outcomes for primary endpoints.
- Less than one third of new drug indications approved by the FDA on the basis of a single trial had at least one post approval trial showing superior efficacy; even fewer used clinical outcomes.
- Approximately 90% of post approval studies of drugs for indications approved on the basis of surrogate markers also used surrogate markers of disease for trial endpoints.

Meanwhile, in Europe, in another study published in the British Medical Journal (BMJ 2017; 359:j4530), the European Medicines Agency (EMA) was also taken to task.

- Among 68 cancer drug indications approved by the EMA in the period 2009-2013, and with a median of 5.4 years’ follow-up, only 35 (51%) were associated with significant improvement in survival or quality of life over alternative treatment options or placebo.
- For the other 33 studies (49%), uncertainty remains over whether the drugs extend survival or improve quality of life.

My Take:

There is an incessant push by Big Pharma, who pays the FDA millions of dollars annually for the new drug approval process, to have the FDA rush drugs to market. When Crappy Little Studies (CLS) with small “N”s, short time frames and often, meaningless clinical surrogates bring expensive drugs to market, everyone loses except the pharmaceutical industry. The problem is compounded when the FDA does not mandate the post approval, “lifecycle drug evaluation” process that it put in place!

Our learning curve with **false surrogate markers** has been slow.... folic acid lowering homocysteine levels for cardiovascular health outcomes, diabetes drugs lowering blood sugars and HbA1cs for mortality improvements, asymptomatic or minimally symptomatic ventricular arrhythmias as a surrogate to prescribe flecainide, and statins for lowering LDL levels as a marker of improved CV outcomes. Surrogates are not going away, but **Be Skeptical** when you read CLS with disease oriented, surrogate outcomes.

Finally, until the FDA sheds its role as Big Pharma’s handmaiden, little will change. Let’s take the federal money being proposed to “Build the Wall” and “Build an Independent FDA.”

You may access previous issues at <https://www.rmhp.org/i-am-a-provider/provider-resources/publications-for-providers>

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