Speaker 1: Welcome to the ASHP Official Podcast, your guide to issues related to medication use, public health, and the profession of pharmacy.

Lindsey C.: Thank you for joining us for the Therapeutic Thursdays podcast. This podcast provides an opportunity to listen in, as members sit down to discuss what's new and ongoing in the world of therapeutics. My name is Lindsey Childs-Kean, a Clinical Assistant Professor from the University of Florida College of Pharmacy. I'll be your host today for the ASHP Therapeutic Thursdays podcast. With me today is Sarah Cruz, a pharmacist and registered dietitian. Sarah completed her dietetic internship at Cornell University in 2007, and is also a graduate of the University of Florida College of Pharmacy.

Lindsey C.: She is board certified in both nutrition support and geriatrics, and as a practicing certified nutrition support clinician. Sarah currently practices as a unit-based pharmacist at Prisma Health Greenville Memorial Hospital in Greenville, South Carolina. Her practice interests include nutrition support pharmacy, sterile compounding, food nutrient and drug interactions, and dietetic practice. Thanks for joining us today, Sarah. Let's get started talking about today's topic, using vitamin D supplementation for indications other than bone health.

Lindsey C.: So I will give the disclaimer that I am not a nutrition support specialist, but I'm very interested in this topic because a lot of our patients are interested in using vitamins to help supplement their health for various reasons. So let's start off talking some of the basics. That here in the United States we have two main forms of vitamin D supplementation, cholecalciferol and ergocalciferol. Help us remember what the primary differences between these two formulations are, Sarah.

Sarah Cruz: Thanks for the question Lindsey, it's great to be talking with you today. Yes, so this is a common question I often hear from patients who've been directed by their physician to take a vitamin D supplement. Do they go with cholecalciferol, which is also known as vitamin D3 or ergocalciferol, whose other common name is vitamin D2? Let's start with cholecalciferol, cholecalciferol or vitamin D3 is considered the more natural of the two different available formulations. Cholecalciferol is the form of vitamin D that your body will produce when unprotected skin is exposed to the ultraviolet B rays of the sun.
Sarah Cruz: Keep in mind that endogenous sources of cholecalciferol or vitamin D3 are derived from animal sources, including fish, especially the fatter varieties such as cod, herring or salmon, and also which comes as a surprise to a lot of people from exposing lanolin from sheep's wool ultraviolet light. On the other hand, ergocalciferol or vitamin D2 is not synthesized by the body naturally but it’s actually derived from plant sources, such as mushrooms and yeast. Just as the human body can make its own vitamin D, a similar process can occur in plants when ergosterol, a steroid compound in plants is subjected to UVB light. Thus, we derive the name ergocalciferol.

Sarah Cruz: In regard to the chemical structure of vitamin D, between ergocalciferol and cholecalciferol, they differ only in the structure, one of their side chains. For vitamin D product formulations, you can find both cholecalciferol and ergocalciferol available over-the-counter, in both capsule form or as oral liquid. It can be found as a single compound product, for example, vitamin D2 or vitamin D3 alone, but they’re also in combination with other vitamins. A lot of times you’ll see calcium and vitamin D together on the shelf or in a multivitamin. The major prescription preparations of oral vitamin D however, is ergocalciferol or vitamin D2. These products are generally available at a much higher strength than the over-the-counter products.

Sarah Cruz: The costs for the over-the-counter cholecalciferol versus ergocalciferol for the most part is comparable and there’s really not a significant price difference between the two. Also, this brings up an important counseling point when you’re speaking to patients about vitamin D supplementation. Patients who are vegan and potentially some vegetarians or really anyone who may be opposed to taking an animal derived source of vitamin D should be directed to take ergocalciferol or vitamin D2.

Lindsey C.: Well, thanks for that review, Sarah, and I certainly had never thought about deriving from an animal source for cholecalciferol. So that's certainly something I'll keep in mind the next time that I'm counseling a patient who needs vitamin D supplementation. So with the two different formulations or the two different types of vitamin D, when would one form of vitamin D be used over the other?

Sarah Cruz: Okay. Yeah, so in terms of supplementation of vitamin D, choosing cholecalciferol or ergocalciferol, it really depends on the patient's unique situation. If
the patient's main concern that they're not getting enough vitamin D in their diet or through sun exposure or does the patient have a known vitamin D deficiency, for those patients who are not known to be vitamin D deficient, I would first suggest starting out with a discussion of vitamin D sources via the diet and try to gain the adequacy of sun exposure. Some dietary sources of naturally occurring vitamin D include egg yolks, cheese, mushroom, and the fatty fish that we discussed earlier. Other food sources which could be fortified with vitamin D2 include dairy products, such as milk or yogurt, breakfast cereals, orange juice, and some soy containing beverages.

Sarah Cruz: If the addition of vitamin D is determined to be needed for general supplementation, like for example, it's a winter season, the patient has little opportunity for sun exposure or maybe there's some concern the patient may not be consuming enough vitamin D from their diet. For children ages one and older and adults, and this includes pregnant and lactating women, adults up to 70 years of age, the recommended dietary allowance or RDA for a healthy population for vitamin D according to the Institute of Medicine is 600 international units a day. For adults age 71 or older, the recommendation is to increase to 800 international units per day.

Sarah Cruz: For adult patients with a known vitamin D deficiency, however, the Endocrine Society recommends treatment with a high dose vitamin D, usually 50,000 international units orally once weekly or 6,000 international units daily for eight weeks followed by a maintenance therapy of 1500 to 2000 international units of vitamin D daily thereafter. It is important that the vitamin D deficient patient have a repeat serum 25-hydroxy vitamin D level, three to four months after the start of therapy to verify that the target serum level has been achieved.

Sarah Cruz: Also, in terms of whether cholecalciferol or ergocalciferol would be the preferred therapy for a patient who is vitamin D deficient, there's been some conflicting evidence in the literature, with some studies showing that vitamin D3 may be more effective in raising serum 25-hydroxy vitamin D levels over D2 when given in a higher bolus dose. However, other studies have found there's no significant difference between the two. The most recent Endocrine Society clinical practice guidelines, for treatment of vitamin D deficiency do consider vitamin D2 and D3 to be basically equivalent in that either is appropriate for the prevention and treatment of vitamin D deficiency.
Lindsey C.: Okay, well that's good to know, Sarah. So I currently live in Florida and you have lived in Florida at different points in your life, and so we have a lot of concern here locally and of course across the country with concern about UV light exposure. With that growing concern, patients are wearing more sunscreen and not getting as much of that natural vitamin D from the sun that you alluded to. So it seems like more and more patients are being diagnosed with vitamin D deficiency. So, what are some of the concerns associated with having a vitamin D deficiency?

Sarah Cruz: Yeah, excellent question. Yeah, in fact, a number of patients are concerned with UV light exposure and are taking steps such that you mentioned, applying sunscreen, putting on a hat, wearing protective clothing when going outdoors, and even avoiding the peak time of day when the UV light exposure from the sun would be at its peak. This is prudent behavior, given how too much exposure to UV light can be linked to the development of skin cancer or melanoma. This growing trend, however, can really affect how much vitamin D a patient is able to produce on their own. According to the American Association of Clinical Endocrinologists, the major cause of vitamin D deficiency is a lack of sun exposure.

Sarah Cruz: But stepping back for a minute from the question at hand, it's important to understand how vitamin D deficiency is defined. A patient's clinical vitamin D status is based on their serum 25-hydroxy vitamin D level. This is a biochemical marker and it reflects those dietary and endogenous vitamin D. At this time, there is not broad consensus for what value precisely indicates that a patient is vitamin D deficient. For example, the Institute of Medicine states that a level of 25-hydroxy vitamin D less than 12 nanogram per ML identifies a patient of having a vitamin D deficiency. However, this differs from the Endocrine Society and the American Association of Clinical Endocrinologists who states that levels less than or equal to 20 nanogram per ML or less than 30 nanogram per ML respectively, correctly identifies such patients.

Sarah Cruz: But back to sun exposure, regarding that, it's been suggested that the body can make anywhere from estimated 10,000 to 20,000 international units of vitamin D and roughly 30 minutes of mid day sun exposure, but this can be only an estimate really because the amount of melanin in your skin as well as other factors such as cloud cover, air pollution, both seasonal and latitude variations and the
strength of UV light may also affect how much vitamin D your body is able to produce. Other risk factors for the development of vitamin D deficiency include, patients who have malabsorptive disease states, such as celiac or Crohn's disease, renal disease, patients who may have extensive burns, individuals who are on antiepileptic medications. Those individuals who are lactose intolerant or may not consume dairy products, or patients that have a milk or seafood allergies and individuals who are overweight or obese.

Sarah Cruz: The most common association that most healthcare providers would make when thinking about vitamin D and its effects on the body, would be related to bone health. But perhaps a very oversimplified explanation, having adequate circulating vitamin D allows the body to more effectively absorb calcium and phosphate from the GI tract. If the circulating levels of vitamin D drop, as would occur in a vitamin D deficiency, less calcium is absorbed from the GI tract and thus less serum calcium is available for bone mineralization. Serum calcium is tightly regulated in the body. If the serum level decreases outside of its normal range, parathyroid hormone will stimulate bone breakdown, and this is to release additional calcium that's stored in the bone in order to return that serum calcium level back to within its normal range. If vitamin D deficiency is prolonged over time, this can lead to weak brittle bones or osteomalacia.

Lindsey C.: Thanks for that overview, Sarah, and I think just most pharmacists are aware of the benefits of supplementing with vitamin D for bone health purposes. But having talked with patients and being a patient myself, I have heard about other indications where vitamin D supplementation might be beneficial. So, can you talk to us a little bit about some of those indications where vitamin D supplementation might be helpful for patients?

Sarah Cruz: That's a great question, Lindsey. Sure we can talk for a few minutes about a couple areas with recently published data, looking at whether vitamin D supplementation, either treat or prevent a disease was found to be beneficial or really not so much. This interest in vitamin D and its role on health and disease has really greatly increased in the last decade or so, and this interest has partly come about from the discovery of vitamin D receptors in tissues outside the skeletal system. This has prompted researchers to question whether vitamin D plays a role in fertility, diabetes,
cardiovascular or pulmonary diseases, depression, immune function, cancer, among other disease states.

Sarah Cruz: For this conversation though, I want to focus on the evidence in regard to vitamin D and depression, as well as vitamin D and cardiovascular disease. In regards to the depression, there's currently not known of a specific mechanism to explain how vitamin D deficiency would directly cause the disease. That being said, there are vitamin D receptors that have been found in the hypothalamus, the prefrontal cortex, the amygdala, the substantia nigra and hippocampus, in addition to other regions of the brain. It's been suggested that vitamin D plays a role in regulating serotonin levels and may affect the synthesis of both dopamine and norepinephrine.

Sarah Cruz: The relationship between vitamin D and these neuro-transmitters may have had an impact on mood and could be a plausible explanation to explain the pathophysiology of depression. But let's look at some of the recent literature. Just published earlier this year, Alavi et al. conducted a randomized placebo-controlled trial, giving either 50,000 international units of vitamin D3 orally, weekly, or placebo at meal times to older adults age 60 or older with moderate to severe depression as measured by the Geriatric Depression Scale. After eight weeks of vitamin D supplementation, there was a statistically significant decrease in the depression score and the vitamin D supplement arm when compared to placebo arm of the study.

Sarah Cruz: So I'd like to contrast this with another trial also published this year, a randomized double-blind, placebo-controlled trial, known as the D VITAL study. So this study protocol gave vitamin D3 supplementation of 1,200 international units per day versus placebo, and participants ranging from 60 to 80 years of age, were assessed for clinically relevant depression symptoms as measured by the Center of Epidemiological Studies Depression Scale, as well as for functional limitations and physical performance. At the end of the year long vitamin D supplementation versus placebo intervention, researchers found no relevant differences between the treatment group or placebo in terms of these primary endpoints.

Sarah Cruz: The results of the D VITAL studies seem to be in line with a recent systematic review and meta-analysis conducted in 2015 by Shaffer et al. which examined randomized controlled trials of vitamin D supplementation for depressive
disorder or depressive symptoms. Although, the number of randomized controlled trials included in this meta-analysis was very few in number, Shaffer et al. concluded that vitamin D supplementation had no overall effect in the reduction of depression symptoms. It was noted by the authors that the studies that were included in this meta-analysis were a very different in how they supplemented vitamin D, regarding the vitamin D dose. For example, some studies gave 600 international units while others gave close to 300,000 international units.

Sarah Cruz: The frequency of the vitamin D administration, as some studies were giving vitamin D daily, some studies were giving vitamin D weekly versus just a one time dose. Also, the duration of therapy, some of the studies ranged from six weeks of therapy to two years. Also, the route of administration varied, so some studies used a fortified cheese product versus a capsule or versus an IM injection of vitamin D.

Lindsey C.: Okay, so it sounds like conflicting data for depressive symptoms with vitamin D supplementation. So what about the biggest cause of morbidity and mortality in our country, cardiovascular disease?

Sarah Cruz: Yeah. So, we’re moving on to vitamin D supplementation and the prevention of cardiovascular disease. Vitamin D has been thought to lower cardiovascular disease risks through multiple mechanistic pathways in the body. In addition to the presence of vitamin D receptors having been found in the heart, there’s also the thought that vitamin D may play an important role in the regulation of blood pressure, inhibition of vascular smooth muscle proliferation as well as indirect involvement in calcium dependent cellular processes. So earlier this year, published in the New England Journal of Medicine, were the results from the greatly anticipated vitamin D and Omega-3 or the VITAL trial.

Sarah Cruz: So this was significant in the fact that this is the largest randomized placebo-controlled trial today that looked at the effects of vitamin D supplementation on the prevention of cardiovascular disease. Some 25,871 participants were randomized, either 2,000 international units of vitamin D paired with one gram of Omega-3 fatty acids per day or placebo. This study actually followed patients for a little over five years, and for the primary endpoint of major cardiovascular events which was
comprised of MI, stroke or cardiovascular death, supplementation with vitamin D paired with the Omega-3 fatty acids did not result in a lower incidence of cardiovascular events than placebo.

Sarah Cruz: Before the VITAL trial, there was the vitamin D assessment or the VITAL study. So this was a randomized double-blind, placebo-controlled study whose results were published in 2017. This study successfully recruited 5,110 participants, ages 50 to 84, who went on to be randomized to either 200,000 international units of vitamin D followed by a 100,000 international units of vitamin D monthly. So they got a loading dose followed by a monthly dose or they receive placebo. The median followup time for the study was about 3.3 years and for the primary end point of interest, which was the incidence of cardiovascular disease, there was no statistically significant differences between vitamin D in the intervention group and the placebo arm.

Sarah Cruz: So in summary, these two recent randomized controlled trials with large samples of participants looking at vitamin D supplementation to prevent cardiovascular disease did not show that vitamin D was more effective than placebo. At this time there was no recommendation by any professional body or guideline that vitamin D supplementation should be routinely added for use in these patient populations.

Lindsey C.: Well, bummer. It sure would have been nice to be able to give our patients who are at risk for cardiovascular disease and complications of vitamin. So that's unfortunate that we don't have the evidence to back up vitamin D supplementation for that indication. One of the things I wanted to circle back to is, you mentioned that patients who are on antiepileptic drugs are at risk for vitamin D deficiency. So can you talk a little bit more about that and what the role of supplementing for those patients is?

Sarah Cruz: That's a great question, Lindsey. The enzyme inducing antiepileptic drugs have been of interest to researchers since the early 1970s, given that these drugs were implicated for conveying an osteoporosis risk. Specifically those antiepileptic drugs that are known to be cytochrome P450 enzyme inducers, such as carbamazepine, phenobarbital, cimetidine, and primidone among others.
Mechanistically speaking, it's thought that these medications can increase in certain liver enzymes that are responsible for converting vitamin D to an inactive metabolite, thus reducing the amount of the bioavailable form.

Sarah Cruz: Unfortunately, randomized controlled trials involving vitamin D supplementation in adult patients on AED therapy is lacking in the literature. There is support, however from observational studies that the prevalence of vitamin D deficiency in this population is a particular concern, which raises the question of whether or not to routinely test for vitamin D deficiency in this population. Also, consider a 2010 prospective longitudinal study by Menon et al. which examined the effect of AED therapy on approximately 31 participants, serum 25-hydroxy vitamin D level. To be included in this study, participants had to have a diagnosis of seizures, they could not currently be on antiepileptic drug therapy and they must have a baseline serum 25-hydroxy vitamin D level greater or equal to 20 nanogram per ML.

Sarah Cruz: So these participants were evaluated monthly for seizure control and at the end of the study, the serum levels of both the antiepileptic drug and the 25-hydroxy vitamin D were collected. At the end of the study period, there was a significant decrease in the serum 25-hydroxy vitamin D levels irrespective of the type of antiepileptic drug used. So in summary, I think it's worth noting that this patient population may be getting increased risk for the development of vitamin D deficiency. Furthermore, the current Endocrine Society practice guidelines support monitoring serum 25-hydroxy vitamin D levels in patients on antiepileptic drug therapy.

Sarah Cruz: In addition, the practice guideline offers the recommendation that patients on anticonvulsant medications will often require at least two to three times more vitamin D, which ranges anywhere from 6,000 to 10,000 international units per day to treat a vitamin D deficiency, followed by a maintenance therapy of 3000 to 6,000 international units per day in order to maintain a serum 25-hydroxy vitamin D of above 30 nanogram per ML.

Lindsey C.: Well, that's really interesting, Sarah. I don't think I have ever heard about the data regarding patients who are on antiepileptic drugs and the risk for being vitamin D deficient. So I've certainly learned something from that. So we talked about the use of vitamin D supplementation for a couple of different indications. Is the
evidence for these different indications different if the patients are vitamin D deficient versus patients with normal levels of vitamin D?

Sarah Cruz: So yeah. In general, I would say that the current body of literature regarding vitamin D testing and treatment is lacking a clear answer to this question. For example, just a few studies I briefly touched on in regard to depression and the prevention of cardiovascular disease and answer to your question earlier, each study was very different in their specific participant inclusion and exclusion criteria. Not all the participants in the aforementioned studies even had a serum 25-hydroxy vitamin D level tested at baseline. So it's really not known as the included participants were in fact vitamin D deficient to begin with prior to starting these supplementation with vitamin D in these studies.

Sarah Cruz: I also think to answer your question, it's made a little bit murkier so to speak because as I had discussed earlier, it's not been clearly defined as to what precise serum level of 25-hydroxy vitamin D a patient needs to have in order to be deficient. The Institute of Medicine, the Endocrine Society and the American Association of Clinical Endocrinologists all have different cutoff points for the serum 25-hydroxy vitamin D level, that would be considered for a patient to have a deficiency.

Lindsey C.: Okay, so I guess in theory, then patients who had normal levels might be getting too much vitamin D. So, is there really such a thing as too much vitamin D?

Sarah Cruz: Yes. Too much vitamin D in the body is called hypervitaminosis D or vitamin D toxicity. Vitamin D toxicity typically occurs as a result of large doses of vitamin D, and would not be caused by doses of vitamin D normally consumed in the diet or via a patient having sun exposure. The intake dose wise of how much vitamin D need to be ingested or in some cases given either parenterally or intramuscularly in order to become toxic is not clear. The Institute of Medicine has defined the tolerable upper intake level for vitamin D as 4,000 international units daily for children greater than nine years of age and healthy adults.

Sarah Cruz: According to the American Association of Clinical Endocrinologists, most patients with vitamin D toxicity will present with a serum 25-hydroxy vitamin D
level of greater than 150 nanogram per ML. The main consequence of vitamin D toxicity is the increase of serum calcium. Thus, the vitamin D toxicity will often manifests with clinical symptoms of hypercalcemia, which can include confusion, nausea and vomiting, dehydration, constipation, muscle weakness, polyuria and polydipsia. So chronic intoxication with vitamin D may contribute also to kidney stone formation, bone demineralization and pain. Keep in mind that not all patients with a vitamin D level greater than 150 nanogram per ML will manifest vitamin D toxicity or be symptomatic.

Sarah Cruz: Factors that may put a patient at increased risk for vitamin D toxicity include intake of higher doses of vitamin D, also the extremes of age, so the very young or very older patients, impaired renal function, concurrent use of thiazide diuretics and some coexisting disease states such as sarcoidosis or tuberculosis. Since vitamin D toxicity typically reveals itself through symptoms associated with hypercalcemia and it's sequelae, patients are treated according to the severity of the hypercalcemia. So hypercalcemia can range from being mild, which may be asymptomatic to moderate or severe in which symptoms may require aggressive treatment. For symptomatic hypercalcemia, usually the acute therapy is a three-pronged approach. First you do volume expansion with isotonic saline, typically at a rate that isn't adjusted to maintain urine output of a 100 to 150 ML per hour.

Sarah Cruz: Second would be the administration of calcitonin dosed at four international units per kg, with ongoing therapy with this agent being based on monitoring of serum calcium levels. Third would be the concurrent administration of either zoledronic acid or Pamidronate IV or if the administration of a bisphosphonate is contraindicated, treatment with the denosumab subcutaneously may be an option. Also, the addition of corticosteroids, for example, hydrocortisone IV or prednisone orally may be beneficial. Corticosteroids are thought to reduce vitamin D stimulated calcium absorption in the GI tract, also increase urinary excretion of calcium and also hepatic vitamin D metabolism to favor the production of inactive vitamin D metabolites. Also finally, in regards to non-pharmacological therapy, patients may want to limit the amount of both vitamin D and calcium in their diet to avoid any additional supplementation.
Lindsey C.: Okay, so certainly you can get too much of a good thing, it sounds like. So are there any patient populations for whom vitamin D supplementation might be harmful?

Sarah Cruz: Yeah, this a great question. So I think in patient as you just mentioned, patients tend to have this perception that taking vitamins and really that could be any vitamin and not just vitamin D, but that taking vitamins and an over-the-counter product or supplement, they perceive this as being harmless. I mean, the patients thinking to themselves, this is a vitamin, vitamins are good for me, so taking more of this vitamin will be a benefit to me, and the patient hears different things from media sources like, "Oh, this vitamin will give me more energy." Or "Hey, I heard on TV that taking vitamin D is going to prevent cardiovascular disease or that maybe I can stop taking my antidepressant because vitamin D is going to alleviate my depression symptoms." So patients may hear these claims and that think that taking supplemental vitamin D is considered both positive and innocuous.

Sarah Cruz: We know, however, that in reality too much of a number of vitamins or nutrients have the potential to be harmful. Especially I would say vitamin D, which is a fat soluble vitamin. Remember that vitamins are either considered water soluble or fat soluble. The water soluble vitamins and an example of this would be the B vitamins such as B12, B6 et cetera. When the water soluble vitamin is ingested and amounts over beyond what a patient may individually require, that excess amount is in fact simply eliminated from the body via normal elimination processes. Fat soluble vitamins, however, which vitamin D is one, any excess consumed beyond the body's requirements are not necessarily excreted but it can be stored in adipose tissue, liver, and skeletal muscle.

Sarah Cruz: When these tissues become saturated with vitamin D, vitamin D may remain in the serum and thus they exists a potential of a buildup of too much and subsequent toxicity, which can be harmful and certainly not benign. So to answer your question is yes. I mean, the patient population for whom additional vitamin D supplementation might be harmful are those patients who are not known to be at risk for vitamin D deficiency or who are not in fact vitamin D deficient. Earlier in our discussion I referenced the recommended daily allowance set forth by the Institute of Medicine for vitamin D daily intake, and above and beyond this daily intake without
regular serum monitoring of the 25-hydroxy vitamin D level, a patient might really be on the path to causing more potential harm than beneficial gains.

Lindsey C.: Okay. Thank you so much Sarah. So, just for my take home points, it sounds like we have some conflicting evidence for the use of vitamin D in for depressive symptoms. There's not a lot of evidence to support the use of vitamin D for cardiovascular purposes. We need to pay close attention to vitamin D levels in our patients taking antiepileptic drugs and then certainly or a refresher of the two different forms of vitamin D that we have and that you can have too much of a good thing, particularly with this being a fat soluble vitamin. Anything else that you wanted to leave our listeners with today?

Sarah Cruz: I think you've hovered on the main points. Lastly just remember that routine screening for vitamin D deficiency in all patients is not currently recommended. If you do come across patients in your practice who may have risk factors, especially multiple risk factors for vitamin D deficiency, it'd probably be prudent to have their 25-hydroxy vitamin D levels checked, and then supplement if needed.

Lindsey C.: Okay, great. Thank you so much, Sarah. That's all the time that we have today. I want to thank Sarah Cruz for joining us, discussing vitamin D supplementation for indications other than bone health. Join us here every Thursday on the Therapeutic Thursdays podcast, where we will talk with ASHP member content matter experts on a variety of clinical topics.

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