

# Dietary Supplements: Navigating the Pharmacologic Influences of Nature's Medicine

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Glucosamine/Chondroitin

The use of dietary supplements occurs in the majority of American adults >20 years old and has been reported to be on the rise by the National Health and Nutrition Examination Survey. People are not only taking more dietary supplements, but taking them without the advice of a health care provider. With the lack of education time and focus on this topic, physicians need to know some evidence regarding the most common supplements used, how to understand dietary supplement labels, and where to find reputable information about dietary supplements. Vitamin D, Omega-3, and Glucosamine/Chondroitin are reviewed here. Also, a description of the various components of a dietary supplement label is explained. Finally, a brief description of independent companies (Consumerlabs.com®, US Pharmacopiedial Convention, Natural Medicine Comprehensive Database, and Natural Standard) as well as the federally run Office of Dietary Supplements are presented.

## DIETARY SUPPLEMENTS

Dietary supplements (referred to as “supplements” throughout this article), as defined by the Dietary Supplement Health and Education Act (DSHEA) of 1994, are:

**“Products (other than tobacco) that are intended to supplement the diet; contain one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their constituents; are intended to be taken by mouth as a pill, capsule, tablet, or liquid; and are labeled on the front panel as being a dietary supplement.”<sup>1</sup>**

The United States Food and Drug Administration regulates supplements differently than food and drug products. Companies producing supplements must register their manufacturing plant, provide their own safety testing prior to bringing a product to market, and keep records of the adverse events of a supplement.<sup>1</sup> Because supplements are not strictly regulated, they can be marketed and purchased directly by consumers. This makes it imperative that family physicians have an understanding of supplements. The goal of this review is to provide information on who uses supplements,

what supplements are used, the evidence of some popular supplements, an explanation of supplement labels, and where to go to find reputable information regarding supplements and their ingredients.

## USE

The National Health and Nutrition Examination Surveys (NHANES) began gathering data on supplement use in the United States in the early 1970s when the prevalence of use was 28% among adult males and 38% among adult females.<sup>2</sup> With subsequent reports, there has been an increase in the percent of Americans who were taking at least one supplement.<sup>3</sup> Since 1999, data continues to be collected every two years and this trend of use does not appear to be slowing down. The last analyzed data from 2007-2010 showed almost half of the U.S. population used at least one supplement.<sup>4</sup> The reports indicate that more women use supplements than men (54% vs. 43%) and their use is highest among non-Hispanic whites (54%), adults >60 years old (67%), and those with more than a high school education (61%).<sup>4,5</sup> Children use supplements less, but there is a positive relationship with their parents' level of education and household income.<sup>6</sup> Another striking fact is that 77% of adults surveyed were taking supplements without a prescription from a health care provider.<sup>4</sup> Among the top reasons why adults older than 20 take supplements are to “improve” (45%) or “maintain” (32.8) overall health.<sup>4</sup>

Data from the 2007-2010 NHANES shows people choose to take multivitamin and mineral supplements more than any other supplement (31.9%), followed by calcium (11.6%),

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omega-3 (9.8%), botanicals (7.5%), vitamin C (7.1%), vitamin D (4.9%), vitamin E (3.7%), and joint supplements (4%), along with other supplements without as much prevalence of use<sup>4</sup>. Other data from a survey of adults who used natural products in the last 30 days showed omega-3 to be the most used at 37.4%, next glucosamine (19.9%), then echinacea (19.8%), along with others including chondroitin (11.2%).<sup>7</sup>

## EVIDENCE

**Figure 1: Summary of the evidence for commonly used supplements.**

<p><b>Vitamin D</b></p> <ul style="list-style-type: none"> <li>• Doses of Vitamin D3 1000-2000IU PO daily up to 10,000IU have been shown to be safe and effective</li> <li>• Keep levels between 40-60nmol/L</li> <li>• No consensus on routine screening for Vitamin D deficiency in asymptomatic, healthy adults</li> <li>• Vitamin D receptor on a majority of cells in the body, checking vitamin D levels can be considered helpful especially in an area where the population does not receive adequate sunlight.</li> </ul>
<p><b>Omega-3 (DHA/EPA)</b></p> <ul style="list-style-type: none"> <li>• SMASH (Salmon [wild pacific], Mackrel [spanish], Anchovies, Sardines, and Herring)</li> <li>• 1-2g PO daily for cardiovascular benefits</li> <li>• 2-4g PO daily anti-inflammatory benefits</li> <li>• 4g PO daily for elevated triglycerides</li> </ul>
<p><b>Glucosamine/Chondroitin</b></p> <ul style="list-style-type: none"> <li>• 1500mg Glucosamine Hydrochloride (500mg PO TID) combined with 1200mg Chondroitin Sulfate (400mg PO TID) can help with moderate-severe knee arthritis pain (GAIT)</li> <li>• 1500mg Glucosamine sulfate (1500mg PO daily) can help with knee arthritis pain (GUIDE)</li> </ul>
<p><b>Multivitamin/mineral</b></p> <ul style="list-style-type: none"> <li>• Do not use unless known deficiency</li> <li>• Correct specific deficiency</li> <li>• Do not have health benefit</li> </ul>

The evidence of some of these supplements has been reviewed, while consensus about others still needs to be hashed out. For example, 400-800 micrograms of folic acid daily for women of childbearing age have been shown to decrease neural tube defects by 50-70%<sup>8</sup>. With data like that, you would expect more than 1.5% of American's to be using it.<sup>5</sup> On the other end of the spectrum are multivitamins. They are the most commonly used supplement, but recently a consensus statement by the United States Preventive Services Task Force (USPSTF) recommended against their daily use unless a patient has a known vitamin or mineral deficiency.<sup>9</sup> Currently, some of the most commonly studied dietary supplements in the literature are: vitamin D, omega-3, and glucosamine/chondroitin.

### Vitamin D

Vitamin D is a fat-soluble vitamin that is thought to be a hormone since a vitamin D receptor was discovered to be

universally expressed in nucleated cells.<sup>10</sup> Vitamin D is rarely found in unfortified foods, so the major source is synthesis from sunlight exposure. Whether ingested or dermally synthesized, vitamin D requires enzymatic conversion in the liver to 25-hydroxyvitamin D (25[OH]D; the major circulating form) and further conversion in the kidney into 1,25-dihydroxyvitamin D (active form). The form that is usually evaluated by venous blood testing is 25[OH]D. There is a major initiative through the Office of Dietary Supplements, as well as other researchers, to get a better understanding of vitamin D. In the NHANES 2005-2006, 42% of adults greater than 20 years old had 25[OH]D levels that were considered vitamin D deficient.<sup>11</sup> A committee from the Institute of Medicine (IOM) reviewed the data and concluded that serum levels of 25[OH]D > 50nmol/L would cover the vitamin D requirements for 97.5% of the population and serum concentrations > 125nmol/L are associated with potential adverse effects.<sup>12</sup> Therapeutic levels of 25[OH]D are targeted between 40-60 nmol/L. This can be achieved through daily dosing with a supplement containing 1000-2000 IUs of vitamin D3 with dosing dependent on the adiposity of the patient, sequestered more with increased adiposity.<sup>13</sup> Doses as high as 10,000 IUs per day have not been shown to cause hypercalcemia or acute intoxication<sup>12</sup> and can be indicated in adults who are vitamin D deficient.<sup>14</sup>

The USPSTF had released a draft document regarding its recommendation for the screening for vitamin D deficiency in asymptomatic individuals at the time of this manuscript preparation. Its conclusion was that screening for vitamin D deficiency is not necessary for healthy, asymptomatic adults.<sup>15</sup> It is difficult to say who is "asymptomatic" since vitamin D deficiency has been associated with a variety of pathologic conditions. Vitamin D deficiency has been shown to have an influence on cardiovascular disease, cognition, bone mineral density, falls, development of diabetes, cancer, the immune system and chronic pain.<sup>16</sup>

### Omega-3

Omega-3 is a type of fatty acid that exists in the phospholipid membrane of every cell in our body. It is the counterpart to omega-6, which is also present in our cells. The biggest difference between these two fatty acids is that omega-6 is pro-inflammatory and omega-3 are anti-inflammatory. The omega-3s are found in the diet as alpha-linolenic acid (ALA; 18:3 omega-3) and eicosapentaenoic acid (EPA; 20:5 omega-3) as well as docosahexaenoic acid (DHA; 22:6 omega-3) with different functions of each of the omega-3s in different cells. ALA is considered an essential fatty acid (EFA) because humans cannot produce it in vivo; both EPA and DHA may be obtained either directly through foods, supplements, or by the enzymatic conversion of ALA.

These fatty acids are known to have pleiotropic effects, including effects against inflammation, platelet aggregation, hypertension, and hyperlipidemia.<sup>17</sup> These effects may be mediated through several distinct mechanisms, including alterations in cell membrane composition and function, gene expression, and eicosanoid production.<sup>17</sup> The standard American diet has a ratio of 10:1 to 25:1 omega-6 to omega-3. The optimal ratio is considered to be 2:118. The IOM has set a recommended macronutrient dose of 0.6 - 1.2 g/day for people > 1 year of age. The best way to get omega-3s is through your diet. You can achieve the minimal needs with two servings of fatty, cold-water fish per week. For the best sources of omega-3 - EPA and DHA, remember the acronym SMASH: Salmon (wild Pacific), mackerel (Spanish), anchovies, sardines, and herring. If you do not reach the recommended dose with your diet, you can take a supplement. Most 1g supplements contain 30% of the active ingredients EPA and DHA, so you must choose wisely. Most experts recommend 1-2 g/day for cardiovascular benefits, 2-4 g/day for anti-inflammatory benefits, and 4 g/day for elevated triglycerides.

### Glucosamine/Chondroitin

Glucosamine and chondroitin are in the body and are used to make cartilage that protects intra-articular bones from compressive forces. One cannot obtain glucosamine or chondroitin from a dietary source. Most glucosamine supplements are made from chitin, which is found in the hard shells of shellfish, while chondroitin is made from shark cartilage, bovine cartilage, or synthetically.

There have been two major studies of glucosamine and chondroitin for treatment of pain from knee osteoarthritis: the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) and the Glucosamine Unum In Die [Once a day] Efficacy (GUIDE) trials. In the GAIT trial, a large, randomized controlled, multi-center population in America was given either 500 mg of glucosamine hydrochloride three times per day, 400 mg of chondroitin sulfate three times per day, both glucosamine and chondroitin, celecoxib 200 mg daily, or placebo for 24 months. There were no significant differences among the groups overall, but a sub-group analysis showed that the combination of glucosamine hydrochloride and chondroitin sulfate helped relieve moderate to severe pain.<sup>19</sup> In the GUIDE trial, a group of patients in Europe was randomized to receive 1500 mg of glucosamine sulfate once daily, acetaminophen 3 g daily, or placebo for six months. The results showed that once daily dosing of glucosamine sulfate was safe and effective for the relief of pain associated with knee osteoarthritis.<sup>20</sup>

## LABELS

Besides knowing the evidence backing the use of a specific supplement, it is just as important, if not more important, to know the contents of that supplement. If patients bring in their supplement bottles for you to read, then you will be able to start deciphering their choices. Understanding the different parts of a supplement label will be the first step in this analysis.

## HOW TO READ A VITAMIN LABEL

Content for this label provided through a grant from Nature Made®

**1 SUGGESTED USE:** For best results, take one tablet daily with a meal. Keep bottle tightly closed. Store in a cool, dry place.

<b>Supplement Facts</b>		
Serving Size 1 Tablet		
Servings Per Container 45		
Amount Per Serving	%	Daily Value
Vitamin D <sub>3</sub> (as Cholecalciferol)	800 IU	200%
Vitamin B <sub>6</sub> (as Pyridoxine Hydrochloride)	10 mg	500%
Calcium (as Calcium Citrate)	500 mg	50%
Magnesium (as Magnesium Oxide)	80 mg	20%
Zinc (as Zinc Oxide)	10 mg	67%
Copper (as Copper Gluconate)	1 mg	50%
Manganese (as Manganese Gluconate)	1 mg	50%
Sodium	5 mg	Less than 1%
Green Tea Leaf Extract	1 mg	4%

\* Daily Value not established.

**7 OTHER INGREDIENTS:** Cellulose gel, Croscarmellose Sodium, Magnesium Stearate

**8 Manufacturer's Contact Information:**  
Distributed by: Company name  
Company Address,  
Phone Number and Website



**10 Caution:** Consult with your physician before taking this product if you are pregnant or nursing.

5 Lot: M123456789

6 Exp.: 12/2024

Image 1: How to Read a Vitamin Label<sup>21</sup>  
(Printed with permission from the AAFP)

There are key aspects to the label that can help the provider understand the supplement:

### 1. Suggested Use

A supplement will contain this group of statements to inform the user of what the company considers the appropriate amount to take and any special instructions on how it should be taken.

### 2. Serving Size

This unit will be the basis of how one can determine the dosage of the ingredients within the supplement. The serving size will tell the user how much they need to take to reach the amounts listed per serving. An example from this label would be if you wanted someone to take 1000 mg of calcium, they would have to take two tablets because each tablet will have 500 mg.

### 3. Percent Daily Value

The percent daily value indicates how the dose of an ingredient in the dietary supplement covers the Daily Recommended Intake (DRI) established by the IOM. These differ among ages and genders. An example from this label would be that the DRI of calcium is 1000 mg per day. Because this dietary supplement only contains 500 mg of calcium per serving, it

has a percent daily value of 50%. The DRI of an ingredient is constant, but the amount per serving of an ingredient can vary.

#### 4. No Percent Daily Value

There are still some ingredients that may offer health benefits and are put into supplements without a DRI having been established by the IOM.

#### 5. Lot Number

A lot number is used with any manufactured product in order to track when and how it was produced as well as what ingredients and equipment may have been used to produce that specific product.

#### 6. Expiration Date

The expiration date is put on the supplement to let the user know how long until the product will not be as potent. Supplements, like most products made of nondurable goods, may not be as effective after they have passed their expiration dates.

#### 7. Ingredients

The ingredients are listed in descending order by weight. Something to watch out for with ingredients is what type of a specific ingredient manufacturers are using to produce the supplement. For example, with the label, the calcium is being provided by calcium citrate. This type of calcium ingredient has different absorption and percent of elemental calcium than the more common form of calcium carbonate. Calcium can also be supplemented with calcium phosphate and calcium lactate, but these are less common due to cost and lower concentration of calcium.<sup>22</sup>

#### 8. Manufacturer's Facility and Contact Information

These pieces of information should be included on all supplements to be used to report adverse events.

#### 9. Quality Marks and Statements

Not all supplements will bear this specific USP seal displayed here, but if it does, then you know it has passed rigorous standards.

#### 10. Cautions and Warnings Statement:

Statements may be included on a supplement that warn specific groups of people with certain medical conditions, allergies, pregnant or lactating, or taking other prescription drugs who should avoid using this supplement. It could also include precautions before taking the supplement or potential side effects of its use.

There are also other important details that can be seen on a supplement label that should not be overlooked.

#### Health Claims

A product can place a health claim on its label but it must be reported to the FDA within 30 days. Most supplements will have a blanket statement to cover liability such as:

*"These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease."*

#### Amount Per Serving

The amount per serving is closely tied to the serving size and percent daily value listed above. This value will tell you how much of a specific ingredient is in one serving of the dietary supplement. Depending on the dose one wishes to take, the serving size can be adjusted based on the amount per serving. You can help patients see if their supplement choice will be cost effective based on the dose they may need.

#### Allergens

As with any product that is ingested, there needs to be disclosures about allergens.

### INGREDIENTS

Figure 3: Resources for verifying ingredients

<p><b>NIH Office of Dietary Supplements (<a href="https://myds.nih.gov/">https://myds.nih.gov/</a>)</b>  <i>Director: Paul M. Coates, Ph.D.</i></p> <ul style="list-style-type: none"> <li>• Searchable databases of federally funded projects, fact sheets, supplement ingredients, supplement labels</li> <li>• Vitamin D Initiative</li> <li>• Evidence-based reviews</li> <li>• Research support</li> <li>• Training and career development</li> </ul>
<p><b>Natural Standard (<a href="https://naturalmedicines.therapeuticresearch.com/">https://naturalmedicines.therapeuticresearch.com/</a>)</b>  <i>Co-Founders: Catherine Ulbricht, PharmD, MBA[c] and Ethan Basch, MD, MSc, MPhil</i></p> <ul style="list-style-type: none"> <li>• Indexed databases on a variety of topics including Food, Herbs, and Supplements; Health and Wellness; Medical Conditions; Commercial Products; and Manufacturers</li> <li>• Advanced and Basic Interactions Checker</li> <li>• Continuing Education</li> </ul>
<p><b>Consumer Lab (<a href="http://consumerlabs.com/">http://consumerlabs.com/</a>)</b>  <i>President: Tod Cooperman, MD</i></p> <ul style="list-style-type: none"> <li>• Membership = \$36 for 12 months or \$59 for 24 months</li> <li>• Independent reviews of products (membership required)</li> <li>• Recalls and Warnings (membership required)</li> </ul>
<p><b>Natural Medicine Comprehensive Database (<a href="http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&amp;s=ND">http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&amp;s=ND</a>)</b>  <i>Editor-in-Chief: Jeff M. Jellin, Pharm.D</i></p> <ul style="list-style-type: none"> <li>• Membership = single user subscription 1 year: \$299, 2 year: \$525, and 3 year: \$725</li> <li>• Daily website updates with evidence-based monographs, interactions, brand product reports, and special reports</li> </ul>
<p><b>United State Pharmacopeial Convention (<a href="http://www.usp.org/">http://www.usp.org/</a>)</b></p> <ul style="list-style-type: none"> <li>• Sets worldwide standards for medicines, food, and supplements</li> <li>• Scientifically tests: 1) consistent quality between batches, 2) consistent quality of ingredients, 3) proper manufacturing practices, and 4) tolerable levels of contamination</li> <li>• Teamed with the Natural Medicines Comprehensive Database</li> </ul>

Once you have read the label, you can then begin to critically analyze the ingredients used. All supplement ingredients are not created equal. The different types of glucosamine and chondroitin used during the GAIT and GUIDE trials highlights the importance of understanding which ingredients are used to make a supplement and how they actually work within the body. In this regard, active ingredients of supplements should be thought about as if they were prescription drugs. Pharmacokinetics, pharmacodynamics, safety, efficacy, potency, bioavailability of an ingredient are important and should be understood in order to direct your patients toward appropriate and intelligent use of supplements.

The underlying pharmacology, physiology, chemistry, and biochemistry of some ingredients are well known while others are less studied. This can be a challenging point in understanding the benefit of different supplements. Family physicians need to know where to go to get the most up-to-date information regarding supplement ingredients. There are a few websites we recommend using as references.

### **The Office of Dietary Supplements**

The Office of Dietary Supplements was established in 1995 within the Office of Disease Prevention at the National Institutes of Health after the passing of the Dietary Supplement Health and Education Act of 1994. Its purpose is to lead the national understanding of supplements by promoting scientific investigation, reviewing the available literature worldwide, compiling databases, and coordinating funding for the NIH.<sup>23</sup> It principally acts as a funding source, with 69% of its 2008 budget going toward grants, but also operates a large database of information for consumers and professionals on common supplements, including a searchable database of federally funded supplement research projects, fact sheets, ingredients, and labels.<sup>23</sup>

### **Natural Standard**

Natural Standard was founded by healthcare providers and researchers in order to analyze scientific data on complementary and alternative medicine. It has numerous senior editors, authors, peer reviewers, and contributors with a wide range of clinical and research expertise. They take a systematic approach to reviewing the literature to provide their databases and interaction checkers. Within the databases, you can find general information about a complementary and alternative medicine modality as well as an in-depth review of articles about it. The interaction checker includes complementary and alternative medicines as well as some common generics used by many patients (eg: Lisinopril).<sup>24</sup>

### **ConsumerLab.com**

ConsumerLab.com® was started in 1999 as an independent tester of health and nutritional products. The results are published on its website and available to members. It also conducts an annual Survey of Vitamin and Supplement Users. Its product testing procedure is detailed on the webpage and includes a random sample purchased in the open market; tests for identity, strength, purity, and disintegration; and retests the product every 12 months to keep the “CL Seal of Approval on the product.”<sup>25</sup>

### **Natural Medicines Comprehensive Database**

The Natural Medicines Comprehensive Database is an independent organization that was established in the fall of 1999 by a group of researchers from the Therapeutic Research Center. This group originally began to write evidence-based, unbiased recommendations in 1985 for pharmacy and prescribing health professionals when it began to receive a large volume of questions regarding natural medicines. It researched the evidence and found that there were no solid studies. The goal was to produce highly objective, evidence-based resources for health professionals. The researchers for this database update their website daily with evidence-based monographs, interactions, brand product reports, and special reports. This information is available with a subscription.<sup>26</sup>

### **United States Pharmacopeial Convention**

The U.S. Pharmacopeial Convention (USP) is a nonprofit organization that has been around since 1820. Since then, the USP has set the standards for the identity, strength, quality, and purity of medicines, food ingredients, and supplements manufactured, distributed, and consumed worldwide. Specific to supplements, the USP has been putting their mark on the labels of companies that have volunteered their products to be evaluated based on the USP's rigorous scientific standards. If a supplement bears this mark then it has passed testing for consistent quality between batches, consistent quality of ingredients, proper manufacturing practices, and tolerable levels of contamination.<sup>27</sup> The USP has even teamed with the Natural Medicines Comprehensive Database to have its mark appear next to supplements that have passed the USP standards and have been reviewed by its team.

## **CONCLUSION**

Over 100,000 patients die each year from pharmacologic treatments, which is leading to disenchantment with the medical profession and its traditional treatment modalities.<sup>28</sup> This article was prepared to give family physicians a resource from which to propel their understanding of supplements. First and foremost, we should take note that a majority of patients are taking supplements<sup>5</sup> and most patients are taking

them without consulting a healthcare provider.<sup>4</sup> We need to be sure to ask patients what supplements they are taking, how much, how often, what brand, and why?

It is commonly stated:

**“Let your health care providers (including doctors, pharmacists, and dietitians) know which dietary supplements you’re taking so that you can discuss what’s best for your overall health. Your health care provider can help you determine which supplements, if any, might be valuable for you.”<sup>29</sup>**

We need to be armed with knowledge of supplements so we can be an active participant in this discussion with them.

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