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DIETARY SUPPLEMENTS

ABSTRACT & COMMENTARY

Buyer Beware: Unapproved Pharmaceutical Ingredients Found in Dietary Supplements

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: Investigators analyzed data collected from 2007 to 2016 regarding FDA warnings. Unapproved ingredients in dietary supplements continue to be found.

SOURCE: Tucker J, Fischer T, Upjohn L, et al. Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Administration warnings. *JAMA Netw Open* 2018;1:e183337.

Adulterate: to corrupt, debase, or make impure by the addition of a foreign or inferior substance or element.[1]

The name Clark Stanley (a.k.a., the rattlesnake king) may not ring bells immediately, but his notoriety as the original snake-oil salesman has survived the test of time. Today, the snake-oil salesman label implies fakery or fraud. This term arose in the early 1900s, after investigators working under the Pure Food and Drug Act of 1905 inspected a shipment of Stanley's anti-inflammatory "snake oil" and found mineral oil to be the main ingredient.[2]

The medical world has moved forward since the early 1900s, but concern about mislabeled and/or adulterated products remains. The Pure Food and Drug Act gave birth to the U.S. Food and Drug Administration (FDA) in 1906. In 1994, the Dietary Supplement Health and Education Act (DSHEA) defined the FDA's role in regulation of dietary supplements, including vitamins, minerals, herbs, amino acids, and enzymes.[3]

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Summary Points

- The FDA tainted products website (Tainted Products Marketed as Dietary Supplements) lists supplements with unapproved ingredients. From 2007 to 2016, 776 products from 146 dietary supplement companies were listed on the site for containing active, unapproved pharmaceutical ingredients.
- Multiple warnings more than six months apart were found for 28 products. Of these products, 67.9% contained new, unapproved ingredients in subsequent warnings.
- The most common adulterants were sildenafil in sexual enhancement products, sibutramine in weight loss supplements, and synthetic steroids in muscle-building supplements.

DSHEA classifies supplements as a distinct category of "food." Because of this classification, the FDA regulates supplements in a separate category than pharmaceuticals, which by definition are meant to treat or control a disease state. Thus, the FDA monitors supplements only after distribution; the FDA plays no role in inspecting or approving supplements before distribution as is required for conventional pharmaceuticals. Products come to the attention of the FDA in several ways, but usually a consumer complaint or FDA screening triggers the process. Evidence of mislabeling or adulteration can lead to a warning to the public and/or the company. If there are dangerous potential health implications, the FDA may issue a recall.[3,4]

FDA screening currently appears to be concentrated at international mail facilities. In March 2018, the FDA announced updated mobile screening technology at these points of entry into the U.S. market.[5] Concerns about this oversight role are numerous. Proponents of the supplement industry mostly believe DSHEA serves the industry well,[6] but others advocate for a more stringent process in the name of consumer safety.[7] Tucker et al approached this study in a neutral fashion to look at the outcomes or trends after a product or company receives an FDA warning. Notably, if a supplement contains active pharmaceuticals approved by the FDA for specific purposes, but at unknown concentrations and/or without a label or identification, the pharmaceutical is characterized as unapproved.

The FDA often works in conjunction with the Federal Trade Commission to issue such warnings, as the two agencies have overlapping but separate mandates.[8] Tucker et al focused only on products with FDA warnings.

The FDA maintains a public website: Tainted Products Marketed as Dietary Supplements.[9] Tucker et al reviewed each entry on this website. To avoid double-counting, multiple warnings for the same product were counted if they were issued more than six months apart.

TYPES OF WARNINGS

The FDA received reports on 776 dietary supplements involving more than 140 companies between 2007 and 2016. The most serious warnings for each product were: voluntary recall (46.4%; 360), public notification (44.1%; 342), news release (7.5%; 58), consumer update (1%; 8), warning letter to company (0.9%; 7), and U.S. Department of Justice press release (0.1%; 1).

TRENDS IN TYPES OF WARNINGS

Increase in public notification and decrease in recall over the study period: Tucker et al noted public notification was used more frequently than voluntary recall in the later years of the study period. Between 2007 and 2012, the number of products undergoing voluntary recall exceeded or was close to the number of public warnings issued. However, from 2012 to 2016, 72.5% of adulterated products were issued a public warning only (no recall). In 2015 and 2016, this trend appeared stronger, with more than 80% of adulterated products receiving public warnings. In all, a voluntary recall was issued for slightly less than half of the identified products. No mandatory recall was instituted.

Single products with multiple warnings: Of the 776 products, 96.2% tested positive only once for adulteration while 3.8% tested positive for unapproved ingredients two or three times. Of these products, 67.9% contained new unapproved ingredients after the first warning.

Multiple pharmaceuticals per product: Although the majority of identified products contained only one active, unapproved pharmaceutical, 20% contained more than one such ingredient. Thirty-three products contained three of more adulterants. Of these 33 products, the majority were marketed for either weight loss or improved sexual function.

Specifics of active, unapproved pharmaceuticals: Most of the identified adulterated products were marketed for either sexual enhancement, weight loss, or muscle building. Table 1 provides a breakdown of the number of products involved and adulterated ingredient(s) found.

ADDITIONAL FINDINGS

In 2009, the FDA initiated a recall of 66 muscle enhancement products. Of the 92 adulterated products identified for muscle-building in this study, the majority (96.7%) were found in the year of the recall (2009; 80.4%) and the following year (2010; 16.3%.)

Table 1: Breakdown of Adulterated Dietary Supplements

Marketed Purpose of Supplement	Number of Adulterated Products Found	Percentage (776 adulterated products identified from 2007 to 2016)	Major Active, Unapproved Pharmaceuticals	Percentage With More Than One Active, Unapproved Pharmaceutical
Sexual enhancement	353	45.5%	1. Sildenafil (47%) — active ingredient in Viagra 2. Structural analog of sildenafil (38%) 3. Tadalafil (20.4%) — active ingredient in Cialis 4. Other phosphodiesterase type 5 inhibitor (7.6 %) 5. Dapoxetine (4%) antidepressant not approved by FDA	18.4% (65 products)
Weight loss	317	40.9%	1. Sibutramine (84.9%) removed from the U.S. market in 2010 2. Sibutramine analogues (6.3%) 3. Phenolphthalein (23.7%) laxative removed from the U.S. market in 1999 4. Fluoxetine (5.4%) anti-depressant 5. Sildenafil or analogue (3.8 %) active ingredient in Viagra 6. Ephedrine (0.6%) stimulant — banned from use in supplements in 2004	25.2% (80 products)
Muscle building	92	11.9%	1. Undeclared anabolic steroids (79%) 2. Declared (labeled) anabolic steroid (0.97%) 3. Aromatase inhibitors (1%) — estrogen receptor blocker used in breast cancer treatment	0.01% (1 product)
Other (pain, gout, bone cancer, sleep, prostate health)	14	1.8%	1. Diclofenac (50%) — prescription nonsteroidal anti-inflammatory drug 2. Dexamethasone (35.7%) corticosteroid 3. Chlorpheniramine antihistamine (21.4%) 4. Indomethacin (21.4%)	78% (11 products)

■ COMMENTARY

Disclaimer from the FDA Tainted Products website:[7] *This list only includes a small fraction of the potentially hazardous products with hidden ingredients marketed to consumers on the internet and in retail establishments. FDA is unable to test and identify all products marketed as dietary supplements on the market that have potentially harmful hidden ingredients. Even if a product is not included in this list, consumers should exercise caution before using certain products. To learn more about how to reduce your risk of encountering a product marketed as a dietary supplement with a hidden ingredient, please visit FDA's Medication Health Fraud webpage.*

In medicine, it is usually wise to tread cautiously and perform confirmatory investigations and studies before adopting new methods, procedures, or interventions.

[… an essential role of the provider is communicating the information about these supplements to our patients, asking patients about use, advising caution, and investigating medical complaints with an awareness of these products and the potential health effect of inadvertent ingestion of the hidden, active pharmaceuticals.]

This study by Tucker et al looking at supplements with adulterated substances identified by the FDA is consistent with other similar investigations. Although it is true that longer periods of study or a more in-depth look at aspects of supplement adulteration and usage could clarify and pinpoint patterns, there seems to be little to gain and true potential harm by waiting for further confirmatory studies.

In 2013, Harel et al published research describing an investigation into class 1 recalls. They noted that of the 332 adulterated products listed on the FDA tainted supplement website between 2007 and 2012, only 222 were subject to a recall. The characteristics of the adulterated products mirrored those described by Tucker et al, with marketing of the most common adulterated products pointed toward sexual enhancement, weight loss, and bodybuilding.

In a 2015 study, Geller et al found that 23,000 emergency department visits and 2,000 hospitalizations each year can be attributed to the use of dietary supplements.[11] Once again, the main culprits were products marketed for sexual enhancement, weight loss, or bodybuilding.

It is no wonder that in a related opinion piece, Dr. Pieter Cohen pointed to "a dereliction of duty" by the FDA. He noted that Congress could reform DSHEA and mandate that supplement manufacturers register with the FDA prior to any distribution or marketing. In keeping with the theme of his editorial, he concluded by assigning blame to the FDA, noting "the agency's failure to aggressively use all available tools to remove pharmaceutically adulterated supplements … leaves consumers' health at risk."[12]

Although not mentioned in these studies, the rapidly growing popularity and widespread availability of hemp products and cannabidiol (CBD) lends urgency to strengthening the ability of the FDA to enforce regulations for unconventional products. As of this writing, the FDA does not consider CBD a supplement, but the status of this product remains murky and subject to question. For the most part, it appears that the FDA is leaning toward the classification of CBD as a drug, which would make CBD-containing products subject to premarketing approval. Despite the FDA position, CBD products can be purchased online and are found in many retail stores as a dietary supplement.[13,14]

In February 2019 (prior to his March 2019 resignation announcement), FDA Commissioner Scott Gottlieb, MD, announced new steps the FDA intends to take to strengthen the regulatory arm of the agency as it pertains to dietary supplements. His announcement included the intention to develop new enforcement policies and to modernize DSHEA.[15] It certainly appears that action on multiple levels is warranted to address a clear problem of active pharmaceuticals in dietary supplements.

Given a position on the "front lines" of medicine, primary care and integrative providers are a natural fit for educating Congress and other lawmakers regarding the implications of lax regulation of widely distributed products such as supplements. Aside from governmental work, an essential role of the provider is communicating the information about these supplements to our patients, asking patients about use, advising caution, and investigating medical complaints with an awareness of these products and the potential health effect of inadvertent ingestion of the hidden, active pharmaceuticals. Two resources, in particular, may be useful to patients and providers interested in verifying safety of supplements. Consumer Lab conducts and

publishes results of independent testing of products.[16] The Botanical Adulterants Prevention Program, backed by three nonprofit groups, publishes a free, up-to-date newsletter and website with information pertaining to adulterated products.[17] Using these and other resources, patients and providers can design an individualized treatment plan with a goal of minimizing risk and maximizing health benefits of supplements and related products. ■

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PAIN

ABSTRACT & COMMENTARY

Group Medical Visits to Treat Pain

By David Kiefer, MD, Editor

Clinical Assistant Professor, Department of Family Medicine, University of Wisconsin; Clinical Assistant Professor of Medicine, Arizona Center for Integrative Medicine, University of Arizona, Tucson

Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: A nine-session group medical visit for Spanish speakers with chronic pain led to statistically significant improvements in pain, fatigue, and depression.

SOURCE: Cornelio-Flores O, Lestoguoy AS, Abdallah S, et al. The Latino Integrative Medical Group Visit as a model for pain reduction in underserved Spanish speakers. *J Alt Comp Med* 2018;24:125-131.

Originally a spinoff from well-child checks, group medical visits (GMVs) have been used for a variety of medical conditions, and are particularly well-suited for chronic illnesses.[1] GMVs usually include both a private component with the healthcare provider (which differentiates this from a support group or class) and a group aspect during which patients participate in a didactic and/or interactive activity with other patients who have received the same diagnosis or are interested in the topic. GMVs may involve just one "class" or a series of meetings over time to address the relevant content. Seen as a way to increase time with patients, encourage social support, promote clinic profitability, improve many outcome measures, and also reduce the tedium that some providers feel by discussing the same information repeatedly,[1-3] GMVs are becoming a popular model with widespread applicability.[3,4]

Along the lines of increasing the use of GMVs, Cornelio-Flores et al examined the efficacy in chronic

Summary Points

- In Boston, 19 people with chronic pain and whose first language was Spanish were enrolled in a nine-week, once weekly, group medical visit.
- A variety of topics were covered during the nine weeks, including meditation, nutrition, and depression.
- Eleven people finished the entire series; benefits were seen in pain, fatigue, and depression, but not in anxiety, perceived stress, or physical functioning.

pain and in Spanish-speaking Latinos, a demographic group that experiences disparity in the treatment of chronic pain. The research group adapted the GMV model to be more "integrative" by using elements of mindfulness-based stress reduction (MBSR) and integrative medicine. There were nine classes (one per week for nine weeks) in this GMV curriculum. They covered such topics as stress, sleep, nutrition, activity, breathing techniques, approaches to lessen inflammation, meditation, acupressure, and integrative approaches to depression.

The researchers enrolled patients who spoke Spanish as their first language and who had musculoskeletal pain for at least 12 weeks and rated their pain at least a four out of 10 (on a 0-10 scale). Patients were excluded if they were pregnant or planning pregnancy soon or had severe mental illness, current substance use, severe medical conditions that would affect their GMV participation, or prior GMV participation. Nineteen patients were enrolled in the study, all of whom attended the first GMV. Only 11 patients completed the nine-session GMV curriculum.

The researchers collected both quantitative and qualitative information. For quantitative data, various scales were used to analyze pain, stress, depression, and sleep; these all had been validated in Spanish. (*See Table 1.*) Comparisons were made between the values in these scales before and after the GMV. Qualitative data were gleaned from focus groups during the last week, when patients were asked about what they learned, their overall experience, and challenges in participating in the groups.

Almost 90% of patients were female, with a mean age of 51.6 years. The mean pain score at baseline was 6.9 (out of 10), which dropped 1.7 points by the end of the GMV series ($P = 0.03$). Comparing the beginning to the end of the GMV, the PROMIS-29 showed improvements in fatigue ($P = 0.01$) and depression ($P = 0.01$), but not physical function ($P = 0.36$) nor anxiety ($P = 0.10$). In addition, the PHQ-8 score dropped a borderline statistically significant 2.89 points ($P = 0.05$), whereas perceived stress dropped insignificantly by 0.56 points ($P = 0.83$).

Table 1: Quantitative Measures and Relevant Scales

Scale	Parameters Measured	Notes
Brief Pain Inventory	Pain (0-10)	"during the last week"
PROMIS-29	Pain interference, sleep, anxiety, depression	
PHQ-8	Depression	
PSS-10	Perceived stress scale	

In the focus groups, patients were satisfied with the GMVs, and noted that they learned from the other patients, that the interactions felt "collaborative," and that there was more perceived time with the healthcare provider. Other comments mentioned improved pain control, better nutrition, and contentment over the fact that the GMVs were in Spanish.

■ COMMENTARY

For the 11 people who completed this GMV series, obvious benefits surfaced, including reduction of pain, fatigue, and depression. It was clearly "feasible," as the authors stated, to use GMVs to reach this demographic and address the difficult-to-treat condition of chronic pain. Obviously, this is a small study (even the authors refer to it as a pilot study), and it needs to be repeated with a control group to be able to say that the results seen were because of the intervention and not some other factor(s). That said, the results corroborate interesting benefits from GMVs for many chronic conditions,[1-4] and these benefits cross the boundaries between mind, body, emotions, and spirit. The researchers' use of a variety of quantitative scales shows this variety of outcome, which, it could be argued (and is supported by the literature), is partly the result of the social support and interaction that comes from patients learning from each other about their common condition.

There is little reason not to consider GMVs for addressing chronic medical conditions in both primary care and medical specialties. However, those planning GMVs have found patient recruitment to be a challenge.[2] There certainly is the need to invest time in creating the curriculum and arranging for visit logistics, charting, and billing. Also, as the researchers did here, it seems like a good idea to be mindful of

which patients might not be appropriate for a GMV. The exclusions of serious mental health diagnoses or medical conditions that would preclude group participation and continuity make sense as clinicians seek to optimize the patient experience in this format.

On the positive side, it is exciting to see an intervention geared toward a demographic that may fall short of receiving quality care for chronic pain. As our society increasingly diversifies, looking for creative ways to meet the needs of patients from a variety of backgrounds will be even more important. Perhaps GMVs are just the approach necessary to increase time with patients in a fiscally sustainable, provider- and patient-friendly way. ■

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BONE HEALTH

ABSTRACT & COMMENTARY

Vitamin D During Pregnancy and for Infant Growth

By Traci Pantuso, ND, MS

Adjunct Faculty, Research Investigator, Bastyr University, Seattle

Dr. Pantuso reports no financial relationships relevant to this field of study.

SYNOPSIS: The Maternal Vitamin D for Infant Growth (MDIG) trial was conducted in Bangladesh to further understand whether prenatal vitamin D with or without postpartum supplementation affects infant growth or other maternal, newborn, and infant outcomes.

SOURCE: Roth DE, Morris SK, Zlotkin S, et al. Vitamin D supplementation in pregnancy and lactation and infant growth. *N Engl J Med* 2018;379:535-546.

Undernutrition in children in Sub-Saharan Africa and South Asia is a global health problem that is directly related to infant growth.[1] Approximately 30% of newborns are small for their age in Bangladesh, with 36% of children younger than 5 years of age stunted (height-for-age z score < -2).[2] Vitamin D is involved in bone mineral metabolism and skeletal development; however, the exact mechanism of action has not been fully elucidated.[3] Rickets is the result of severe vitamin D deficiency, which leads to secondary hyperparathyroidism, demineralization of the skeleton, and impaired bone elongation.[3] In the United States, rickets is still diagnosed in children. The American Academy of Pediatrics (AAP) recommends 400 IU per day of vitamin D for infants who are exclusively or partially breastfed starting in the first few days of life as prevention.[4] There is a lack of evidence demonstrating whether of vitamin D supplementation during pregnancy and the postpartum period will improve skeletal linear growth.

Previously, Roth et al conducted a trial demonstrating improvements in linear growth with maternal vitamin D supplementation during the third trimester.[5] In this study, they investigated whether supplementation in women during pregnancy and throughout the postpartum period, in a population of women and young infants with high incidence of vitamin D deficiency, would improve infant growth measured using the International Fetal and Newborn Growth Consortium for the 21st Century Project recommendations.[6,7]

Summary Points

- Maternal vitamin D supplementation during pregnancy or during the postpartum period had no significant effect on infant length or other anthropometric outcomes by 1 year of age in a population with prenatal vitamin D deficiency.
- Measurements of 25(OH)D concentration levels in maternal and infant serum and in cord blood were dependent on vitamin D dose.

The Maternal Vitamin D for Infant Growth (MDIG) trial was a randomized, double-blind, placebo-controlled study, with five parallel dose groups investigating the effects of vitamin D supplementation. A

total of 1,300 healthy pregnant women between 17 and 24 weeks of gestation were enrolled in this study between March 2014 and September 2015 at the Maternal and Child Health Training Institute in Dhaka, Bangladesh. Inclusion criteria for the study included preliminary screening, medical screening by a study physician, and obstetric ultrasound. Exclusion criteria are listed in Table 1.

Vitamin D status was assessed by measuring 25(OH) D concentration in maternal blood, cord blood, and infant blood. The authors also measured parathyroid hormone (PTH) and monitored both pregnant women and infants for hypercalcemia through serum calcium measurements, and calcium:creatinine concentrations of infants at 3 and 6 months of age.

The 1,300 pregnant women were randomized to one of five parallel groups with weekly supplementation. Baseline characteristics were similar across all groups. The five groups are as follows: 1) placebo group, which received a placebo during the prenatal period and for 26 weeks postpartum; 2) 4,200 IU of vitamin D3 (cholecalciferol) per week with no postpartum treatment; 3) 16,800 IU of vitamin D3 per week with no postpartum treatment; 4) 28,000 IU of vitamin D3 per week with no postpartum treatment; and 5) 28,000 IU of vitamin D3 weekly prenatal treatment with 26 weeks of postpartum treatment. The authors tested the tablets measuring the vitamin D3 concentration. Tablets with different doses were identical in appearance and taste and were administered routinely under direct observation by trial personnel. The participants also received calcium (500 mg/day), iron (66 mg/day), and folic acid (350 mcg/day) throughout the intervention phase. Infants were assessed at 9 and 12 months of age, and visits were conducted either at a clinic or in the home.

Women who participated in the study were between 18 and 40 years of age. At baseline, 64% of women had a vitamin D deficiency, which was defined as a 25-hydroxyvitamin D concentration of < 12 ng/mL. They were dispersed equally among the five groups. Breastfeeding patterns and use of micronutrients were similar across all groups. Adherence to the treatment was high in this study, with 90% of scheduled doses received by more than 90% of women during the prenatal period and by more than 80% of women during the postpartum period. There was no difference in adherence between the groups. A total of 1,164 infants were assessed at 12 months for mean length-for-age z scores. The mean standard deviation length-for-age z score at one year was -1.00 ± 1.04, and the prevalence of stunting was 16%. Stunting is defined as the height or length less than two standard deviations below the standard median for age and sex. The z score is the statistical measurement that demonstrates the number of standard deviations that the infant's length measurement is from the mean.

Table 1: Exclusion Criteria

- Altered vitamin D metabolism, currently taking vitamin D supplementation to correct vitamin D deficiency, and/or previous enrollment in the MDIG trial during a prior pregnancy
- Hypercalcemia
- Self-reported medical history of medications or conditions that would predispose a woman to vitamin D sensitivity
- Active tuberculosis, sarcoidosis
- Parathyroid disease
- Renal or liver failure, history of renal/ureteral stones
- Use of antiseizure medications
- High-risk pregnancy (hemoglobin < 70 g/L)
- Proteinuria defined as ≥ 300 mg/dL
- Hypertension ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg

The authors found no significant difference in stunting between the five groups. Maternal and infant concentrations of vitamin D serum levels and cord blood were found to be dose-dependent on the vitamin D supplementation level. Vitamin D also demonstrated a dose-dependent decrease in maternal PTH concentrations at delivery. The 28,000 IU vitamin D group with both supplementation during pregnancy and throughout the postpartum period had significantly lower PTH concentrations at six months postpartum than the other groups. To evaluate for vitamin D toxicity, serum calcium is the best-known biomarker and was measured in this study. There were no confirmed cases of hypercalcemia found during pregnancy, indicating that there were no cases of vitamin D toxicity. Eight postpartum women and six infants were found to have asymptomatic hypercalcemia, which was not found to be significantly different across the groups. The authors reported that the 4,200 IU/week vitamin D dose was enough to eliminate maternal vitamin D deficiency in this study.

■ COMMENTARY

The study authors found that vitamin D supplementation starting between 17 and 24 weeks of gestation and continuing to either delivery or six months' postpartum did not significantly improve length-for-age z scores during the first year of life. One major study limitation was the initiation of supplementation between weeks 17 and 24 of gestation. The authors of an earlier study demonstrated that vitamin D concentrations may be much more influential earlier in pregnancy and that increased rates of pregnancy and live birth have been found in women with elevated serum

concentrations of vitamin D before conception but not at week 8 of gestation.[8,9] Another criticism of this study is that the placental machinery for vitamin D metabolism and signaling is activated early in pregnancy but decreases at term. Roth et al did not account for this, because the supplementation initiation was later in pregnancy.

Study strengths included the measurements of maternal and infant vitamin D levels that confirm a dose-dependent increase, the confirmation of the amount of vitamin D in the supplements, and an adequately powered study. The authors also evaluated the incidence of hypercalcemia and found lower levels of PTH in the 28,000 IU group supplemented during pregnancy and the postpartum group.

Currently, the American College of Obstetricians and Gynecologists does not recommend that physicians routinely assess vitamin D levels in women desiring to become pregnant.[10] More research needs to be performed to further understand the role of vitamin D in the reproductive system and to determine the efficacy and dose of vitamin D in women desiring to become pregnant. Continuing evidence demonstrates that serum vitamin D levels may not be the best indicator of vitamin D status. Thus, ordering vitamin D serum levels and treating patients with vitamin D supplementation for indications other than bone health may be premature. More research needs to be performed to understand the relationship of vitamin D with pregnancy outcomes and infant health. The findings of this study only demonstrated that vitamin D supplementation initiated between 17 and 24 weeks of gestation did not improve stunting among Bangladeshi infants at birth or 12 months. Additional research from this study may help better explain the authors' findings.

The World Health Organization does not recommend routine vitamin supplementation during pregnancy.[11] Although, the role of vitamin D in pregnancy is unclear, we do know that women should maintain a sufficient vitamin D serum levels for bone health.[12] From this study, we know that the lower dose of 4,200 IU of vitamin D weekly did replete deficient pregnant women and that even the higher dose of 28,000 IU weekly did not demonstrate toxicity. The role of vitamin D in infant linear growth is not clear from this study because vitamin D supplementation was initiated at 17 to 24 weeks and not earlier in pregnancy. Research into the role of vitamin D in pregnancy, lactation, and infant growth is not well understood. At the very least, clinicians should follow the AAP recommendation that infants receive 400 IU vitamin D per day shortly after birth. ■

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ABSTRACT & COMMENTARY

Social Media Use and Depression in Teens

By Jessica Orner, MD

Family Medicine Physician, Lebanon, PA

Dr. Orner reports no financial relationships relevant to this field of study.

SYNOPSIS: These investigators noted a correlation between adolescent social media use and depressive symptoms, online harassment, poor sleep, low self-esteem, and poor body image. However, causality could not be determined.

SOURCE: Kelly Y, Zilanawala A, Booker C, Sacker A. Social media use and adolescent mental health: Findings from the UK Millennium Cohort Study. *EClinicalMedicine* 2018;6:59-68. doi:10.1016/j.eclinm.2018.12.005.

With information surfacing about worrisome content spliced into online videos intended for children,[1] there has been increased public focus on examining the effect of social media on child mental health. Researchers also have been studying this topic for several years.

According to results published by the Pew Research Center in November 2018, 45% of U.S. teens reported they are online "almost constantly."[2] They reported using the platforms Snapchat, Instagram, and YouTube most often. Forty-five percent of teens 13 to 17 years of age reported that the effect of social media has been neither positive nor negative, while 31% reported mostly positive and 24% reported mostly negative experiences. For teens who recounted a positive effect from social media, the main reasons included connecting with friends and family (40%), ease of finding information (16%), and meeting others with the same interest (15%). Of those who reported that social media has had a mostly negative effect, the top concern was that social media leads to more bullying.[2]

In this U.K. report on social media use and adolescent mental health, Kelly et al focused specifically on depressive symptoms. They hypothesized that numerous potential explanatory pathways connect mental health and social media use. Although previous researchers have evaluated several potential pathways, Kelly et al evaluated several potential pathways simultaneously, including online harassment, poor sleep, poor self-esteem, and poor body image. The idea was that the association between depressive symptoms, social media, and any of the previously mentioned pathways could be influenced by other pathways. For example, an adolescent's relationship with poor body image and depressive symptoms could be mediated partially by poor self-esteem. Overall, there is also a concern that young people with poor mental health may be more apt to use social media for prolonged periods.

Summary Points

- Investigators found an association between social media use and depressive symptoms was larger for girls than boys.
- There appear to be multiple potential pathways between social media use and depressive symptoms, including online harassment, poor sleep, low self-esteem, and poor body image.

Data for this study were pulled from the Millennium Cohort Study of U.K. children born between September 2000 and January 2002. The cohort included 19,244 families and was stratified to represent all U.K. countries, including disadvantaged and ethnically diverse areas. Cohort data were collected at nine months, three years, five years, seven years, and 14 years. Caregivers were asked about socioeconomic circumstances and social and emotional difficulties when the children were 11 years of age. At age 14 years, cohort members completed computer-assisted questionnaires about social media use, mental health, online harassment, sleep, self-esteem, and body image. The questionnaires included the Mood and Feelings Questionnaire — short version (SMFQ); a questionnaire on online harassment, sleep, self-esteem, and body image; and information about average hours of weekday social media use.

The SMFQ consists of 13 items that assess symptoms arising from depression that occurred over the previous two weeks. Information on average hours of social media use was reported as less than one hour, one to less than three hours, three to less than five hours, or more than five hours. One to three hours was the most prevalent. The Millennium Cohort Study team created the questionnaire on harassment, sleep, self-esteem,

and body image, and it was similar to those used in other large surveys. It also included a self-esteem assessment based on the Rosenberg scale, which is widely used in social science research.

The researchers controlled for family income, family structure (i.e., one- vs. two-parent households), and cohort age in years. Using information from when the cohort participants were 11 years of age, researchers attempted to control for internalizing disorder symptoms. Internalizing disorders include depression, anxiety, and dissociative and obsessive-compulsive disorders.

The average age of participants was 14 years. More girls reported greater than three hours of social media use than boys (43.1% vs. 31.29%, respectively). The association between depressive symptoms and social media was more pronounced for girls (test for interaction, $P < 0.001$). Those living in lower-income homes and one-parent households were more likely to use social media for five or more hours daily.

None of the evaluated potential pathways showed specific gender differences. Since this study was based on cross-sectional data, causality and the direction of association of the pathways cannot be inferred. For example, the investigators were unable to determine if online harassment led to poor body image and depression. Using multivariable linear regression models, researchers determined the most pronounced routes between depressive symptoms and social media were found to be via poor sleep and online harassment. The researchers noted that the association between online harassment and depression also included pathways through body image issues, self-esteem, and poor sleep. The research showed that all the proposed pathways seemed to be interconnected.

■ COMMENTARY

Although the study was not completed in the United States, a similarly diverse population lives in the United Kingdom. An interesting finding is that both greater than five hours of social media use and no social media use were associated with low self-esteem. More research is ongoing regarding the role of social media culturally for teens.[2] However, there are studies that show a correlation between active social media use with positive outcomes and passive social media use with negative outcomes.[3]

Although the authors admitted that social media use can be beneficial, they chose to focus on the potential negative effects on adolescent mental health. It would be interesting and beneficial to see what potential pathways exist between social media and good mental health, as a large percentage of teens in the Pew survey reported positive effects and the study findings showed an association between low self-esteem and lack of social media use.

Since this study was based on cross-sectional data, there were several limitations. The researchers were not able to evaluate the role of different types of social media use, the time of day of social media use, or the "fear of missing out." Further research in this field could assess the role of the fear of missing out and whether it leads to prolonged social media usage or increased emotional investment.

Based on these results, it would appear prudent for primary care physicians and mental health professionals to include counseling and discussion about social media use at well-child visits and mental health appointments for both users and nonusers of social media. If social media seems to be associated with negative effects, consider discussing potential effects on sleep, bullying, body image, and self-esteem, as these may be high-yield areas based on this study. Interventions may include limiting overnight use, encouraging active participation, and focusing on positive social connection. ■

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CME QUESTIONS

1. **Which of the following statements is true based on the analysis of trends in dietary supplements associated with FDA warnings?**
   a. About 33% of the adulterated supplements contained very small quantities of active pharmaceuticals; the remainder included significantly higher quantities and are more potentially dangerous to consumers.
   b. The FDA stated that consumers are aware of the risks involved in taking supplements.
   c. The FDA has identified all adulterated substances on the market.
   d. The most common supplements adulterated with active pharmaceuticals were marketed for sexual enhancement, weight loss, or bodybuilding.

2. **Which of the following is true regarding the effect of group medical visits for Spanish speakers with chronic pain?**
   a. No change was seen in depression scores.
   b. No change was seen in anxiety scores.
   c. Pain improved, but not significantly.
   d. Generally, the qualitative reports were not favorable.

3. **At what dose of vitamin D were parathyroid hormone levels found to be significantly lower six months' postpartum?**
   a. No significant difference was found among doses ranging from 4,200 IU to 28,000 IU per week
   b. At the 4,200 IU weekly dose
   c. At the 28,000 IU weekly dose during pregnancy only
   d. At the 28,000 IU weekly dose during pregnancy and six months' postpartum

4. **According to the study by Kelly et al, which of the following is a potential pathway associated with depressive symptoms and social media?**
   a. Online harassment, sleep, self-esteem, and body image
   b. Sleep, smartphone usage, body image, and online harassment
   c. Body image, fear of missing out, sleep, and smartphone usage
   d. Online harassment, type of social media use, sleep, and body image

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Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
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