



## Peanut Allergy...in a Nutshell

### Learning Objectives

1. Describe the signs and symptoms of an allergic reaction to peanuts.
2. Discuss the prevalence of peanut allergy.
3. Discuss preventative treatments for peanut allergy.
4. Summarize the drug treatment of an anaphylactic reaction to peanuts.

### About the Author:



Brad Gilchrist is a 1990 graduate of the University of Iowa College of Pharmacy (B.S., R.Ph.). His current position at DDIS is Staff Pharmacist II-Academic Research. In addition to indexing articles for the database, his other main responsibility is overseeing the acquisition, formatting and indexing of the FDA Approval Packages.

### Introduction

Cow's milk, eggs, soy, wheat, peanuts, tree nuts (walnuts, hazelnuts, almonds, cashews, pecans and pistachios), fish and shellfish account for the majority of food related allergic reactions.<sup>1,2</sup> Peanuts, tree nuts, fish and shellfish are most commonly associated with anaphylaxis. Peanut allergy is one of the more prevalent and serious food allergies. Peanut allergy is an immediate immunoglobulin E (IgE) type I hypersensitivity reaction.<sup>3</sup> Signs and symptoms of peanut allergy may include nausea, vomiting, diarrhea, abdominal pain, urticaria, angioedema, bronchospasm, hypotension, loss of consciousness and death.<sup>4</sup>

The initial reaction occurs at the local site of entry of the allergen. Peanut induced allergy begins when one of the various peanut proteins crosses a mucosal barrier and binds to mast-cell bound IgE sensitized to peanut.<sup>5</sup> The peanut protein cross-links IgE attached to the Fc receptors of the mast cell, inducing degranulation and release of immunological mediators. Other parts of the body may be affected when IgE enters the circulation and binds to circulating basophils and other tissue-fixed mast cells throughout the body. Sicherer et al<sup>6</sup> reported that about half of all children with peanut allergy have allergic manifestations in 1 target organ system, 30% have symptoms in 2 systems, 10-15% in 3 systems, and 1% in 4 systems.

### Allergenicity

In botanical terms, a peanut is not a nut but a legume. Varieties of peanuts include: Virginia, Spanish, Valencia, and Runner. They contain varying but similar amounts of the different peanut proteins.<sup>7</sup> Three major peanut (*Arachis hypogaea*) protein allergens responsible for inducing reactions are: Ara h 1, Ara h 2 and Ara h 3.<sup>8</sup> One peanut contains about 200 mg of protein.<sup>9</sup> Doses as low as 100 micrograms of peanut protein may induce allergic symptoms in some individuals.<sup>10</sup> In one report, 11 persons allergic to peanuts reported having experienced an allergic reaction after being kissed on the lips or cheek by someone who had recently eaten peanuts.<sup>11</sup> Reactions to airborne peanut protein have also been reported in commercial airlines when numerous packets of dry roasted peanuts were opened at once.<sup>12</sup> In a clinical study, 30 children with significant peanut allergy were confined in a room to breathe room air while 3 ounces of peanut butter was held 12 inches from their noses for 10 minutes.<sup>13</sup> No reactions were observed or subjectively reported by any of the subjects.

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One third of these same children did have local skin reactions that did not progress when peanut butter was applied to a small area on their backs. These reports illustrate the fact that the threshold amount necessary to induce allergy varies from person to person, as does the type of reaction experienced. The amount of peanut protein that only induces hives or itching in one person may induce anaphylaxis and death in another person. Generally, the greater the amount of exposure to peanut, the more likely a severe reaction is to occur.

Peanut allergy, for many, is lifelong, but some do “outgrow” the hypersensitivity or develop a tolerance to peanuts.<sup>14-17</sup> One study of peanut allergic children found that 20% developed a tolerance to peanuts.<sup>15</sup> Authors of a more recent study concluded that persons with a history of peanut allergy with peanut-IgE levels less than 5 kilounits of antibody per liter ( $kU_A/L$ ) have at least a 50% chance of developing a tolerance to peanuts.<sup>18</sup> They also found, however, that peanut allergy recurred in some subjects.

## Prevalence

The reports of children outgrowing their allergy to peanuts are counterbalanced by the reports of increased incidence of peanut allergy in children. Two studies, one in the United States (U.S.) and one in the United Kingdom (U.K.), reported a doubling in the incidence of peanut allergy in children less than 18 years of age.<sup>19,20</sup> In 1997, a random digit dial telephone survey throughout the U.S. by Sicherer et al<sup>21</sup> found the prevalence of reported peanut allergy to be 0.4% in children less than 18 years of age. Five years later, in a similarly designed nationwide telephone survey, the prevalence of reported peanut allergy among children  $\leq 18$  years significantly increased from 0.4% in 1997 to 0.8% ( $p = .05$ ).<sup>20</sup> They also found a male predominance of peanut and tree nut allergy in children ( $p = .02$ ) but a female predominance in adults ( $p = .08$ ). No specific geographic area in the U.S. reported a significantly higher rate of peanut or tree nut allergy. Alarming, only 74% of children and 44% of adults were evaluated by a physician after their first reactions, despite involvement of multiple organ systems.

Data from 2 sequential cohorts of children from the Isle of Wight, U.K. also indicated a doubling of the incidence of peanut allergy.<sup>19</sup> Parents of 1273 children born between September 1, 1994, and August 31, 1996, on the Isle of Wight completed a questionnaire related to allergic reaction symptoms. The average age of the

children was 3.2 years, and 1% (13/1273) were reported to have peanut allergy. This was a twofold increase compared to a similar cohort of 4-year old children surveyed who were born between January 1, 1989, and February 28, 1990, on the Isle of Wight. In this cohort of 1218 children, 0.5% (6/1218) were reported to have a peanut allergy. This difference, however, was not found to be statistically significant ( $p = .2$ ).

## Immunotherapies

There are no approved, effective treatment options for curing peanut allergy. At the moment, strict avoidance of peanut and peanut-containing products is the best preventative measure. Avoidance of peanuts, however, is not as easy as it may seem. Extraordinary care must be taken to eliminate contact with or ingestion of peanuts, as peanuts and peanut by-products are commonly used in food preparation. Hidden sources of peanuts such as chili, egg rolls, cookies, candy and pastries have been documented as inducing anaphylaxis and death in peanut allergic asthmatics.<sup>22</sup> Persons with peanut allergy should verify the peanut content of all food items before consumption as peanuts may be present in unexpected foods.

Trials of immunotherapy with administration of aqueous peanut extract have only been done in small populations with inconsistent results and significant side effects. In one trial, 1 person developed anaphylactic shock and died after erroneous administration of a maintenance dose of peanut extract.<sup>23</sup> In this same study, 11 persons with a history of hypotension, acute bronchospasm and/or generalized urticaria after peanut ingestion were randomized to treatment with placebo or rush immunotherapy with diluted peanut extract in an attempt to desensitize the subjects to peanuts. Over a 5-day period, patients received increasing doses of diluted peanut extract. The starting dose of rush immunotherapy was individualized and based on a person's sensitivity to peanuts. A typical starting dose was 0.05 mL of peanut extract diluted to 1:10,000 (weight/volume) administered subcutaneously. Subjects received 4 injections per day, an hour apart on days 1-4 and 2 injections on day 5. After day 5, a maintenance dose of diluted peanut extract 1:100 weight/volume was given once a week for 4

weeks. It was during this time that a patient randomized to placebo therapy was mistakenly given the maintenance dose of diluted peanut extract and died of anaphylactic shock. The study was stopped prematurely. Despite the accidental death and the lack of data to perform statistical analysis, the authors believed the immunotherapy was effective. Three of the 4 patients who completed the protocol had received peanut immunotherapy. Upon oral peanut re-challenge, these 3 patients displayed a 67-100% decrease in symptom scores and a 1000-fold reduction to total loss of skin test reactivity to peanuts. The only placebo patient who completed the protocol showed no reduction in symptom score or skin test sensitivity upon re-challenge. Out of 120 injections administered, adverse events occurred in 16 (13.3%) of cases. Urticaria and asthma were the main side effects.

A similar but longer-duration study was conducted by several of the same authors of the previously mentioned trial.<sup>24</sup> Twelve adults with a history of immediate peanut hypersensitivity were randomized to treatment with placebo or rush immunotherapy with diluted, defatted peanut extract. The rush immunotherapy schedule was the same as in the previous study<sup>23</sup> except maintenance therapy was continued for 1 year instead of only 1 month. After 8 weeks of maintenance therapy, an attempt was made to increase the interval between maintenance doses by 1 week every 2 months, up to once monthly. Oral peanut challenges were performed before immunotherapy and after 1 month and 1 year of maintenance therapy. All 6 subjects receiving rush immunotherapy had a decrease in peanut sensitivity after 1 month of therapy ( $p = .0002$ ). Three of the 6 subjects, however, were unable to tolerate the maintenance dose of diluted peanut extract. Consequently, at the end of the year there was partial to complete loss of the increased tolerance to peanut challenge initially seen in these 3 subjects. Side effects of therapy were high with 23% reporting systemic reactions during rush immunotherapy and 39% during maintenance therapy. There was no overall change in peanut sensitivity after 1 year of therapy in the placebo group. The authors concluded that immunotherapy with this formulation of peanut extract was unacceptable for widespread use because of the high incidence of systemic reactions.

While active immunotherapy with allergenic extracts has proven unacceptable, passive immunotherapy with a new humanized IgG1 monoclonal antibody TNX-901 shows potential. TNX-901 inhibits the binding of IgE to mast cells and basophils. Eighty-four patients with a history of peanut allergy were randomized to receive either subcutaneous TNX-901 150 mg, 300 mg, 450 mg or placebo every 4 weeks for 4 doses.<sup>25</sup> At baseline, the mean threshold sensitivity to peanut flour ranged from 178-436 mg in the four different treatment groups. Between weeks 14 and 15, the authors found that the mean threshold of sensitivity to peanut, based on an oral challenge with peanut flour, increased in a dose-responsive manner. A strong trend in increased threshold of sensitivity was associated with increasing doses of TNX-901. When compared with placebo, the increase was only significant for the 450 mg group ( $p < .001$ ). Twenty-one percent of the patients in the 300 mg group and 24% of those in the 450 mg group were effectively desensitized and able to ingest at least 8 g of peanut flour (~8 peanuts) versus less than 10% of placebo patients. The difference between all treatment groups and placebo, however, was not statistically significant. TNX-901 appeared to be well tolerated. Pain at the injection site was reported by 13 to 14 patients in each group. These reactions were generally considered mild in nature except in one patient in the 450 mg group who had moderate erythema or edema on two occasions.

## Anaphylaxis

Anaphylactic reactions to peanut are well documented. Clinically, anaphylaxis refers to rapidly developing generalized reactions that include pruritus, urticaria, angioedema, hypotension, wheezing, bronchospasm, nausea, vomiting, abdominal pain, diarrhea, uterine contractions and/or direct cardiac effects including arrhythmias.<sup>26</sup> A common initial set of symptoms includes a sense of impending doom and generalized warmth or flush. The warmth is characterized by tingling or pruritus of the skin, especially on the palms of the hands and/or soles of the feet, as well as on the lips and the genital area. Complaints of a lump in the throat, throat tightness, hoarseness, difficulty swallowing, inspiratory stridor, chest tightness, wheezing, or shortness of breath are significant signs that immediate action should be taken.<sup>27</sup> Symptoms usually occur within minutes of exposure but, in some cases, signs and symptoms may not surface until up to an hour after exposure.

Biphasic anaphylaxis may also occur in up to 20% of cases.<sup>28</sup> In these cases, the initial signs and symptoms of anaphylaxis may subside on their own or from treatment but then reappear 1-8 hours later. Biphasic reactions have been documented as occurring as long as 24-38 hours after the initial reaction.<sup>28-30</sup>

Epinephrine is the drug of choice for treating anaphylaxis due to peanut allergy. People with peanut allergy should be prescribed self-injectable epinephrine containing devices such as EpiPen<sup>®</sup> or EpiPen Jr<sup>®</sup> and be instructed to carry them at all times. Guidelines prepared by the Joint Council of Allergy, Asthma & Immunology recommend an initial adult dose from 0.2 mL to 0.5 mL of a 1:1000 (weight/volume) dilution (0.2 to 0.5 mg base) subcutaneously or intramuscularly. This may be repeated every 10 to 15 minutes as needed up to 2 maximum of 1 mg per dose. The pediatric dose is 10 micrograms (0.01 mg) per kilogram of body weight up to a maximum of 500 micrograms (0.5 mg) per dose or 0.5 mL of 1:1000 (weight/volume). This dose can be repeated every 15 minutes for 2 doses and then every 4 hours as needed.<sup>27</sup>

There is evidence that the intramuscular route is superior to subcutaneous administration. One study reported that epinephrine injected intramuscularly into the thigh was better absorbed than when injected intramuscularly or subcutaneously into the upper arm in adults.<sup>31</sup> Similarly, in children the intramuscular absorption of epinephrine was also found to be quicker and more complete than the subcutaneous route.<sup>32</sup> The authors of these two studies recommended intramuscular administration into the thigh as the preferred route for treating anaphylaxis, though studies are needed to confirm this suggestion.

Once a patient's condition is stabilized with epinephrine, diphenhydramine and ranitidine may be started. The doses for adults are oral, intramuscular or intravenous diphenhydramine 25-50 mg every 4 to 6 hours as needed and ranitidine 50 mg intravenously or 150 mg orally every 8 hours as needed. In children the recommended doses are oral, intramuscular or intravenous diphenhydramine 1.25 mg/kg every 4 to 6 hours as needed and ranitidine 1.25 mg/kg intravenously or 2 mg/kg orally every 8 hours as needed.<sup>33</sup>

Persistent hypotension should be managed with intravenous fluid support using crystalloid or colloid and possibly vasopressor therapy. Bronchospasm may be treated with inhaled or intravenous beta-

agonists. Persons who have been on beta-blockers prior to an anaphylactic reaction may not respond to epinephrine. In those patients, intravenous glucagon 1 mg should also be administered as a bolus.<sup>27</sup> A continuous infusion of 1-5 mg of glucagon per hour may be given if needed.

To reduce the chance of protracted or recurring anaphylaxis, corticosteroids are also recommended though their efficacy has not been proven.<sup>27</sup> The recommendation for adults is intravenous methylprednisolone 125 mg or oral prednisone 50 mg every 6 hours as needed. Children may be given intravenous methylprednisolone 1 mg/kg or oral prednisone 1 mg/kg every 6 hours as needed.<sup>33</sup>

## Conclusion

Peanut allergy is a potentially life threatening condition that is on the increase. When a peanut allergic reaction does occur, fast diagnosis and action are required. All persons with peanut allergy should be evaluated by an allergist and carry an EpiPen<sup>®</sup> or EpiPen Jr<sup>®</sup> with them at all times. Immunotherapy with peanut extract is not a reliably effective method of desensitization. The new humanized IgG1 monoclonal antibody TNX-901 has shown promising results in its first trial. As of yet, however, it has not been approved by the United States Food and Drug Administration. More long-term studies in larger populations are needed to determine if it will find a place in the treatment of peanut allergic patients. Until further medical breakthroughs, avoidance of peanuts remains the best preventative therapy for persons with peanut allergy.

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**CE REGISTRATION**

ACPE # 020-000-04-030-H01

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TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

PEANUT ALLERGY...IN A NUTSHELL

NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

CITY \_\_\_\_\_ STATE \_\_\_\_\_ ZIP \_\_\_\_\_

SOCIAL SECURITY NUMBER (OPTIONAL) \_\_\_\_\_

PHARMACY LICENSE NUMBER(S) \_\_\_\_\_

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date \_\_\_\_\_

(circle the correct answer)

1. Peanut allergy is a \_\_\_\_\_ hypersensitivity reaction.
  - a) type I
  - b) type II
  - c) type III
  - d) type IV
2. The best available therapy for preventing allergic reaction in peanut sensitive individuals is \_\_\_\_\_.
  - a) avoidance of peanuts
  - b) passive immunotherapy with anti-IgE monoclonal antibodies
  - c) active immunotherapy with diluted peanut extract
  - d) active immunotherapy with diluted tree nut extract
3. Which of the following chronic therapy drugs could decrease a person's response to epinephrine in the case of anaphylaxis?
  - a) sertraline
  - b) atenolol
  - c) betaseron
  - d) insulin
4. When administering epinephrine, the quickest absorption has been reported to occur when it is given \_\_\_\_\_.
  - a) subcutaneously into the upper arm
  - b) subcutaneously into the thigh
  - c) intramuscularly into the upper arm
  - d) intramuscularly into the thigh
5. When a person is experiencing an anaphylactic reaction to peanut, \_\_\_\_\_ should be administered immediately.
  - a) oxygen
  - b) insulin
  - c) epinephrine
  - d) glucagon
6. Biphasic anaphylaxis has been reported to occur in \_\_\_ of patients experiencing anaphylaxis.
  - a) 20%
  - b) 30%
  - c) 40%
  - d) 50%
7. In two separate studies, the prevalence of peanut allergy in children has been shown to be \_\_\_\_\_.
  - a) decreasing
  - b) unchanged
  - c) increasing
  - d) related to geographic region
8. \_\_\_\_\_ percent of people with peanut allergy have been reported to "outgrow" it.
  - a) Thirty
  - b) Twenty
  - c) Ten
  - d) Zero
9. According to the Guidelines prepared by the Joint Council of Allergy, Asthma & Immunology, the recommended initial adult dose of epinephrine for treating anaphylaxis is \_\_\_\_\_.
  - a) 0.2 mL to 0.5 mL of a 1:1000 (weight/volume) concentration subcutaneously or intramuscularly
  - b) 0.2 mL to 0.5 mL of a 1:100 (weight/volume) concentration subcutaneously or intramuscularly
  - c) 2.0 mL to 5.0 mL of a 1:1000 (weight/volume) concentration subcutaneously or intramuscularly
  - d) 2.0 mL to 5.0 mL of a 1:1000 (weight/volume) concentration intravenously
10. In peanut allergic persons, initial signs and symptoms of anaphylaxis may \_\_\_\_\_.
  - a) occur within minutes of ingesting peanut protein
  - b) not occur until an hour after ingesting peanut protein
  - c) include a sense of impending doom
  - d) all of the above

**PROGRAM EVALUATION**

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
Important to pharmacists	Agree		Disagree		
	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me \_\_\_\_\_ hours and \_\_\_\_\_ minutes to read this article and complete the assessment questions.

# FDA DRUG/BIOLOGIC APPROVALS

New drugs approved by the FDA **June 2004 through August 2004**. An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

Generic Name Trade Name (FDA Therapeutic Classification)*	Sponsor (Approval Date)	<i>IDIS</i> Drug Term Drug Number ( <i>IDIS</i> Citations)	Indication/Use Dosage Form	<i>IDIS</i> Disease Term Modified ICD-9-CM Number
<b>Acamprosate Calcium</b> <i>Campral</i> (1P)	Lipha (July 29, 2004)	ACAMPROSATE 95000022 (89 citations)	Maintenance of alcohol abstinence Tablet	Depend/Abuse, Alcohol NEC 303.
Baltieri DA, Andrade AG. <b>Acamprosate</b> in alcohol dependence: a randomized controlled efficacy study in a standard clinical setting. <i>J Stud Alcohol</i> . 2004; 65:136-139. ( <i>IDIS</i> Article Number 519895) Investigators conducted a double-blind trial for 24 weeks with 75 alcohol dependent patients who were randomly assigned to take acamprosate 1.998 mg/day or placebo for 12 weeks and were followed up for another 12 weeks. Acamprosate was well tolerated and on an intention-to-treat basis, using the Kaplan-Meier survival curve, showed improved relapse results over placebo (log-rank test, p=0.02).				
<b>Duloxetine Hydrochloride</b> <i>Eli Lilly</i> (1S)	Cymbalta (Aug. 3, 2004)	DULOXETINE 28160710 (38 citations)	Major depressive disorder Capsule	Disorder, Depressive NEC 311.
Goldstein DJ, Lu Y, Detke MJ, Wiltse C, et al. <b>Duloxetine</b> in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. <i>J Clin Psychopharmacol</i> . 2002; 63:225-231. ( <i>IDIS</i> Article Number 518861) This randomized, double-blind, placebo-controlled trial included 353 patients with confirmed major depression who were treated with either duloxetine at 20 mg twice daily, duloxetine 40 mg twice daily, paroxetine 20 mg once daily or placebo for 8 weeks. Results showed that duloxetine 40 mg twice daily was superior to placebo in total change and superior to paroxetine in improvement on mean 17-item Hamilton Depression Rating Scale by 3.62 points and 2.39 points respectively.				
<b>L-Glutamine</b> <i>NutreStore</i> (1SV)	Nutritional Restart (June 10, 2004)	GLUTAMINE 56260002 (6 citations)	Short bowel syndrome Oral powder for solution	Malabsorption, Intest NEC 579.
<b>Pentetate Calcium Trisodium</b> <i>Pentetate Calcium Trisodium</i> (1P)	Pharma Hameln GmbH (Aug. 11, 2004)	PENTETATE CALCIUM TRISODIUM 64000096 (3 citations)	Radiation contamination Injection	TX/AE- Radioisotope/Radiation 990.
<b>Pentetate Zinc Trisodium</b> <i>Pentetate Zinc Trisodium</i> (1P)	Pharma Hameln GmbH (Aug. 11, 2004)	ZINC PENTETATE 64000015 (2 citations)	Radiation contamination Injection	TX/AE- Radioisotope/Radiation 990.
Burda AM, Sigg T. Pharmacy preparedness for incidents involving weapons of mass destruction. <i>Am J Health-Syst Pharm</i> . 2001; 58:2274-2284. ( <i>IDIS</i> Article Number 473740) This report presents a summary of weapons of mass destruction, including biological, chemical and nuclear weapons, and the treatments that can be provided by health care facility pharmacists. A section of the report highlights chelating agents to be used in case of radiation contamination, <b>pentetate calcium trisodium</b> and <b>pentetate zinc trisodium</b> , and indicates sources from which these agents can be obtained.				

# AND KEY REFERENCES

Generic Name Trade Name (FDA Therapeutic Classification)*	Sponsor (Approval Date)	IDIS Drug Term Drug Number (IDIS Citations)	Indication/Use Dosage Form	IDIS Disease Term Modified ICD-9-CM Number
<b>Technetium 99m Tc Fanolesomab</b> <i>NeuroSpec</i> (1S)	Palatin Technologies (July 2, 2004)	TC 99M FANOLESOMAB 78040262 (6 citations)	Imaging appendicitis Injection	Radioisotope scan, GI 92.04

Rypins EB, Kipper SL, Weiland F, Neal C, et al. 99MTC anti-CD 15 monoclonal antibody (Leutech) imaging improves diagnostic accuracy and clinical management in patients with equivocal presentation of appendicitis. *Ann Surg.* 2002; 235:232-239. (IDIS Article Number 478271)

A multi-center, open-label study of 200 patients, ranging in age from 5-86 years, evaluated the efficacy of intravenous technetium **99M Tc fanolesomab** in correctly diagnosing appendicitis and found the imaging drug effective in both identifying patients with appendicitis (90% sensitivity) and identifying patients without appendicitis (87% specificity). The drug was well tolerated and the accuracy, positive predictive value and negative predictive value were 88%, 74% and 95%, respectively.

**\*Chemical Type:**  
1 - New molecular entity

**Therapeutic Potentials:**  
P - Priority Review - Significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.  
S - Standard Review - The drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.  
V - Orphan Drug

## About the Author:

Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the IDIS database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.



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Thank you in advance for your prompt attention to your subscription renewal and your continued support of the *Iowa Drug Information Service*.

# New Subscriber Training – Botswana

The Division of Drug Information Service (DDIS) was able to play an important role in providing training for key pharmacy leaders in the Botswana government. Ron Herman, R.Ph., Ph.D., traveled to Gaborone, Botswana for 5 days in May to provide hands on training for the *Iowa Drug Information Service (IDIS)* database and the provision of drug information services.

The Botswana Department of Health and Social Welfare has taken a number of steps toward its Vision 2016 Health Goals. The Pharmaceutical Services Division published its Drug Management Guidelines in 2000. The guidelines outline good management practices to ensure the continuous availability of essential drugs of good quality, safety and efficacy in health centers in Botswana. By 2002 the Ministry of Health had implemented the Botswana National Drug Policy that put in place the structures necessary to achieve the goals of the Drug Management Guidelines. It also called for the establishment of a National Drug Information Center to serve as a resource for the National Standing Committee on Drugs which is responsible for establishing and maintaining a national formulary. By 2004 this Drug Information Center was taking shape.



Joyce Kgatlwane, Pharm.D.  
Director, Drug and Toxicology Information  
Service (DaTIS)



Ron Herman, R.Ph., Ph.D. with two trainees, Ms.  
B. Mohiemang and Ms. D. Hussain

The Drug and Toxicology Information Service (DaTIS), under the leadership of Joyce Kgatlwane, Pharm.D., is now using the *IDIS* database to provide the literature support necessary to make wise decisions about which drugs will be included in the Botswana Essential Drug List. Dr. Herman devoted several days to hands on training using *IDIS/Web* and then spent a half day with each of the three trainees to ensure their competency with the resource.

Mr. Atamalang Kgosiemang, Chief Pharmacist and Director of Medical Stores for Botswana, communicated his sincere appreciation on behalf of the Minister of Health for providing this training. Botswana pharmacists now have a new tool to combat the many health challenges that the people of Botswana face. DDIS was honored to be invited to DaTIS.

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# Impaired physical function, muscle weakness, and persistent nonspecific musculoskeletal pain probably related to vitamin D deficiency

Perspective from an



**IDIS Subscriber**

While reviewing the December 2003 issue of the *Mayo Clinic Proceedings*, I was surprised to learn that Plotnikoff and Quigley<sup>1</sup> described 150 patients with non-specific pain syndromes refractory to standard therapy, 93% of whom had deficient levels of vitamin D. These patients had presented to an inner city primary care clinic in Minneapolis, Minnesota. The population included Somalian, Mexican, and Southeast Asian (Hmong, Cambodian or Laotian) immigrants and non-immigrants including African Americans, white Americans of Scandinavian and Northern European descent, and American Indians (Lakotan, Dakotan and Ojibwe). Over 90% of this group had been evaluated medically for their persistent pain syndrome within the previous year. None of them had been screened for vitamin D deficiency. The authors recommend screening all outpatients with persistent nonspecific musculoskeletal pain for vitamin D deficiency. Although I had never actually been involved with the management of a patient with rickets or osteomalacia, it was my understanding, and I suspect it is widely taught that nutritional vitamin D deficient rickets/osteomalacia is uncommon in the United States. Cases of rickets in the United States were known to occur in children of vegetarian mothers who avoid milk products, in children who were not weaned to vitamin D fortified milk by age 2, and in low birth weight infants who were fed parenterally. The contribution of vitamin D deficiency to osteomalacia in the elderly is controversial. The following discussion is based on my review, using PubMed and *IDIS*, of the English language literature from 1966 to 2004, describing an association between vitamin D status and functional impairment, myopathy, or pain syndromes. Recommended reviews of vitamin D include, Plotnikoff and Quigley<sup>2</sup>, Fraser<sup>3</sup> and Holick<sup>4</sup>.

## Case Reports

Holick<sup>5</sup> states that pain and vitamin D deficiency have been documented in the scientific literature for over 100 years. He cites British, German, and American literature from 1889, 1919, and 1922. In the modern era, Gloth and colleagues<sup>6</sup> account of 5 patients with low serum 25-hydroxycholecalciferol (25-OHD) levels, who presented with severe pain syndromes that did not respond to the use of analgesics including narcotics, but resolved within days or weeks after vitamin D therapy was begun. One of their patients had the following course. "A 68-year-old man lived in his home with his son for many years before coming to a nursing home. He had been confined at home in a dark, dingy room because he was too weak to walk. His medical history included hypertrophic cardiomyopathy, renal insufficiency, and diabetes mellitus with diabetic nephropathy. Medications included captopril, nortriptyline, and oxycodone-

acetaminophen (after several admissions the patient was eventually transferred to Dr. Gloth's service at the Mason F. Lord (MFL) Chronic Hospital and Nursing Home). The patient continued to do poorly, refusing to participate in physical therapy and often crying out with pain that was not relieved with narcotics or antidepressants at documented therapeutic levels. Physical examination showed an emaciated man. . . decreased range of motion in both legs (secondary to pain). Tenderness to light pressure on the skin surface was also present. . . The serum level of 25-OHD was low normal (32 nmol/L reference range 25 to 138 nmol/L). Within one week after the patient received a single oral dose of 50,000 IU of ergocalciferol and was placed on a regimen of 400 IU daily, his pain resolved and he began to participate in physical therapy and whirlpool treatments for his pressure sores."

In another of their cases the serum level of 25-OHD was <12 pmol/L. The patient's pain resolved within a week after a single dose of oral ergocalciferol 50,000 IU plus a quart of milk daily plus three milkshakes daily. Six months later the pain returned but resolved after a seven day course of oral ergocalciferol 50,000 IU plus a multivitamin. Two months later a similar pain syndrome returned with new onset weakness and lethargy. Again the serum 25-OHD level was low at 30 nmol/L. For the third time the patient experienced pain relief within one week after a single dose of oral ergocalciferol 50,000 IU and beginning a daily dose of 1200 IU ergocalciferol.<sup>6</sup> This information should be particularly relevant to those caring for the homebound elderly or nursing home patients who have not had adequate casual exposure to sunlight.

Ziambaras and Dagogo-Jack<sup>7</sup> described two cases with significant proximal muscle weakness whose strength improved after normal serum 25-OHD levels were restored. Their first patient, a 57-year-old woman had reported rib and lower back pain six months prior to referral. The pain was refractory to over the counter analgesics. She had also reported muscle aching, progressive lower extremity muscle weakness and difficulty in climbing stairs and arising from a sitting position. Although she had always been active, she reduced her physical activity because of easy fatigability. She lost 30 pounds in the six to nine months prior to admission in spite of eating her normal diet. On physical examination she could not rise from a squatting position without assistance. Lying supine she was unable to raise her legs against mild resistance. Her reflexes were normal, sensation was intact, and her gait was normal. There was no tenderness or muscle atrophy. Serum calcium was low, the intact serum parathyroid hormone (PTH) level was elevated and the serum 25-OHD was undetectable. Skeletal x-rays were unremarkable. Fecal fat levels > 50% of fecal solids, were consistent with steatorrhea. A biopsy of the small intestine was consistent with celiac disease. A diagnosis of vitamin D deficiency due to malabsorption was made. A gluten free diet was instituted and the patient was begun on ergocalciferol 50,000 IU orally daily. Her serum 25-OHD levels returned to normal within two months. Her muscle strength improved steadily and had returned to normal at her six month follow up visit. Their second patient was a 19-year-old from Nepal who came to the United States for medical treatment. He gave a two year history of progressive leg weakness, with recent difficulty climbing stairs and standing up from a sitting position. He also complained of proximal upper extremity weakness, less severe than in his legs. He had been a strict vegetarian all his life, avoiding all animal products including dairy products. He worked long hours in an office with little exposure to sunlight. On physical examination he had a broad-based waddling gait. He had significant proximal muscle weakness in both lower and upper extremities. His reflexes were normal, sensation was intact and the remainder of his examination was unremarkable. His serum calcium was low, serum 25-OHD was undetectable, and intact PTH level was elevated, his vitamin B<sub>12</sub> level was 110 pmol/L. Skeletal x-rays showed bilateral demineralization of the distal bones in the lower extremities. A

working diagnosis of dietary vitamin D deficiency was made and the patient was begun on 50,000 IU of oral ergocalciferol daily. The patient was discharged on 50,000 IU of oral ergocalciferol twice weekly. At a four month follow up visit his weakness no longer interfered with his activities of daily living.

Prabhala and colleagues<sup>8</sup> described five cases of severe myopathy associated with vitamin D deficiency. In each case the diagnosis was either delayed because of the belief the myopathy was associated with concomitant neurologic disease or unrecognized because of the insidious onset of the myopathy. Each patient was confined to a wheelchair due to weakness and immobility, their weakness had been attributed to other causes. Each of the five cases described by Prabhala and colleagues<sup>8</sup> presented in western New York state over an 18 month period. Their serum 25-OHD levels ranged from 12 to 32 nmol/L before vitamin D therapy. Two of the cases had histories of long-standing diabetic neuropathy. In both cases with a history of diabetic neuropathy the weakness had been attributed to the neuropathy until the vitamin D deficiency was recognized. They emphasize that diabetic neuropathy is primarily a sensory syndrome and rarely causes severe proximal muscle weakness resulting in immobility. One of their patients presented with the following syndrome. "A 37-year-old African American woman with Type 1 diabetes mellitus (hemoglobin A<sub>1c</sub> level 8.6%) was seen with aches and pain and increasing muscle weakness. The weakness started in the lower limbs and had spread to the upper limbs. She had increasing difficulty combing her hair for the past 2 months and was confined to a wheelchair. She had retinopathy, peripheral neuropathy with multiple amputations of the toes, 1 gram daily proteinuria, and hypertension. Examination revealed decreased proximal muscle strength (3/5) in all 4 limbs." She was treated with ergocalciferol 50,000 IU orally once a week for six weeks. Her aches and pains gradually remitted. She gradually regained strength, and became mobile in 3 to 4 weeks. At follow up she was pain free and able to walk and climb stairs. They suggest that severe myopathy due to vitamin D deficiency is relatively common, insidious in onset, and easy to treat once recognized. In each of the five cases they described, vitamin D therapy resulted in a resolution of the body aches and pain and restoration of normal muscle strength in 4 to 6 weeks.

## Vitamin D use in various populations

Janssen and colleagues<sup>9</sup> have reviewed the impact of vitamin D deficiency on muscle function and falls in the elderly population. The data they reviewed indicated that vitamin D supplementation in healthy elderly groups has not been shown to decrease fall risk. On the other hand, vitamin D supplementation in elderly patients with vitamin D deficiency improved muscle strength and was associated with fewer falls and nonvertebral fractures.

In a series of 824 elderly patients aged > 70 years from 11 European countries over 30% of men and 40% of women had wintertime serum 25-OHD levels of < 30 nmol/L.<sup>10</sup> Gloth and colleagues<sup>11</sup> at Johns Hopkins report that even though average vitamin D intake in the United States is reportedly among the highest in the world, the vitamin D status of many elderly people is low. They studied 32 homebound individuals (had not been outside in the previous six months) with serum 25-OHD levels < 37.5 nmol/L. Most of the patients were immobile at the outset of the study. Those patients whose serum 25-OHD levels increased by at least 7.5 nmol/L also demonstrated improvement in their Frail Elderly Functional Assessment (FEFA) scores. The authors call for larger studies and suspect that vitamin D therapy could become an integral addition to the regimens of frail elderly patients. They went on to study a larger group of nursing home and homebound, sunlight deprived (confined indoors for at least 6 months) elderly patients.<sup>12</sup> They reported that 54% of community dwellers and 38% of nursing home residents studied had 25-OHD levels of < 25 nmol/L. Vitamin D deficiency may be common among both nursing home and the homebound elderly in the United States.

Thomas and colleagues<sup>13</sup> studied vitamin D status in 290 consecutive admissions to a general medical ward at the Massachusetts General Hospital. They reported that 57% were considered to be vitamin D deficient (serum 25-OHD < / = 37.5 nmol/L) and 22% were considered to be severely vitamin D deficient (serum 25-OHD levels < / = 20 nmol/L). Their results suggest that vitamin D deficiency is common in general medical inpatients with vitamin D intakes that exceed the recommended daily amounts and in patients without apparent risk factors for vitamin D deficiency.

## Vitamin D recommended daily allowance

“In 1997 new higher recommended adequate daily intakes for vitamin D were established by the Institute of Medicine of the United States National Academy of Sciences. They are:<sup>14</sup>

children and adults to age 50 years: 200 IU/day

men and women aged 50 to 70 years: 400 IU/day

men and women older than 70 years: 600 IU/day

There is some evidence that daily vitamin D input from all sources are in the range of 3000-5000 IU in healthy adults.<sup>4</sup> To ensure 25-OHD serum levels exceed 100 nmol/L a total daily supply of 4000 IU of vitamin D is required.<sup>15</sup> The majority of vitamin D available to healthy adults results from casual exposure to sunlight.

## Exposure to natural sunlight

The high energy ultraviolet B radiation that is primarily responsible for skin problems is the same radiation that produces precholecalciferol in the skin.<sup>3</sup> Clothing absorbs most ultraviolet light, therefore covering the skin with any type of clothing will prevent photosynthesis of precholecalciferol in the skin. Use of a sunscreen with a sun protection factor > 8 will prevent photosynthesis of precholecalciferol in the skin. Glass and most plastics efficiently absorb ultraviolet B radiation.

Direct exposure of uncovered skin to sunlight is necessary for photosynthesis of precholecalciferol to occur in the skin.

## Acceptable serum level for 25-OHD

There is no consensus on the normal value for serum 25-OHD levels.<sup>3,4,14</sup> Most laboratories currently consider the lower end of the normal range for serum 25-OHD to be 37.5 nmol/

L. Several recent reviews agree that there is strong support for considering 80 nmol/L as the lower acceptable limit for serum 25-OHD levels.<sup>3,4,14</sup>

## Vitamin D supplementation and safety issues

“Except in cases of hypersensitivity, there is no evidence of adverse effects with serum 25-OHD levels < 140 nmol/L. A dose of 10,000 IU daily would be required to produce serum 25-OHD levels around 140 nmol/L.”<sup>15</sup> When pharmacologic doses of vitamin D are prescribed follow up monitoring for vitamin D toxicity must include serum and urine calcium levels, which would be elevated and would always be associated with serum 25-OHD levels > 220 nmol/L if the patient were vitamin D toxic. Serum and urine calcium levels should be obtained before starting vitamin D therapy and after several weeks of therapy or any dose increase.<sup>16</sup> Vieth<sup>15</sup> has compiled data describing the effect of vitamin D doses on 25-OHD serum levels, and the relationship between toxic vitamin D doses and 25-OHD serum levels. There are no reported cases of vitamin D intoxication from chronic excessive exposure to sunlight.<sup>3</sup>

## Calcium intake with oral vitamin D therapy

Vitamin D therapy must always be accompanied by an adequate oral calcium intake. An adequate oral calcium intake is 1500 mg daily of elemental calcium.

## Comment

The recent description of persistent, nonspecific musculoskeletal pain associated with vitamin D deficiency in an inner city primary care clinic extends previous reports from elderly housebound, nursing home, and general medical patients. Because of the general belief in the medical community that vitamin D deficiency was eliminated by the United States program of food supplementation, it is rarely considered in the work up for nonspecific musculoskeletal pain syndromes. These

syndromes may occur before the classic clinical presentation of osteomalacia with its well described radiological changes and dull aching bone pain.

The impressive rapid clinical improvement in both pain and myopathy syndromes after treatment with vitamin D provides strong empiric support for obtaining 25-OHD levels in patients with such syndromes and for a therapeutic trial of vitamin D in all such patients with 25-OHD levels below 100 nmol/L.

To my knowledge there are no randomized clinical trials of vitamin D therapy for either nonspecific musculoskeletal pain syndromes or severe proximal muscle weakness. Empiric vitamin D regimens for the treatment of vitamin D deficiency associated with success include ergocalciferol 50,000 IU orally once weekly for eight weeks.<sup>14</sup> Holick<sup>14</sup> recommends 50,000 IU of ergocalciferol orally once or twice a month for the prevention of vitamin D deficiency.

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**EDITOR'S NOTE:**

FROM TIME TO TIME, WE PUBLISH ARTICLES CONTRIBUTED BY IDIS SUBSCRIBERS. AN ARTICLE FROM DAVE MACE, B.S.PHARM., IS INCLUDED IN THIS ISSUE. DAVE MACE IS FROM AN INSTITUTION THAT IS A LONG-STANDING IDIS SUBSCRIBER, UTILIZING THE DATABASE ON A REGULAR BASIS. HIS ARTICLE ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE ARTICLE DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL. WE WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

**About the Author:**

*Dave Mace, R.Ph., Drug Information Specialist, wrote this article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.*



Iowa Drug Information Service

Telephone: 319-335-4800  
 US Toll-Free: 800-525-IDIS  
 Fax: 319-335-4440  
 E-mail: IDIS@uiowa.edu

Web Site: <http://www.uiowa.edu/~idis>



Iowa Drug Information Network

Telephone: 319-335-4199  
 US Toll-Free: 800-525-4347  
 Fax: 319-335-4440  
 E-mail: IDIN@uiowa.edu

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**Division of Drug Information Service**

The University of Iowa  
 100 Oakdale Campus N330 OH  
 Iowa City, IA 52242-5000 USA

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