

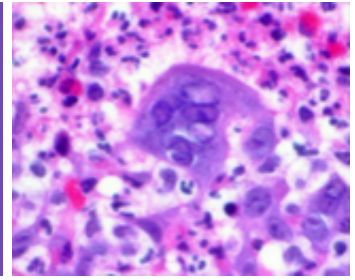


# eLITERATURE REVIEW

## eMedicalDermatology Review

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## Welcome to Volume 2 of eMedicalDermatology Review



With the launch of this issue, we want to welcome back our returning subscribers, say hello to our newly registered clinicians, and thank the more than 2100 of you receiving this issue for your involvement in this program. In Volume 2, we'll continue to provide you with current, clinically relevant data on topics important to helping you improve outcomes in your patients. The topics will be delivered bi-monthly: 6 bi-monthly newsletters and 4 case-based podcasts. Topics will include: Safety of Biologics, Autoimmune disorders, Connective tissue disease, Fillers and others.

[The Program Directors, Author, and Editors of eMedicalDermatology Review.](#)

## September 2009: VOLUME 2, NUMBER 1

### *Health Implications of Vitamin D*

#### In this Issue...

Vitamin D deficiency has been shown to have important health consequences, both skeletal and nonskeletal in nature. Since vitamin D deficiency has been associated with increased rates of certain types of cancer, as well as with other diseases such as multiple sclerosis and type 1 diabetes, it is important for clinicians to discuss adequate vitamin D intake with their patients. Although sun exposure has been clearly linked to an increased risk for skin cancer, including melanoma, emerging data indicate that vitamin D, which can be produced in the skin by ultraviolet B (UVB) light, may also have a protective effect in terms of skin cancer risk. Moderate, sensible sun exposure may be a component in the maintenance of adequate vitamin D levels in some patients.

In this issue, we discuss recent publications that review the definition, prevalence, metabolism and function of vitamin D; the relationship between vitamin D and melanoma; the effects maternal vitamin D intake during pregnancy; vitamin D therapy for patients with cystic fibrosis; and the long-term use of calcitriol ointment for the treatment of mild to moderate plaque psoriasis.

## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Discuss the importance of vitamin D in skeletal and nonskeletal health
- Summarize what is known about the relationship between vitamin D and melanoma
- Describe how topical vitamin D can be used for the treatment of certain skin disorders

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#### Length of Activity

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 1 contact hour Nurses

#### Release Date

September 22, 2009

#### Expiration Date

September 21, 2011

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**Dr. Long** has disclosed no relationships with commercial supporters.

### ***Unlabeled/Unapproved Uses***

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## COMMENTARY

In the 2007 article by Holick, reviewed in this issue, the author notes that vitamin D deficiency is widespread and has important health consequences related to increased risk for osteoporosis, as well as for certain types of cancer and other disorders. Since a limited number of naturally occurring and fortified sources of vitamin D are available in the diet, other sources of vitamin D become necessary. The sun can be a significant source of vitamin D, depending on the time of year, a person's skin pigmentation, and latitudinal location of residence. Sun avoidance and the use of sunscreens that block UVB rays are likely contributing to the prevalence of vitamin D deficiency.

As recently reported by Egan and reviewed in this issue, the lifetime risk for melanoma is increasing. Interestingly, a 2007 meta-analysis found that there was no overall significant effect of sunscreen use on the risk for melanoma.<sup>1</sup> The same study revealed that a latitude of >40° and use of sunscreen were both associated with an increased risk for melanoma.<sup>1</sup> This is consistent with the notion that higher vitamin D levels may lower an individual's risk for melanoma and improve patient outcomes, as those living at higher latitudes are more likely to be vitamin D-deficient. The fact that many sunscreens in the United States block only UVB rays is of concern, since this allows for longer exposure to ultraviolet A (UVA) rays, which are now also thought to contribute to the development of melanoma.

The potential role played by vitamin D in decreasing the risk for melanoma is exciting. However, although one large case-control study found a reduced risk for melanoma

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associated with dietary vitamin D intake, the results of several other studies evaluating vitamin D intake and melanoma risk have been disappointing.<sup>2</sup> A prospective cohort study conducted in 2009 found no decreased risk for melanoma with higher vitamin D intake; however, the total vitamin D intake in this study was relatively low—that is, 132 IU in the lowest quartile and 680 IU in the highest.<sup>2</sup> Therefore, the effect of higher doses of vitamin D on melanoma risk remains unknown.<sup>2</sup> Studies evaluating vitamin D intake and melanoma risk have been limited by lack of data with respect to serum 25-hydroxyvitamin D levels. Perhaps there is a more direct relationship between higher serum 25-hydroxyvitamin D levels and decreased risk for melanoma. Conversely, a few studies have suggested increased melanoma risk with higher vitamin D intake from foods.<sup>2</sup>

Additionally, vitamin D has been found to play an important role in the innate immune system, including the development of antimicrobial peptides produced in leukocytes and on epithelial surfaces.<sup>3</sup> The only human cathelicidin, hCAP-18, has a defined vitamin D-dependent mechanism, and may be the link between higher 25-hydroxyvitamin D levels and decreased risk for upper respiratory tract infections and early childhood wheezing.<sup>3</sup> Although data regarding vitamin D and asthma remain conflicting, Erkkola and colleagues illustrated that vitamin D levels may be particularly relevant in utero. In this study, higher maternal intake of vitamin D was associated with lower rates of asthma and allergic rhinitis at 5 years of age. No effect was found with respect to the incidence of eczema, however. Again, the average daily intake of vitamin D in this study was low, at 260 IU. Optimal vitamin D supplementation during pregnancy may have positive health consequences for children. This area requires additional study and is particularly relevant, as a 2007 study found that in the Northeast, a significant percentage of mothers and neonates have low vitamin D levels at birth.<sup>4</sup>

Khazai and associates examined the efficacy of oral vitamin D vs UV light for the treatment and prevention of vitamin D deficiency in patients with cystic fibrosis (CF). Individuals with CF have high rates of vitamin D deficiency because of poor fat absorption and decreased sun exposure. Low bone mineral density in CF patients is associated with diminished lung function. In non-CF patients, vitamin D insufficiency has a direct relationship with poor lung function, and vitamin D has been shown to improve insulin sensitivity, both salient issues for CF patients. Weekly administration of oral vitamin D3 was found to be the most successful regimen, compared with treatment with oral vitamin D2 or UV light. The UV light group was hindered by noncompliance; however, even when those patients were excluded, the oral D3 therapy group had the highest increase in serum 25-hydroxyvitamin D levels. These findings are in agreement with earlier studies that demonstrated the superiority of vitamin D3 to vitamin D2 for the treatment of vitamin D deficiency.<sup>6,7</sup> More recent studies from 2008 have shown smaller daily doses of vitamin D2 (1000 IU) to be equivalent to doses of vitamin D3 (1000 IU).<sup>5</sup> Extending these findings to patients without CF, oral vitamin D supplementation appears to be superior to indoor UV light therapy for maintaining adequate vitamin D levels.

In their review, Lebowitz and coworkers present recent safety data regarding the use of calcitriol ointment in patients with plaque psoriasis, and illustrate the role of topical vitamin D therapies in the treatment of skin diseases.

The area of research surrounding vitamin D use is expanding rapidly, including its relationship with skin disease, particularly nonmelanoma and melanoma skin cancer. It is important to be aware of the risk factors for vitamin D deficiency, as well as the fact that a significant proportion of the population has suboptimal vitamin D levels. As the link between disease and vitamin D deficiency is convincing, it is therefore essential that we counsel our patients to receive adequate vitamin D. It has become clear that even "healthy" diets do not provide adequate amounts of vitamin D and that oral vitamin D supplements are necessary. Sensible outdoor sun exposure (UVB) can be a significant source of vitamin D, and may be a reasonable option for those patients without a personal or family history of melanoma and who do not burn easily. Depending on latitudinal location, 15 to 30 minutes outside twice per week without sunscreen in the summer months may be a reasonable way for some patients to maintain healthy vitamin D levels. However, oral vitamin D supplements would still be necessary in wintertime. Clearly, this is not the best option for those who are dark-skinned, as they may require 6 to 7 times that exposure to produce the needed amount of vitamin D, or for the elderly,

who lose 70% of their ability to make vitamin D in the sun as they age. Every patient should be considered on an individual basis, and additional investigation is warranted to determine the optimal vitamin D regimen for obtaining the greatest health benefits.

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## VITAMIN D DEFICIENCY

Holick MF. **Vitamin D deficiency** *N Engl J Med.* 2007;357(3):266-281.

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In 2007, Holick reviewed the prevalence and definition of vitamin D deficiency. The author outlined the metabolism and function of vitamin D, along with what is known about the relationship of vitamin D to multiple health problems, both skeletal and nonskeletal in nature. He discussed sunlight and UVB radiation as a source of vitamin D.

Serum level of 25-hydroxyvitamin D is used to define vitamin D status. A 25-hydroxyvitamin D level of  $\geq 30$  ng/mL is considered sufficient. One billion people worldwide are deficient in their levels of vitamin D. National Health and Nutrition Examination Survey (NHANES) data indicate that 42% of black girls and women are vitamin D-deficient. Studies have also demonstrated a high prevalence of vitamin D deficiency in the elderly, in Caucasian preadolescent girls, and in populations who shield their skin from the sun. An intake of 700 to 800 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> is necessary to reduce a person's risk for nonvertebral and hip fractures.

The active form of vitamin D controls genes responsible for cellular proliferation, differentiation, apoptosis, and angiogenesis, and is also a potent immunomodulator. Vitamin D deficiency is associated with a 30% to 50% higher risk for colon, prostate, and breast cancer, as well as higher mortality from these cancers. Vitamin D deficiency is also associated with a higher risk for multiple sclerosis, Crohn's disease, and type 1 diabetes. Low vitamin D levels have been shown to increase insulin resistance, decrease insulin production, and be associated with the metabolic syndrome. Additionally, vitamin D deficiency is associated with congestive heart failure and increased blood levels of inflammatory factors. Children born to inner-city women with vitamin D deficiency are at increased risk for wheezing illnesses.

There are multiple causes of vitamin D deficiency, with the most common including reduced skin synthesis due to sunscreen use, skin pigmentation, latitude of a person's



residence, or aging. Obesity is also a risk factor, as vitamin D is sequestered in adipose tissue and is less bioavailable. Breastfeeding is a risk factor as well, since breast milk contains relatively low levels of vitamin D.

The author of this study indicates that the current recommendations for daily vitamin D intake of 200 IU in children and adults up to 50 years of age, 400 IU for adults 51 to 70 years of age, and 600 IU for those 71 years of age or older are inadequate. Holick lists a number of strategies for the prevention and treatment of vitamin D deficiency, including daily, weekly, or monthly doses of vitamin D supplements. He states that sensible sun exposure can provide an adequate amount of vitamin D<sub>3</sub>, depending on the time of year and latitude.

Vitamin D deficiency is a widespread and significant health problem, as it is associated with a higher risk for certain cancers, and such other diseases as multiple sclerosis and type 1 diabetes. Humans obtain vitamin D from sunlight, diet, and dietary supplements. There are few foods that naturally contain or are fortified with vitamin D. It is therefore difficult, even with a "healthy" diet, to maintain adequate vitamin D levels. Holick emphasizes that the skin has a great capacity to make vitamin D, even in the elderly. Both sensible sun exposure and the use of dietary supplements are necessary for the maintenance of adequate vitamin D levels.

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## VITAMIN D AND MELANOMA RISK

Egan KM. **Vitamin D and melanoma.** *Ann Epidemiol.* 2009;19(7):455-461.

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Egan reviewed the available data regarding the relationship between vitamin D and melanoma. Melanoma is the sixth most common cancer diagnosis in the United States. UVB (>280 to 315 nm) exposure is associated with the development of melanoma and nonmelanoma skin cancer (NMSC). Emerging evidence indicates that longer-wave UVA (320 to 400 nm) also contributes to the incidence of skin cancer. Although UVB is efficiently absorbed by DNA, UVA is absorbed poorly by DNA but can penetrate deeper into the skin to the approximate depth of the epidermal/dermal junction, where the melanocytes reside. Currently, many of the sunblocks available in the United States protect against UVB only.

Keratinocytes and other cells in the epidermis synthesize the active form of vitamin D, 1,25-dihydroxyvitamin D. The vitamin D receptor (VDR) is present in melanocytes and melanoma cells. Studies have shown that 1,25-dihydroxyvitamin D inhibits cell proliferation, and induces differentiation in melanoma cells and those expressing the VDR. Local skin production of active vitamin D also influences the innate and acquired immunity of the skin, as well as the inflammatory response of the skin to sun damage. In vitro treatment with 1,25-dihydroxyvitamin D was shown to protect primary human keratinocytes against the induction of cyclobutane pyrimidine dimers, the principal mutation in UVB carcinogenesis. Cyclobutane pyrimidine dimers are found in 90% of squamous cell carcinomas and 50% of basal cell carcinomas, but rarely in melanomas.

Observational studies have shown a clear relationship between sun exposure and risk for melanoma and NMSC, but this relationship is less direct for melanoma. Basal cell and squamous cell cancers occur in chronically sun-exposed skin, whereas melanoma often develops on body sites that receive intermittent sun exposure (or no exposure). A history of sunburn has consistently been linked to melanoma, but cumulative lifetime sun exposure does not appear to be a risk factor. Interestingly, outdoor workers have lower-than-expected rates of melanoma, and Egan suggests that this may be related to higher

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circulating 25-hydroxyvitamin D levels. However, outdoor workers are more likely than indoor workers to have melanoma in chronically sun-exposed sites.

Melanoma occurring on body sites that receive intermittent sun exposure most often shows mutations in *BRAF* and/or *NRAS*, which is in contrast to melanoma occurring on chronically sun-exposed skin, which does not exhibit these mutations.

Egan cites a quantitative review from 2007 that concluded there is no overall association between the regular use of sunblock and melanoma risk. The author suggests that this lack of a protective effect of sunblock toward melanoma risk may be due to more prolonged UVA exposure and decreased skin production of vitamin D, as sunscreens in the United States block mainly UVB rays. A positive association has been reported between sunbed exposure and melanoma risk. Modern sunbeds emit 95% UVA rays, the intensity of which may be 10 to 15 times higher than midday sun, in powerful tanning units. Studies examining vitamin D from the perspective of diet and melanoma incidence have shown varying results. Studies have also analyzed several common polymorphisms in the VDR in relation to melanoma risk, aggressiveness, and prognosis. Evidence supports the fact that carriers of the less active (f) allele of *Fok1* (*F/f*) are at modestly elevated risk for melanoma, as are homozygous carriers of b, a, or T alleles of the *Bsm1*, *Taq1*, and *Apa1* restriction fragment length polymorphisms.

Although melanoma rates are much lower among non-Caucasians than among Caucasians in the United States, their 5-year survival rates are lower: 75% vs 93%, respectively. Blacks are more likely to be diagnosed with acral subtypes or melanoma at higher stages of disease. After adjusting for stage, African Americans with melanoma still have a poorer outcome. Egan states that it is not known whether the higher prevalence of vitamin D deficiency in African Americans is associated with their poorer outcomes.

It is unclear whether those with higher ambient biologically effective UVB doses have a better melanoma survival rate in the United States. Studies have shown a more favorable prognosis in patients with melanoma arising in chronically sun-exposed skin. This may be due to higher local levels of 1,25-dihydroxyvitamin D. However, this is not supported by the fact that melanoma on the neck or scalp, which are chronically sun-exposed sites, have worse survival rates than does melanoma on the trunk or extremities.

Sun exposure is clearly an important risk factor for melanoma. Studies are needed for evaluating serum 25-hydroxyvitamin D concentrations and melanoma risk, as well as for devising prevention strategies. The author concludes that the outcome of UV exposure with respect to melanoma incidence most likely depends on a balance between beneficial and harmful effects of UV. VDR polymorphisms may have an effect on this balance. UVA may contribute to the development of melanoma, which is particularly relevant, as a majority of sunblocks in the US protect against UVB only.

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## MATERNAL VITAMIN D INTAKE DURING PREGNANCY AND RISK FOR ASTHMA AND ALLERGIC RHINITIS

Erkkola M, Kaila M, Nwaru BI, et al. **Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children.** *Clin Exp Allergy*. 2009;39(6): 875-882.

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Erkkola and colleagues examined the effect of maternal intake of vitamin D during pregnancy on the risk for asthma, allergic rhinitis, and atopic eczema by 5 years of age in a cohort of children with major histocompatibility complex, class II, DQ beta 1, an HLA haplotype that increases susceptibility to type 1 diabetes. Validated questionnaires were used at 5 years of age in 1669 children to assess for asthma, allergic rhinitis, and atopic eczema. Maternal diet was evaluated by a food-frequency questionnaire, and vitamin D intake was divided into quartiles.

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The authors reported an inverse association between dietary vitamin D intake and total vitamin D intake during pregnancy, and risk for asthma and allergic rhinitis, in offspring at 5 years of age, even after adjusting for potential confounders. Interestingly, vitamin D supplements alone were not associated with any outcome. The investigators did not find a statistically significant association between maternal vitamin D intake and atopic eczema at 5 years of age in these children.

The results of this study are in agreement with those of 2 earlier cohort studies demonstrating that maternal vitamin D intake is inversely associated with wheezing in offspring.<sup>1,2</sup> These studies did not find an association between maternal vitamin D intake and risk for respiratory infections, eczema, or atopic sensitization. Conversely, a UK birth cohort study found that children born to women with the highest vitamin D levels during late pregnancy were more likely to have visible eczema by 9 months of age and to have reported asthma by 9 years of age.<sup>3</sup> Additionally, in a 1966 birth cohort study in Finland, infants given 2000 IU of vitamin D by mouth daily for the first year of life were more likely to develop atopy, allergic rhinitis, and asthma by 31 years of age.<sup>4</sup> These patients were also shown to have a much lower risk for type 1 diabetes.

It is important to note that the average total daily intake of vitamin D in Erkkola's study was relatively low at 260 IU. Moreover, data regarding serum 25-hydroxyvitamin D levels in mothers and children are unavailable. The children's vitamin D intake was also not included in the authors' analysis because of lack of data, which may be a confounding variable.

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## EFFICACY OF ORAL VITAMIN D AND UV LIGHT THERAPY IN PATIENTS WITH CYSTIC FIBROSIS

Khazai NB, Judd SE, Jeng L, et al. **Treatment and prevention of vitamin D insufficiency in cystic fibrosis patients: comparative efficacy of ergocalciferol, cholecalciferol, and UV light**. *J Clin Endocrinol Metab*. 2009; 94(6):2037-2043.

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Khazai and coworkers sought to compare the efficacy of 3 regimens of vitamin D therapy in patients with cystic fibrosis (CF), who are known to have a high prevalence of vitamin D deficiency due to fat malabsorption and lack of sunlight. The 3 treatment arms were (1) cholecalciferol (D3) 50,000 IU orally once per week; (2) ergocalciferol (D2) 50,000 IU orally once per week; and (3) UV light therapy to the lower back in a seated position, with a portable UV indoor tanning lamp at a distance of 14 inches, for 3 to 10 minutes (depending on skin type) 5 times per week. Efficacy of the 3 treatment regimens was evaluated with parathyroid hormone and serum 25-hydroxyvitamin D levels at baseline, and after 12 weeks of therapy.

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A total of 30 patients with CF participated in this study; 68% were vitamin D-insufficient at baseline (25-hydroxyvitamin D levels <30 ng/mL). Mean baseline 25-hydroxyvitamin D levels did not differ among the groups. Both oral forms of vitamin D increased serum 25-hydroxyvitamin D levels; however, the net increase was much larger in the D3-treated group— $25.3 \pm 2.8$  ng/mL—compared with  $8.8 \pm 2.8$  ng/mL in the D2-treated group. Among patients in the D3-treated group, 100% achieved vitamin D sufficiency, compared with 60% of those in the D2-treated group. Of note, the D2-treated group experienced a decrease in serum 25-hydroxyvitamin D3 concentrations. Moreover, the UV light group had a net increase in 25-hydroxyvitamin D levels of only  $5.2 \pm 3.4$  ng/mL, which was not significant. It is important to note that although 80% of the patients were compliant with the oral regimen, only 55% were compliant with UV therapy. Examining the data from the 5 out of 9 patients who were compliant with UV therapy, the rise in 25-hydroxyvitamin D levels was similar to that observed in those treated with D2 (ie, 11 ng/mL).

Both oral vitamin D2 and vitamin D3 were effective in raising 25-hydroxyvitamin D levels—D3 more than D2. Overall, the use of UV light therapy was limited by poor compliance, but was found to be equivalent to vitamin D2 after excluding noncompliant subjects. The authors noted a confounding variable—the fact that the D3 and D2 capsules contain different carriers—that is, powder-based vs oil-based, respectively.

These findings are consistent with those from previous studies showing that vitamin D3 is superior to vitamin D2 in increasing serum 25-hydroxyvitamin D levels.<sup>1,2</sup> More recent studies have shown that lower daily doses of vitamin D2 (1000 IU) are equivalent to the same dose of vitamin D3 (1000 IU).<sup>3</sup> The authors suggest that a possible explanation for this divergence is the fact that vitamin D3 binds more avidly to vitamin D-binding protein (DBP), which confers a longer circulating half-life, especially when administered in larger doses.

The authors raise a potential concern regarding the decrease in serum 25-hydroxyvitamin D3 levels after treatment with vitamin D2. They note that the primary circulating form of 25-hydroxyvitamin D is D3, which is produced in the skin and contained in most dietary sources. Ergocalciferol (D2) is the most commonly available prescription form of vitamin D in the United States. The authors agree with those who have suggested that ergocalciferol not be used as a supplement for the treatment of vitamin D insufficiency.

Depending on latitude, many people in Europe and the United States can only generate vitamin D from the sun in the summer months. This article explores the idea of using UV light to generate vitamin D. In addition to the cost of a portable indoor UV tanning lamp, this study illustrates that compliance with such a regimen is limited. Even after excluding patients who were noncompliant with UV light therapy, the increase in 25-hydroxyvitamin D levels was not as large as in the D3-treated group. It is possible that UV light therapy could be equivalent to vitamin D3 therapy if a larger surface area of the skin was exposed, along with an increased frequency and duration of UV light.

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# TOPICAL VITAMIN D THERAPIES IN PATIENTS WITH MILD TO MODERATE PLAQUE PSORIASIS

Lebwohl M, Ortonne JP, Andres P, Briantais P. **Calcitriol ointment 3 µg/g is safe and effective over 52 weeks for the treatment of mild to moderate plaque psoriasis.** *Cutis.* 2009;83(4):205-212.

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Lebwohl and associates conducted an open-label, multicenter trial to evaluate the safety of long-term use of calcitriol ointment 3 µg/g for the treatment of mild to moderate plaque psoriasis.

The study included 324 participants; of these, 233 completed at least 180 days of treatment and 136 completed 52 weeks. The proportion of study patients with clear or minimal psoriasis increased over time—from 11.1% during the first 3 months, to 22.1% during the third to sixth months, to 37.3% during the sixth to ninth months, to 47.1% during the ninth to twelfth months. A marked improvement was noted by 52.6% of the participants at 26 weeks and by 63.8% at 52 weeks. Mean body surface area affected also decreased over time. Adverse events associated with study treatment were noted in 13.9% of the participants. No serious adverse events were considered to be related to the study drug. Pruritus and folliculitis were the most common dermatologic adverse events, each reported in 3.1% of the participants. In all, 8 patients discontinued the study because of adverse events—4 related to the study treatment (irritant dermatitis, pruritus, kidney pain, and urine abnormality). A total of 10 (3.1%) of the patients experienced ≥1 episode of hypercalcemia, which was not associated with treatment duration. In all but 1 participant, the calcium value was within 5% of the upper limit of the reference range. A total of 11 (3.4%) of the patients experienced hypercalciuria during the study.

The study findings are consistent with those from several earlier studies that have shown the safety and tolerability of calcitriol ointment 3 µg/g, which is now approved by the US Food and Drug Administration for the treatment of mild to moderate plaque psoriasis in patients ≥18 years of age. It is important to note that this study was funded by Galderma Laboratories, the manufacturer of calcitriol ointment. For the treatment of psoriasis symptoms, calcitriol ointment may be an improved alternative over calcipotriene (synthetic vitamin D3 product), which has been shown to cause skin irritation in approximately 20% of treated patients. A previous randomized, investigator-blind, left-right comparison study conducted in 2003 demonstrated that calcitriol ointment caused less irritation in sensitive skin areas than did calcipotriene; however, both agents were found to be equally effective.<sup>1</sup>

## References

1. Ortonne JP, Humbert P, Nicolas JF, et al. [Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg q\(-1\) ointment and calcipotriol 50 microg q\(-1\) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas.](#) *Br J Dermatol* 2003;148:326-333

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