Vitamins As Therapy In The 1990s

Randall Swain, MD, and Barbara Kaplan, PharmD

Background: **At one time vitamins were considered as essential nutrients needed only in very small amounts to prevent deficiency syndromes. Many vitamins and their derivatives, however, are currently being used in the mainstream of medicine as therapeutic modalities.**

Methods: **A MEDLINE literature search for clinical reviews and original studies on the use of vitamins in medicine was conducted along with a search of the obtained papers' bibliographies. The primary years of search were 1990–1994. Research reports written before 1990 were used after cross-referencing from more recent articles.**

Results and Conclusions: **Based on the literature review, several recommendations for the use of vitamins for treatment and prevention are presented. They include topical vitamin A derivatives (tretinoin) for the treatment of acne and age-related skin damage, oral vitamin A derivatives for severe cystic acne (isotretinoin) and psoriasis (etretinate), vitamin D_3 for the treatment and prevention of osteoporosis in postmenopausal females, topical vitamin D in psoriasis patients, and niacin for serum cholesterol reduction. Folate appears to decrease the incidence of neural tube defects if given in the preconception phase of pregnancy. Finally, recent preliminary evidence suggests the possible benefit of antioxidants (vitamins C, E, and beta-carotene) in the prevention of atherosclerosis and cancer. (J Am Board Fam Pract 1995; 8:206-16.)**

Recently the lay press has emphasized vitamins as the panacea for the 1990s. In fact, physicians often see results of the latest vitamin study first on the evening news before it appears in any journal, and after critical review the reader might find that particular study shows only a possible epidemiologic association. Vitamins are widely used by the American public. Annual sales of over-the-counter vitamin products are in excess of $3 billion.[1] What are the true medical indications for using vitamins as therapy? Our purpose is to review the current indications and uses of vitamins as therapy for some select medical conditions, including acne, psoriasis, osteoporosis, and hypercholesterolemia. We will also critically review recent studies on the antioxidants and assess their usefulness for clinical practice for the primary care physician.

Methods

A literature search was conducted using MEDLINE to select clinical reviews and original studies on the use of vitamins in medicine. The years covered were 1990 to 1994. The key words employed were "vitamins," "antioxidants," "cancer prevention," "skin diseases," and "hypercholesterolemia." Research articles published before 1990 were cited after cross-referencing from more recent articles.

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From the Department of Family Medicine and Sports Medicine (RS), and the Department of Clinical Pharmacy (BK), West Virginia University – Charleston Division. Address reprint requests to Randall Swain, MD, Department of Family Medicine, West Virginia University – Charleston, 1201 Washington Street East, Suite 108, Charleston, WV 25301.

Skin Conditions and Vitamin Therapy

Acne

Although not a disabling condition, acne vulgaris is almost universal in the teenage population and results in much social and psychological concern. Topical retinoic acid, or tretinoin (Retin-A), is a derivative of vitamin A that has been used for this condition since its introduction in liquid form in 1971. Acne is thought to be caused by excess sebum production, keratinization disorders, and increases in the bacteria *Propionibacterium acnes*.[2] Most other nonvitamin therapies only address sebum production by utilizing drying agents (alcohol, benzoyl peroxide) or focus on bacteria control with antibiotics either topically (benzoyl peroxide, erythromycin, clindamycin) or orally (erythromycin, tetracycline). Often patients improve, but relapse is common.

When a patient with acne is examined, the physician looks at the face to see whether inflammation predominates. The back and chest are also examined for inflammation. Topical agents that are applied to the face are not effective once

systemic involvement occurs. If local inflammation exists, local antibiotics can be useful; if general inflammation exists, a systemic antibiotic is often necessary.

Most cases of acne will benefit from topical application of tretinoin. This agent works by normalizing the keratinization process of the pilosebaceous unit and helps prevent obstruction of the follicular unit. Therapy is begun with the 0.025 percent formulation, and a small amount is applied to the face at bedtime. The beneficial effects often take several weeks and initially can make the condition mildly worse as the old follicles are replaced. Side effects are mild but include some stinging and reddening of the treated areas and possible photosensitivity. Treatment can sometimes require stronger formulations (0.05 percent, 0.1 percent) or can occasionally be decreased to three times a week. The regimen will vary with each patient.

Although topical tretinoin cream is helpful for severe cystic acne, it might not be sufficient, even for those treated concurrently with antibiotics. If these more conservative approaches fail, use of systemic vitamin A derivatives has been effective. The preparation being used widely now is isotretinoin (Accutane). The dosage is initially begun at 0.5 mg/kg to 1.0 mg/kg divided into two doses. The maximum recommended dose is 2 mg/kg/d. The tablets come in 10-mg, 20-mg, and 40-mg capsules. Usually, a 50 percent reduction in the number of facial lesions is evident after 2 months, and the same reduction is seen in other parts of the body at 3 months. Treatment course usually lasts 4 to 6 months and improves the condition by an average of 85 percent. Beneficial effects often last many months after discontinuation. If, 2 months after discontinuing isotretinoin, further treatment is needed, then a repeat course can be considered. A recent 9-year follow-up study showed that only 23 percent required retreatment with isotretinoin and that 61 percent of those treated initially were still clear.[3]

Unfortunately, side effects are not uncommon, and close monitoring must be maintained for those receiving isotretinoin therapy. Transient abnormalities of liver function tests, lipids, and glucose can occur during therapy, and routine testing is often performed monthly by physicians. Much more common are the following mucocutaneous side effects, which occur in up to 90 percent of patients receiving isotretinoin: cheilitis (dry, blistering lips), dry eyes or nose, eye irritation, pruritus, epistaxis, mild alopecia, and some photosensitivity.[4] Sometimes patients are unable to wear prescription contact lenses as a result of these types of side effects.

Other more rare side effects can include pseudotumor cerebri, premature epiphyseal closure, and birth defects.[5] The teratogenicity of this drug has been well documented, and most physicians will require documentation that absolute birth control is being practiced throughout the treatment course.[6] Often in female patients the physician will obtain serial pregnancy tests with the other required blood work. The risk of birth defects is extreme; about 30 percent of women who become pregnant during treatment will have abnormal fetal development. Defects are widespread and include craniofacial, cardiac, and central nervous system abnormalities. The manufacturer recommends that women of childbearing age practice contraception during treatment and for 1 month before and 1 month after treatment with isotretinoin. In addition, many physicians advise a pregnancy test 2 weeks before initiating therapy.

Sun-damaged and Aging Skin

Within the last several years much publicity regarding the positive effects of topical tretinoin on sun- and age-related damage to the skin has been generated. Multiple, well-controlled studies have been performed on elderly patients and have shown that topical tretinoin can reverse skin wrinkling, thickening, and sagging, reduce the number of senile lentigines (brown liver spots), and reduce numbers and sizes of actinic keratoses that are considered to be precancerous.[7-9] Not only is there subjective improvement, but pathologic improvement has also been observed on skin biopsies, i.e., a decrease in the amount of type I collagen formation.[10]

Therapy is prescribed in a manner similar to that for patients who use isotretinoin for acne; however, most physicians suggest that 3 times a week dosing is optimal. Often elderly patients will require only the 0.025 percent preparation. Side effects, as mentioned previously, include skin redness and photosensitivity. A sunscreen is advised during outside activities. Apparently a new retinoid, arotinoid methyl sulfone, is as effective as

topical tretinoin but causes much less scaling and local irritation. This product, however, is not currently available in the United States.[9,11]

Psoriasis

Psoriasis is a dermatologic disorder classified in the group of papulosquamous diseases. It is a chronic condition causing large red plaques with considerable amounts of scale. The lesions usually appear on the scalp, elbows, knees, and the gluteal folds. Often the lesions are present in a linear fashion, called Koebner phenomenon, and nail pitting is present in most patients. The disorder is a lifelong process with constant changes in the numbers and sizes of skin lesions. The cause of psoriasis is poorly understood; however, 30 percent of patients have a family history of the disease. Treatment in the past has included topical tars, which are quite messy, topical anthralin, psoralens with ultraviolet light (so-called PUVA therapy), and methotrexate. Considerable utilization of potent topical corticosteroids has also been necessary in the past.[12]

Recently a topical derivative of vitamin D has been approved by the Food and Drug Administration (FDA) for use in psoriasis patients (calcipotriene [Dovonex], 0.005 percent ointment). Although its mechanism of action is not well understood, it probably involves the normalization of cell proliferation.[13] In double-blind, placebo-controlled studies on patients with mild to moderate psoriasis, topical calcipotriene, when applied twice daily, was effective at clearing the plaques of psoriasis.[14-16] These improvements were detectable within 1 to 2 weeks, while maximum effects were observed at 6 to 8 weeks. Up to 63 percent of the patients treated experienced marked improvement.

When compared with betamethasone valerate ointment (0.1 percent), a high-potency topical corticosteroid, calcipotriene was shown to be slightly more effective, although both agents were highly efficacious.[17,18]

Side effects of topical calcipotriene are few. The most common problem is skin irritation, which was observed in 5 to 10 percent of patients. In most patients the local irritation resolved despite continued treatment.[19] Facial regions are particularly prone to this irritation; therefore, treatment is not recommended for the face. Good hand-washing is also advised, as irritation can result from transferred ointment. Studies have been conducted for up to 1 year with no other adverse effects noted and no loss in potency.[19] Unfortunately, two case reports have noted serum hypercalcemia after large amounts of the ointment were used in a short amount of time (4, 100-mg tubes in 10 days; and 2, 100-g tubes in 7 days).[20] As a result, a maximum of a 100-g tube per week has been recommended. Patients should be instructed to apply a thin layer to the affected skin twice daily and to rub it in gently and completely. In a double-blind, placebo-controlled study of psoriasis patients using topical calcipotriene, patients had no change in calcium levels,[21,22] so abnormal serum calcium metabolism should be a rare finding. In summary, topical calcipotriene appears to be a rational first-line for mild to moderate psoriasis. Primary care physicians should be comfortable prescribing this agent, because it is so nontoxic; however, base-line and periodic calcium determinations should probably be made, especially with patients who have extensive areas of involvement.

For severe psoriasis researchers have sought alternatives to oral methotrexate and oral bursts of prednisone, because of the toxic side effects of these medications. Another derivative of vitamin A, systemic etretinate, has been used with success in pustular, erythrodermic, and plaque-type psoriasis as well as psoriatic arthropathies.[23] The problem with all of the systemic vitamin A compounds, however, is a narrow therapeutic index and high potential for teratogenesis. Another problem with etretinate is that the half-life in some can be as long as 120 days.[24] The manufacturer recommends contraception for 2 years after use of this product.

Isotretinoin (Accutane) has little effect on psoriasis unless used with psoralens combined with ultraviolet light (PUVA).[25] Etretinate (Tegison) is often effective as monotherapy for pustular and erythrodermic psoriasis at a recommended starting dose of 0.75 to 1 mg/kg/d in divided doses with a maximum of 1.5 mg/kg/d. Erythrodermic psoriasis might respond to lower initial doses, e.g., 0.25 mg/kg/d. Attempts should be made to lower the maintenance dose to 0.5 to 0.75 mg/kg/d after 8 to 16 weeks of therapy.[23] Therapy is usually discontinued when the patient's lesions have sufficiently resolved. Etretinate can cause a transient exacerbation of psoriasis during the initial period

of therapy. In addition, patients should be counseled to administer this drug with food, which increases the absorption. Often for plaque-type psoriasis, monotherapy with etretinate is not sufficient. In his review,[23] Fritsch states that only slightly more than one-half of patients show a 75 percent response after 8 weeks of treatment. Often, combinations with topical corticosteroids, tar, anthralin, ultraviolet light B (UVB), and PUVA are necessary. Methotrexate is not recommended in combination with etretinate because of the combined risk of liver toxicity. After 3 to 4 weeks, any psoriatic-associated joint symptoms are often decreased.

In contrast to retinoids used for the short-term treatment of acne (maximum of 6 months), one problem with the use of etretinate for psoriasis is the chance of long-term toxicities. In a review on the subject, Vahlquist[26] stated that the three main at-risk organ systems are the liver, the musculoskeletal system, and the cardiovascular system. The liver can be directly adversely affected by etretinate, and chronic hepatitis might result. Risk factors for liver toxicity include previous toxicity with vitamin A derivatives, liver disease, and severe obesity. Monitoring liver function tests is recommended as well as avoiding alcohol. Prompt discontinuation of the drug should occur if the results of liver function tests are markedly abnormal (greater than three times the upper limits of normal). Musculoskeletal side effects include myalgias, diffuse idiopathic skeletal hyperostosis, premature epiphyseal closure, and extraskeletal ossification. The exact incidences of these findings have not been established. Vahlquist recommended minimizing dose and duration of therapy with etretinate, avoiding prescribing the drug for children who have open epiphyses, and monitoring the patient's skeletal system with radiographic studies every 2 to 3 years. The major cardiac problems are produced by the ability of the drug to decrease high-density lipoprotein (HDL) cholesterol and to increase low-density lipoprotein (LDL) cholesterol, which might increase the patient's chance for premature cardiovascular disease.[27] Monitoring periodic lipid levels is suggested.

Because of the potential adverse effects, it appears that long-term treatment with etretinate is probably best left to dermatologists; they are prepared to handle the many complications associated with treatment and the need for adjuvant therapies. In rural areas, however, where health care access is difficult, it would be appropriate to work with a specialist to administer care to a patient under this regime.

Osteoporosis and Vitamin D

Since its role in the pathogenesis of rickets was elucidated, vitamin D has long been known to be associated with aspects of bone health. The main function of this vitamin in humans is the maintenance of intra- and extra-cellular calcium levels. Most humans are able to meet the daily requirements of vitamin D by being exposed to sunlight for 5 to 10 minutes, 4 to 5 times per week. What role vitamin D plays in those with osteoporosis is unclear. It is known that active vitamin D metabolites are found to be 30 percent lower in women with postmenopausal osteoporosis than in their age-matched counterparts without osteoporosis.[28] One hypothesis for how vitamin D might help prevent bone calcium loss is that vitamin D derivatives increase absorption of calcium in the small intestine.

Earlier trials using calcitriol (1, 25-dihydroxy vitamin D_3), an active metabolite of vitamin D, have been inconsistent. Two out of nine studies[29,30] showed a decrease in bone mass, and three other studies revealed increased bone mass.[31-33] The remaining three studies done with calcitriol showed no difference in bone mass or fracture rate.[34-36] Only the studies by Gallagher, et al.[32] and Tilyard, et al.[37] showed any decrease in fracture rates; however, Tilyard, et al.[37] have appropriately recognized that there were many differences between all these studies. They cite differences in enrollment criteria, dosage of calcitriol, and efficacy criteria. The main discrepancy appeared to have been the small numbers in most studies, leading to possible inaccuracies attributable to low statistical power. Also, many of these researchers looked at bone mass rather than fracture rate as an endpoint. It can be expected that most patients with postmenopausal osteoporosis will continue to lose bone mass under treatment, although perhaps at a slower rate. The more pertinent question to study seems to be, is the fracture rate affected? Conversely, in the Tilyard, et al. study[37] a large number of patients were enrolled, and a protective effect of calcitriol on the rate of fracture was found.

Data can be extrapolated from the two largest studies because of their large size and superior research methodology. In women who had mild to moderate postmenopausal osteoporosis, Tilyard, et al.[37] showed a highly significant decrease in vertebral fracture rates after 2 years of therapy with 0.25 mg of calcitriol twice a day compared with a control group on 1 g/d of calcium.[37] Fracture rate was reduced from 25 fractures per 100 patient-years in the control group compared with 9.3 in the treatment group in the second year. In the third year an even greater benefit was seen: 31.5 fractures per 100 patient-years in the control group compared with 9.9 in the treatment group. This study also showed that there were 11 nonvertebral fractures in the vitamin D group and 22 in the calcium group. A subsequent study with an even larger population (1763) confirmed that another vitamin D_3 derivative (cholecalciferol) plus 1.2 g/d of calcium seemed to decrease the risk of hip fractures by 43 percent and other nonvertebral fractures by 32 percent.[38] It seems that vitamin D_3 treatment plus calcium in the postmenopausal woman could be effective at decreasing fractures, but this combination needs to be compared in studies with estrogen replacement plus calcium. Vitamin D_3 might be an effective alternative to those who are not candidates for estrogen or those who will not use hormone replacement because of the possibility of menstruation.

One concern with the treatment with vitamin D_3 metabolites is the risk of hypercalcemia. Tilyard, et al.[37], however, found no safety differences in their study between calcium-treated groups and calcitriol-treated groups. Only 2 of the 314 patients in the calcitriol group had to drop out of the study because of persistent hypercalcemia. In the larger study by Chapuy, et al.[38] the treatment groups took vitamin D_3 and calcium. Only 1 patient of 1634 had mild elevations of calcium levels. None had renal calculi. Nevertheless, serial calcium determinations seem to be necessary when using this regimen. Also, some authors advocate monitoring urine calcium levels to keep the level less than 8.75 mmol/d to help prevent nephrolithiasis, even though this adverse event has not been clinically important in the large studies. The most common side effects appear to be gastrointestinal.

In summary, vitamin D_3 derivatives seem to be a viable alternative in the prevention of postmenopausal osteoporosis in those who are unable or unwilling to take estrogen replacement therapy. Comparison studies with hormonal therapy, etidronate, and calcitonin are needed before widespread use is advocated.

Niacin and Hypercholesterolemia

Niacin is an essential vitamin comprising two isomers — nicotinic acid and nicotinamide. It was first reported to be an effective cholesterol-lowering agent in 1955 both in normal subjects[39] and in those with high cholesterol levels.[40] Several studies have documented the reduction of mortality in atherosclerosis among users of niacin.[41-43] Niacin was recognized as a first-line therapy for hyperlipidemia in 1988[44] and again in the most recent recommendations in 1993.[45] A considerable amount of attention has recently been given to HDL cholesterol and its beneficial effect on atherosclerosis and heart disease. Of the currently available cholesterol-lowering agents, niacin is the most effective drug at elevating the HDL levels. It elevates HDL levels up to 37 percent higher than base-line levels[46] compared with the 10 percent elevation that gemfibrozil achieves.[47] Niacin is also effective in lowering triglyceride levels from 35 to 55 percent and LDL levels by 20 to 35 percent.

Despite its efficacy and extremely low cost, niacin has not been used as extensively as other, more expensive agents (e.g., hydroxymethylglutaryl-CoA reductase inhibitors, gemfibrozil), partly because the pharmaceutical industry has promoted other more profitable agents. Because nicotinic acid is available over the counter at very reasonable prices, minimal promotional activities are attempted. Another problem is the perceived difficulty with side effects. Side effects can include cutaneous flushing, gastric irritation, nausea, pruritus, skin rash, and elevation of liver enzymes. Additionally, niacin is not recommended for diabetic patients or those who have gout, as it has a tendency to exacerbate these conditions by causing glucose intolerance or hyperuricemia. Nevertheless, several studies have shown niacin to be well tolerated by 73 to 83 percent of patients who were usually noncompliant.[48,49] Nearly 100 percent of patients experience cutaneous flushing 20 to 30 minutes after ingesting this medication. This reaction can be circumvented by taking 5 grains of aspirin or 400 mg of ibuprofen 30 min-

utes before taking the niacin, a prophylactic strategy that complicates the regimen. In his recent editorial recommending the increased usage of niacin for cholesterol reduction, Felicetta[50] notes that most patients experience tachyphylaxis to the flushing after a few weeks. The more serious side effects are the elevation of liver enzymes and, occasionally, frank hepatitis. These reactions are almost always associated with the sustained release form as opposed to the immediate release form.[51] A recent study by McKenney, et al.[52] confirmed this finding by showing that 52 percent of those who received the sustained release niacin developed hepatotoxicity compared with none of those taking the immediate release product.

For these reasons a rational way to prescribe niacin is to have the patient get over-the-counter immediate release niacin and start with small doses three times daily with each meal (50 to 100 mg three times per day). Gradually increase each dose slowly and obtain serial cholesterol and liver function tests 3 weeks after each major dosage change. Eventually, 1 to 3 g orally three times a day are necessary to obtain the desirable reductions in serum cholesterol. Patient education and premedication with 5 grains of aspirin or 400 mg of ibuprofen, if necessary, will help avoid noncompliance resulting from the facial flushing side effects.

Vitamins and Prevention

Perhaps the most exciting possible uses of vitamins are in the area of disease prevention in normally healthy individuals who get adequate nutrition. Two examples are folic acid to avoid neural tube defects in the pregnant population and antioxidant vitamins to prevent heart disease and cancer.

Epidemiologic studies have shown that 0.4 mg/d of folic acid in the periconceptional period leads to a 72 percent reduction in the risk of recurrent neural tube defects in live births.[53] Recently another case-control study by Werler, et al.[54] also revealed a 60 percent reduction in the risk of first-time neural tube defects. In fact, the US Public Health Service now recommends that all women of child-bearing age receive 0.4 mg of folate per day.

The possibility of reducing two of the nation's largest killers, cancer and heart disease, is certainly an exciting prospect. Recent media attention highlighting antioxidant vitamins (i.e., beta-carotene, vitamin C, and vitamin E) in reducing the risk of heart disease and cancer has exposed some of the problems with epidemiologic research and revealed the need for randomized, blinded, placebo-controlled trials to evaluate the potential of these agents.

Interest in the cardioprotective effect of vitamin therapy began when studies showed that oxidation of LDL might be the true proatherogenic step.[55-57] Both α-tocopherol (vitamin E) and ascorbate (vitamin C) have been reported to decrease the susceptibility of LDL to oxidation.[58-61] Subsequent studies of LDL oxidation, however, failed to show any short-term benefit from combined antioxidant therapy compared with vitamin E alone.[62-64] Two large, prospective, case-control studies were primarily responsible for bringing this issue to the public forum. Rimm, et al.[65] observed more than 39,000 male health professionals for 4 years using dietary and health questionnaires. Controlling for other cardiac risk factors, they found a relative risk for cardiac disease to be 0.63 in patients consuming more than 100 IU of vitamin E per day (recommended daily allowance [RDA] 30 IU/d) for at least 2 years compared with those not taking vitamin E supplementation. Beta-carotene was not associated with a decreased incidence of atherosclerosis in those who had never smoked. In smokers, however, there was a reduced relative risk of 0.30, and in previous smokers, 0.60. In this study vitamin C did not seem to reduce coronary disease in any groups. The authors concluded that vitamin E might be effective in the reduction of heart disease risk. Previously, research showed that 10 to 100 times the RDA of vitamin E is needed to increase resistance of LDL to oxidation.[59-64] Fortunately, this level of intake seemed nontoxic during a moderate follow-up period.[64] The authors also concluded that vitamin C might not be effective, because it acts as a free radical scavenger only in hydrophilic environments, as it is water soluble, and the atherosclerotic areas are lipophilic. Another study by Stampfer, et al.,[67] observing 87,000 female nurses and using a prospective case-control design, showed a reduced relative risk of heart disease (0.66) in patients with median daily vitamin E intakes of approximately 200 IU/d. Vitamin C and beta-carotene consumption were not actively studied.

The popularity of antioxidants recently decreased when a randomized, double-blind, placebo-controlled primary-prevention trial on

more than 29,000 elderly male smokers, during a 5- to 8-year period, failed to show any benefit in cancer prevention.[68] Other previous epidemiologic work had shown a possible benefit in antioxidants in the prevention of cancer, especially of the lungs.[69-73] The mechanism for cancer reduction was hypothesized to be due to antioxidant effects and the possible control of cell growth and differentiation. These authors' observations can be criticized because of several factors. First, the focus of the study was lung cancer, and the microscopic changes that begin this process could have taken place before the relatively short 5- to 8-year study period. Also, the dosage of vitamin E was relatively small (50 IU/d) compared with previous epidemiologic findings that showed 100 IU or higher to be effective. Thus, the potential benefits of antioxidant vitamins might not be sufficient to offset the negative effects of cigarette smoking, the dosage of vitamin E might not have been sufficient, or the study period might not have been sufficiently long. Second, vitamin C was not studied in this trial. Finally, the authors stated that there was a very slight increase in the rate of hemorrhagic stroke in those taking vitamin E (7.8 percent versus 5.2 percent). They did not state whether this finding was statistically significant.

Table 1. Cost Comparison Chart of Selected Vitamin Products.

Brand Name	Generic Name	Dosage Strength and Form	Cost Per Month (Brand) ($)†	Cost Per Month (Generic) ($)‡
Accutane*	Isotretinoin	20 mg, 40 mg, capsules	326.14 378.91	N/A
Aquasol A*	Vitamin A	10,000 IU, capsules	34.94§	2.17
Aquasol E	Vitamin E	100 IU, capsules	64.38	2.51
Delta-D	Cholecalciferol (D_3)	400 IU, capsules	5.00‖	3.00¶
Dovonex*	Calcipotriene	0.005%, ointment	39.1 74.37#	N/A
N/A	Beta-carotene	25,000 IU, capsules	N/A	4.02
Niacor*	Niacin	500 mg, tablets	12.80	3.72
Os-Cal	Calcium carbonate with D	250 mg, 500 mg, tablets	69.41 82.37**	4.83 5.13
Protegra	Vitamin E, vitamin C, beta-carotene, zinc, copper, selenium, manganese	200 IU vitamin E, 250 mg vitamin C, 3.0 mg beta-carotene, 7.5 mg zinc, 1.5 mg selenium, 1.5 mg manganese; tablets††	7.93	N/A
Retin-A*	Tretinoin	0.025% cream, 0.01% gel, 0.05% liquid	23.82 45.24 19.20 45.4 37.92‡‡	N/A
Rocaltrol*	Calcitriol	0.25 µg, capsules	96.33	N/A
Tegison*	Etretinate	10 mg, 25 mg, capsules	53.91 84.36§§	N/A

N/A — information not available
*Prescription products, otherwise, listed products are over-the-counter or nonprescription status.
†Cost for the brand name product was obtained by using the average wholesale price (AWP) for the corresponding strength from the 1993 *Drug Topics Redbook*[74] for package sizes of 100 units.
‡Cost for the generic product was obtained by averaging the AWP for three available generic products for package sizes of 100 units, unless otherwise noted.
§Brand name price is the AWP for 30 mL of the 5000-IU drops.
‖Brand name price is the AWP for 250 of the 400-IU capsules.
¶Generic price is the AWP for 90 of the 400-IU capsules.
#Brand name price is the cash price for 30 mg and 60 mg of cream, respectively.
**Brand name prices are the AWP for 60 of the 250 mg and 500 mg tablets, respectively.
††Protegra tablet package size=50 tablets.
‡‡Brand name prices are the AWP for 20 mg and 45 mg of the cream and gel; liquid price is the AWP for 28 mL (cc).
§§Brand name prices are the AWP for 30 of the 10-mg and 25-mg capsules.

Summary

Antioxidant therapy is probably one of the most exciting areas in medicine. Information given to patients should remain conservative until prospective clinical trials can be conducted. Patients who are already taking antioxidant vitamins (such as Protegra, Lederle) are unlikely to experience any major toxicity with this regimen. Large doses of beta-carotene can sometimes cause a yellowish discoloration of the skin. Patients can experience toxicities from some over-the-counter vitamin

Table 2. Recommended Daily Allowances (RDAs) of Selected Vitamins; Deficiency Signs and Toxicities.*

Vitamin	RDA†	Deficiency Signs and Symptoms	Signs of Toxicity
Fat soluble A	5000 IU	Night blindness. Bitot spots, photophobia, xerosis of cornea, corneal distortion, increased susceptibility to infection, follicular hyperkeratosis and drying, loss of appetite, impaired taste and smell, impaired equilibrium, increased cerebrospinal fluid (CSF) pressure	Hypervitaminosis A syndrome: fatigue, malaise, lethargy, abdominal upset, bone and joint pain, throbbing headaches, insomnia, restlessness, night sweats, loss of body hair, brittle nails, rough and scaly skin, peripheral edema, chronic liver disease. Actual toxicity reported with doses of 25,000 IU: single doses of greater than 660,000 IU have caused central nervous system symptoms (nausea, vomiting, vertigo, increased CSF pressure): larger doses could be fatal
D	400 IU	Reflected as calcium abnormalities, specifically those involved with bone formation; rickets manifested by soft bones and deformed joints; osteomalacia	Hypervitaminosis D: anorexia, nausea, weakness, weight loss, polyuria, constipation, vague acnes, stiffness, soft tissue calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure (1600-2000 IU)‡
E	30 IU	Infants: edema, hemolytic anemia, reticulocytosis, thrombocytosis. Adults: erythrocyte hemolysis, deposition of ceroid (age) pigments, creatinuria, altered erythropoiesis, myopathy	Relatively nontoxic at doses of 100 to 1000 IU daily; hazards or long-term high-dose therapy unknown; ?platelet dysfunction
Water soluble B_{12} (cyanocobalamin)	6 μg	Macrocytic anemia, glossitis, epithelial changes along digestive tract, paresthesia, poor muscle coordination, mental confusion, agitation, optic atrophy, hallucinations, and overt psychosis	Excessive doses have not resulted in toxicity, nor has any benefit been reported from nondeficient patients taking large quantities of B_{12}
B_6 (pyridoxine)	2 mg	Infants: convulsive disorders, irritability; adults: pellagra-like dermatitis, scaliness around nose, mouth and eyes, oral lesions, peripheral neuropathy, dulling mentation	Severe sensory neuropathy and ataxia (1 g/d)
Beta-carotene	0.6 μg	See vitamin A section	Carotene does not produce toxicity rapidly due to its slow rate of conversion to vitamin A: eating large amounts of carrots may result in carotenemia, which can produce a yellow skin hue
Folic acid	400 μg	Macrocytic anemia (see vitamin B_{12})	Usually none; occasional seizure observed with intravenous doses greater than 15 mg
Niacin	20 mg	3 Ds (dermatitis, diarrhea, dementia)="pellagra," characteristic rash, neuropathy, glossitis, stomatitis, proctitis	Gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea), hepatotoxicity, skin lesions, tachycardia, hypertension, atopecia, flushing, hyperkeratotic pigmented skin lesions, pruritis, peptic ulcer, (doses greater than 1 g/d can cause GI symptoms and flushing)
C (ascorbic acid)	60 mg	Malaise, weakness, capillary hemorrhages and petechiae, hyperkeratotic follicles, swollen hemorrhagic gums, bone changes, impaired hearing; (scurvy)	Increased oxalate excretion, which can produce nephrolithiasis, possible hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency, GI disturbances

*From Covington TR, et al.[75]
†RDA represents the recommended daily allowance for the various vitamins for adults and children 4 years of age and older.
‡Dose at which toxicities have been observed.

preparations, especially the fat-soluble vitamins A and D; therefore, moderation of vitamin intake should be encouraged until further data on the beneficial effects of antioxidants are obtained.

A comparison of the costs of various vitamins and their derivatives (Table 1) and the recommended daily allowances and signs of toxicity of available vitamins (Table 2) are included for reference.

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