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Melatonin for Shift-Work Insomnia

By Aaron H. Burstein, PharmD

As much as 7% of the American labor force works rotating shifts or exclusively night shifts.[1] One difficulty in working such shifts is the transition back to a regular sleep/wake cycle. Melatonin has been advocated as an antioxidant to slow aging, an adjunct to cancer chemotherapy, a contraceptive, and a promoter of sleep, especially for jet lag, another type of shift in sleep schedule.

Pharmacology and Mechanism of Action

Melatonin is an endogenous hormone synthesized within the pineal gland through a series of metabolic conversions. (*See Figure 1.*) The cascade is stimulated by release of norepinephrine in response to lack of light and is inhibited by retinal exposure to light.[2]

It is unclear how melatonin affects sleep. Melatonin secretion is typically synchronized to a 24-hour light/dark cycle. Secretion begins at approximately 10 PM and reaches highest concentrations (90 pg/ml) between 2 AM and 4 AM. Secretions subsequently decrease to less than 10 pg/ml during daylight hours. Because of its relatively short half-life (30-60 min), melatonin's effects on sleep are unlikely to be exclusively the result of direct hypnotic action. Melatonin-induced mild hypothermia (0.5-1° F decrease) may be responsible for induction of sleep.[2,3]

During periods of night-shift work, the circadian pattern of melatonin secretion is advanced, resulting in maximum secretion during daylight and facilitation of daytime sleep.[4] The altered pattern of secretion may result in a decrease in nighttime sleep duration and an increase in number of daytime naps when the worker is not working nights. It has been suggested that melatonin use prior to retiring for nighttime sleep may reset the pattern and facilitate sleep in individuals experiencing insomnia due to varying work schedules.

Clinical Trials

Literature evaluating melatonin use for shift-work insomnia is limited to four relatively small studies. All were randomized, double-blind, placebo-controlled, crossover studies.[1,5-7] (*See Table 1 for a summary of clinical trials.*) These studies evaluate melatonin's ability to facilitate daytime sleep in subjects working night shifts[5-7] or nighttime sleep upon completion of a block of night shifts.[1] Additionally, one study evaluated efficacy in a simulated night-shift model,[8] and another, available only in abstract, examined degree of phase shift in endogenous melatonin production during a week of night shifts with daily melatonin administration prior to daytime sleep.[9] The three largest and highest quality trials are described below.

James and colleagues evaluated the ability of melatonin to reset the biological clocks of emergency medical services personnel working rotating night shifts.[5] Twenty-four volunteers (mean age 28 ± 8 years) were initially enrolled to compare 6 mg oral melatonin (Vitamin Research Products, Inc.) and placebo taken 30 min prior to daytime sleep for 3-5 days. Subjects received two cycles of melatonin and two cycles of placebo. Subjects were assessed daily by completing visual analogue scales (VAS) for sleep quality, mood, and job performance. Additionally, evaluations of sleep latency, number of awakenings, sleep efficiency, and duration of daytime naps were recorded. Melatonin was associated with fewer awakenings (P = 0.011) than placebo. No differences in sleep latency, total sleep time, or sleep efficiency were noted. No significant improvement in sleep quality, mood, or job performance was evident following treatment with melatonin relative to placebo. Minor study limitations include relatively narrow age range (20-41 years) and failure to address potential confounding factors such as sleep environment and prior sleep patterns. *Level I, minor limitations* (*See Figure 2 for an explanation of the evaluation standards and scales used in rating clinical studies.*)

Jorgensen and colleagues evaluated melatonin's ability to improve daytime sleep and/or nighttime alertness in 20 emergency physicians.[6] During a block of night shifts, subjects received 10 mg sublingual melatonin (Source Naturals Products) or placebo each morning in a randomized crossover manner. Each treatment was evaluated during one block of night shifts. Subjects maintained sleep logs during daytime sleep and completed the Stanford Sleepiness Scale three times during the night. At the conclusion of a block of night shifts, VAS measures of impression of day sleep and night alertness were completed. Only 18 subjects were evaluable; two were excluded because of alcohol or sedative medication ingestion. Exogenous melatonin failed to significantly improve VAS measures of daytime sleep and night-work alertness. While there were trends toward longer duration, shorter sleep latency, fewer premature awakenings, and a small difference between amounts of desired and actual sleep, no statistically significant differences were detected. Melatonin was associated with a statistically significant improvement in alertness at the end of a night shift compared to placebo. The authors concluded that melatonin may offer a modest benefit. However, data do not clearly support such a statement. Limitations include a homogenous population (89% male, mean age 32 years, range 25-40 years), insufficient description of inclusion/exclusion criteria, lack of statistical power, and evaluation of each treatment over a single block of nights. *Level II, major limitations*

Wright and colleagues evaluated effects of melatonin on cognitive function, manual dexterity, mood, length of sleep, and/or quality of sleep in 15 emergency physicians following a block of two night shifts.[1] Beginning the evening following the last night shift worked, subjects were randomized to receive 5 mg oral melatonin (Nature's Vision) or placebo 30 min before retiring. Assessments included Karolinska Sleep Scale, VAS assessment of tiredness in the morning and evening of day one and in the morning of treatment days two and three, VAS for global assessment of recovery from the night-shift work, and characteristics of sleep (time to fall asleep, hours slept, awakening frequency). No differences between groups were found for any measurements. According to the authors, melatonin appeared to

The Pharmacist's Dietary Supplement Alert, ISSN 1527-7348, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

PUBLISHER: Brenda L. Mooney.

EDITORIAL GROUP HEAD: Leslie G. Coplin.

ASSOCIATE MANAGING EDITOR: Paula L. Cousins.

GST Registration Number: R128870672

Periodical postage pending at Atlanta, GA.

POSTMASTER: Send address changes to ***The Pharmacist's Dietary Supplement Alert***, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail Address:

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Editorial E-Mail Address: paula.cousins@medec.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States

$229 per year (Student/Resident rate: $120).

Outside the United States

$259 per year plus GST (Student/Resident rate: $135 plus GST).

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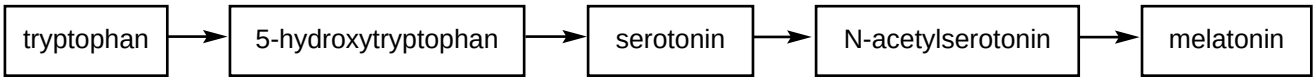
Figure 1

The conversion of melatonin



be of limited value in aiding recovery of emergency physicians from night-shift work. Limitations include inconsistency of the primary outcome measure with the stated objective; sample size calculation was based on a primary outcome measure of global assessment of recovery rather than on changes in the outcome measures stated by investigators. This small study also had insufficient description of study participants (concurrent medications, disease states) and evaluated each treatment only once rather than repeatedly over multiple blocks of night shifts. *Level I, major limitations*

Adverse Effects

Generally well tolerated, melatonin's most common side effects include sedation, headache, mild hypothermia (decrease in temperature of 0.5-1° F), and next day tiredness.[1-3,5,6] Other infrequently reported side effects include depression, tachycardia, pruritis, nightmares, and increased seizure activity in neurologically impaired pediatric patients.[2,3]

Contraindications

Information regarding melatonin use in pregnancy and lactation is lacking. Women attempting to conceive should avoid melatonin as it may have contraceptive potential at high doses.[10] Melatonin should be used cautiously and/or avoided in patients with autoimmune diseases and allergies (potential for immune system stimulation),[11] cardiovascular disease (potential for coronary artery vasoconstriction in animal models),[12] depression (exacerbation of dysphoria),[13] and neurologic conditions including epilepsy.[14] Patients with hepatic impairment should use with caution because of potential for impaired clearance by the cytochrome p450 (CYP) system.[2]

Interactions

Limited human data are available characterizing drug interactions with melatonin. Results from in vitro studies suggest an inhibitory effect of melatonin on CYP activity, especially 1A2, 2C, and 3A.[15-17] Melatonin is primarily metabolized by CYP1A2; it is unclear if melatonin has enzyme-inducing potential.

Administration with fluvoxamine, a known inhibitor of CYP1A2 and CYP2C19, resulted in great increases in melatonin concentration.[18] Clearance may be reduced in patients taking concurrent chlorpromazine.[2] Animal studies have shown melatonin enhances anxiolytic effects of benzodiazepines through binding with GABA receptor sites,[2] and may potentiate neuromuscular blockade induced by agents such as succinylcholine.[2]

Formulation and Dosage

Suggested melatonin doses for use in sleep disorders range from 0.3-10 mg administered approximately 30-60 min before retiring. The optimal effective dose, if any, is not known.

Synthetic melatonin is available in capsule, liquid, and sublingual, immediate-release, and controlled-release tablet formulations. There are theoretical advantages to different forms that involve higher immediate levels for sleep induction vs. sustaining higher levels that mimic physiological secretion patterns; an optimum dosage form is not known. Although tablet content usually seems consistent,[19] studies have found various quality problems with at least nine different brands of tablets.[20]

Conclusion

These melatonin studies do not show benefit for

Figure 2

Level of evidence and grading recommendation

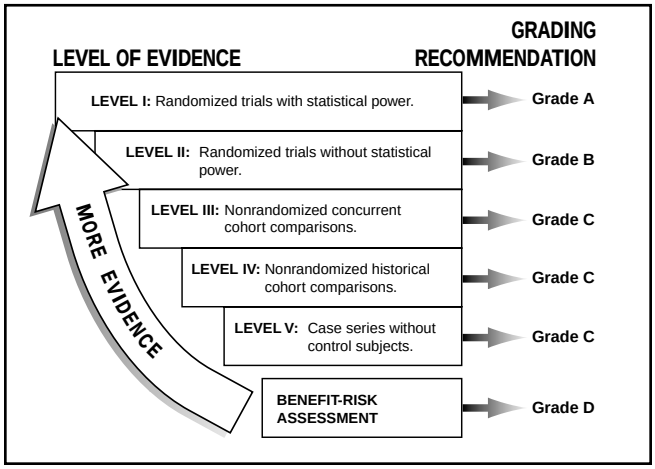


Table 1

Clinical trials of melatonin in shift-work

Trial	N	Dose	Results	LOE†	Limitations
James[5]	24	6 mg oral	No differences in sleep parameters	I	Minor
Wright[1]	15	5 mg oral	No differences in sleep parameters	I	Major
Jorgenson[6]	20	10 mg SL§	No significant differences in sleep parameters	II	Major
Folkard[7]	17	5 mg oral	Increased subjective sleep quality	II	Major

† = Level of Evidence
§ = sublingual

improving daytime sleep, nighttime work performance, or transition back to nighttime sleep; however, concerns exist with the small patient experience reported. Future studies should enroll more subjects, establish a dose response, and improve trial methodologies.

Recommendation

Current evidence does not support a recommendation for melatonin use by shift workers. Patients considering melatonin should be informed of the lack of evidence to support this particular indication. Patients also should be counseled about the potential for adverse effects and drug interactions. *Grade B* ❖

Dr. Burstein is a Pharmacokineticist in the Clinical Center, Pharmacy Department of the National Institutes of Health. The views presented in this article are those of the author and do not necessarily represent the policy of the National Institutes of Health (NIH), the NIH Clinical Center, or the Food and Drug Administration.

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Tea Tree Oil for Fungal Infections

By Eric Harvey, PharmD, BCPS, MBA

NATIVE AUSTRALIANS HAVE USED BOILED LEAVES OF *Melaleuca alternifolia* as a topical anti-infective for hundreds of years. The plant was given its common name, tea tree, following Captain James Cook's exploration of New South Wales in 1770. During World War II, Australian manufacturers added tea tree oil (TTO) to metal cutting oils as an anti-infective in an attempt to reduce workers' risk of infection from on-the-job lacerations.[1,2]

TTO is currently promoted as a treatment for cutaneous fungal infections including tinea pedis and onychomycosis. It also is used to treat acne, prevent bacterial infections, and as a skin disinfectant.[1-3]

Pharmacology and Mechanism of Action

Terpinen-4-ol is the most abundant (40-60% of total volume) antimicrobial compound in TTO followed by 1,8-cineole and alpha-terpineol. In vitro antimicrobial activity has been documented against many common yeasts and fungi including *Candida albicans*, other *Candida* sp., *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum canis*, and *Malassezia furfur*.[3,4] Based on in vitro data, topical application of TTO in concentrations of 5% v/v or higher should be adequate to eradicate these organisms from skin surfaces.[3-5] TTO also has demonstrated activity against many important gram-positive and gram-negative bacteria including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Propionibacterium acnes*.[1,2]

Clinical Trials

A randomized, double-blind controlled trial (RDBCT) in 121 patients with symptomatic tinea pedis used tolnaftate 1% cream (Tinaderm®), TTO 10% in sorbolene cream base, or sorbolene cream base (as placebo) bid for four weeks.[6] A negative fungal culture excluded 15 patients originally randomized. The mycological cure rate of tolnaftate (85%) was statistically superior to both TTO (30%) and placebo (21%). Symptoms of scaling, itching, inflammation, and burning were individually rated. Symptom scores (0 = absent to 4 = very severe) were summed for each visit; a reduction by 2 points or more in total score was considered symptom improvement. At week 4, 46%, 22%, and 9% of tolnaftate, TTO, and placebo patients, respectively, had both improvement of symptoms and a negative culture; 12%, 43%, and 32% had improvement of symptoms only. Tolnaftate and TTO were both statistically superior to placebo for rate of symptom improvement. One tolnaftate patient reported mild erythema that resolved without treatment interruption; no patients dropped out because of side effects. The relatively high symptom improvement rate in the placebo arm may reflect the impact of routine washing and drying of feet as a condition of study participation. The symptom scoring method used to assess treatment response is neither standardized nor easily replicated. An absolute standard of "complete symptom resolution" would have been more reliable and useful. *Level II, major limitations*

In another RDBCT, 117 patients with culture-proven toe onychomycosis were treated with 1% clotrimazole solution or 100% TTO bid for six months.[7] Outcomes were not statistically different between clotrimazole (n = 53) and TTO (n = 64) as measured by mycological cure rate (clotrimazole 11%, tea tree oil 18%), resolution of symptoms at the end of therapy (61% and 60%, respectively), or resolution of symptoms three months after therapy ended (55% and 56%, respectively). The study had 80% power to detect a difference in cure rate of at least 20%. Four clotrimazole patients and one TTO patient were lost to follow-up. Three clotrimazole patients and five TTO patients reported erythema, irritation, or edema; four dropped out because of adverse effects (their treatment arms were not specified). Symptom status was obtained by a physician's subjective assessment of "full," "partial," or "no" resolution. Both "full" and "partial" resolution were combined and considered positive results. A more absolute measure of symptom resolution would have been more reliable. The low mycological cure rate reported for treatment with topical clotrimazole lends credence to the suspicion that a systemic antifungal may have been a better active control. Another limitation is the lack of a placebo arm. *Level I, major limitations*

A case series of patients with a variety of foot conditions has lent support to TTO's antifungal claims.[8] Treatment was not blinded and was given for highly variable durations to treat culture positive tinea pedis or toe onychomycosis. Twelve people used an 8% TTO ointment daily to treat seasonal athlete's foot. Eight reported resolution of tinea pedis symptoms and cultures were negative. The other four reported relief from symptoms but cultures remained positive. Seven of eight patients with toe onychomycosis reported symptom resolution with 100% TTO treatment, but cultures remained positive. A second case series reported satisfactory results in 18 of 23 cases following 100% TTO twice daily for fungal

Table 1

Human trials of tea tree oil (TTO) and cutaneous fungal infections

Trial	N	Fungal site	TTO	Control	Results	LOE†	Limitations
Buck[7]	117	nail	100% oil	clotrimazole (C)	C = TTO	I	Major
Tong[6]	121	skin	10% cream	tolnaftate (T), placebo (P)	T = TTO > P	II	Major
Belaiche[9]	23	nail and skin	100% oil	NA	18/23 reduced symptoms	V	Major
Walker[8]	12	skin	8% ointment	NA	12/12 reduced symptoms, 8/12 negative cultures	V	Major
Walker[8]	8	nail	100% oil	NA	7/8 reduced symptoms, 8/8 positive cultures	V	Major

† = Level of Evidence

skin or nail infections.[9]

Adverse Effects

Adverse effects were reported infrequently; adverse effects are most commonly reported with use of 100% TTO products and include contact dermatitis with a vesicular rash and eczema with erythema, edema, and scaling.[10-13] Ataxia and drowsiness occurred in two toddlers who ingested less than 15 ml of 100% TTO. Both children fully recovered following administration of activated charcoal and symptomatic support.[14,15]

Interactions

There are no reported interactions for TTO.

Contraindications

There are no contraindications to use of TTO products other than allergy. Pregnant or lactating woman should avoid use, as no safety information exists; the extent of cutaneous absorption has not been quantified.

Formulation and Dosage

TTO is available as an essential oil or as an ingredient in lotions, creams, or shampoos. Based on in vitro data, concentration should be 5-10% or higher.[3-5] Twice daily topical application is the most common regimen used in trials. The Australian government has set a standard for *Melaleuca alternifolia* oil of at least 30% terpinen-4-ol and no more than 15% 1,8-cineole (eucalyptol).[11] Other species such as *M. quinquenervia* and *M. cajuputi* produce niaouli oil and oil of cajuput, respectively, and are occasionally labeled as TTO. These oils have a very different composition, are used for aromatherapy, and should not be used as a substitute for *M. alternifolia*.[2]

Conclusion

In vitro studies have documented antimicrobial properties of TTO. (*See Table 1 for a summary of clinical trials.*) Two large controlled studies (Level of Evidence I and II) appear to demonstrate clinical effects for reduction of symptoms of tinea pedis and onychomycoses similar to topical pharmaceutical agents and there is further support from case series evidence. However, results of the controlled studies are severely weakened by major methodological limitations. TTO benefits have not been proven.

Recommendation

Available evidence does not support a recommendation for tea tree oil use as a reliable topical antifungal therapy. Patients should be made aware that research has not yet confirmed TTO's reliability or relative value compared to pharmaceutical agents. Based on the preliminary evidence, the adverse effects profile, and the relatively benign indications, TTO may be tried as a topical agent if desired by the patient. As 100% TTO is more likely to cause contact dermatitis, TTO-containing creams may be a wiser choice. *Grade B* ❖

Dr. Harvey is a Clinical Pharmacy Specialist at drugstore.com in Seattle, WA.

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Literature Briefs

With Analysis by Cydney E. McQueen, PharmD

Cellasene™ for the Treatment of Cellulite

Source: Lis-Balchin M. Parallel placebo-controlled clinical study of a mixture of herbs sold as a remedy for cellulite. *Phytother Res* 1999;13:627-629.

Objective: To determine the effect of Cellasene™ on cellulite, weight gain, and body fat.

Design and Setting: Randomized, controlled trial conducted from the School of Applied Science in London. The study was commissioned by BBC Watchdog Healthcheck Television and results were televised.

Subjects: Twenty-three women (25-45 years old) who thought they had cellulite problems. Exclusion criteria included medications, pregnancy, epilepsy, thyroid disease, and use of anticellulite preparations within the last month. Subjects agreed to make no diet or exercise changes during the trial.

Treatment: Cellesene, containing extracts of bladderwrack, grape seed, sweet clover, *gingko biloba*, borage and fish oils, and soy lecithin. The herbal product Colonease™ (aloe vera, clary sage oil, parsley seed oil, and peppermint oil, and soy lecithin) was used as a control and considered a placebo.

Dose/Route/Duration: One capsule Cellasene or Colonease bid for eight weeks.

Outcome Measures: Weight, body fat percentage, cellulite scores, and measurements of hips, both thighs, and one knee self-assessed by subjects and independently by the author.

Results: The only significant changes between groups were an increase in body weight in the Colonease group and an increase in the independent cellulite score in the Cellasene group. Three Cellasene and two Colonease subjects felt they had a decrease in cellulite, which was not confirmed by the author's cellulite scores. Body weight in seven of 11 Cellasene patients increased up to 3 kg at end of treatment; "most" women said they had experienced gain of up to 5 kg in the first weeks of the study. Eight of the nine Colonease patients reported bloating and weight gain, especially in the first few weeks of the study. Women reporting weight gain decreased food intake because of the gain. One Cellasene patient dropped out because of considerable weight gain, and two Colonease subjects dropped out (one bereavement, one loss to follow-up).

Level of Evidence: Level II, major limitations

Strengths: The author's conclusion that Cellasene does not effect cellulite in most patients is in accordance with the data presented.

Limitations: One of the strongest limitations is that Colonease is a product with pharmacological effects, including at least one of the same ingredients as the active treatment, though probably in smaller amounts. Groups were not similar after randomization in regard to weight or knee measurement—apparently, changes were made after assignment because of "friendships and transport problems." Most subjects did not abide by their agreements and made diet or exercise changes during the trial because

of weight gain. The treatment dose used is less than that recommended by the manufacturer and compliance was not monitored. The "cellulite score" used was not explained and is not a validated scale.

Comments: The many serious study limitations prevent a firm conclusion of complete lack of efficacy.

Clinical Impact: This study provides information on weight gain as a possible side effect of Cellasene. No decision can be made in regard to efficacy. ❖

Vanadyl Sulfate in Non-Insulin-Dependent Diabetes Mellitus

Source: Goldfine AG, et al. Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: In vivo and in vitro studies. *Metabolism* 2000;29:400-410.

Objective: To determine the effects of vanadyl sulfate (VS) on glycemic control and insulin sensitivity.

Design and Setting: A comparison study at Brigham and Women's Hospital of three doses of VS with a one-week baseline monitoring period, a one-week placebo run-in, and a two-week follow-up. Randomization or blinding status is not specified.

Subjects: Type II diabetic patients (5 female, 11 male; 38-65 years of age). Patients were "free of major active cardiovascular, pulmonary, renal, or hepatic disease," had no history of joint replacement, and normal Hgb and Hct.

Treatment: Vanadyl sulfate 75 mg (n = 3), 150 mg (n = 5), or 300 mg (n = 8) daily.

Dose/Route/Duration: 25, 50, or 100 mg capsules three times daily with meals for six weeks.

Outcome Measures: Blood glucose and HbA_{1c}, insulin sensitivity studies, hepatic glucose production, concentrations of insulin-sensitive cellular enzymes, oxidative vs. non-oxidative glucose disposal, and tissue oxidative stress.

Results: There was a statistically significant decrease in HbA_{1c} at week 6 for the 150 mg and 300 mg dose groups (from 7.8% to 6.8% and 7.1% to 6.8%, respectively). The 300 mg group also had a significant decrease in mean fasting glucose. There were no significant changes in weight or caloric consumption in any group. The 300 mg group also experienced a significant decrease in cholesterol, primarily because of a decrease in HDL. Although insulin sensitivity improved in the 150 mg and 300 mg dose groups, the modest changes were not enough to produce a significant change in glucose utilization. Results of oxidative stress studies and tests of other tissue enzyme patterns revealed no differences from placebo. No patients required reduction in hypoglycemic medications during the study. Peak vanadium levels increased with no relation to side effects. All 300 mg dose subjects had some GI side effects—cramping, discomfort and/or diarrhea—requiring treatment with medication. Some patients on 150 mg experienced GI side effects, but did not require treatment. No dropouts occurred because of side effects and no hypoglycemic episodes occurred.

Level of Evidence: Level II, major limitations

Strengths: Compliance was monitored and was > 95%. Discussions of clinical relevance and the conclusion that "more potent analogs of vanadium" will be needed before it can be therapeutically useful are appropriate.

Limitations: Although compliance to treatment was monitored, no mention is made of compliance with the four-times-daily self-testing of blood glucose. No power calculation was performed, sample size was very small, and randomization and blinding status are unknown.

Comments: This study examined both clinical effects and possible mechanisms of action. Although information was obtained on pharmacological effects of VS, some inconsistencies in data leave many questions unanswered. Long-term safety is unconfirmed.

Clinical Impact: Although high doses of VS do lower HbA_{1c}, diarrhea associated with these doses may cause further glucose control problems in diabetic patients. The low doses used in many supplement formulations for diabetics are not like to significantly affect gycemic control. ❖

In Future Issues:

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Chromium Use in Diabetics
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Saw Palmetto for Benign Prostatic Hyperplasia