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Russell H. Greenfield, MD (executive editor), discloses that he speaks on behalf of Nature's Way, in conjunction with their *Lactobacillus reuteri* product. Mary L. Hardy, MD (fact sheet editor), Judith L. Balk, MD, MPH, FACOG, Assistant Professor, Magee-Womens Hospital, University of Pittsburgh, Pittsburgh, PA (peer reviewer), and Paula L. Cousins (managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

The Use of Melatonin in the Treatment of Hypertension

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HYPERTENSION IS A RISK FACTOR FOR CARDIOVASCULAR AND CEREbrovascular disease, two of the top three causes of mortality for adults in the United States.[1] It stands to reason that successfully controlled blood pressure (BP) can mitigate risk for both conditions. Despite the array of antihypertensive drugs available and widespread implementation of lifestyle modifications such as the DASH diet, optimal BP control remains elusive for most hypertensive patients.[2,3]

There is mounting evidence, however, from ambulatory blood pressure monitoring (ABPM) in clinical studies, highlighting that loss of the diurnal pattern of BP may be an important factor that impacts development of cardiovascular complications in hypertensive patients. Therefore, the use of melatonin may provide an additional novel approach to BP control for a subset of patients who exhibit disturbed circadian organization.

Central Pacemaker Function

Endogenous circadian rhythms in mammals are regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which acts via the sympathetic and parasympathetic nervous systems and imposes a 24-hour time table to many biological functions, including production of the hormone melatonin in the pineal gland. In general, humans are diurnal creatures, programmed to be out when the sun is shining and asleep in bed at night. As the body's clock, the SCN is synchronized with the outside world via afferent input of light signals, which access the SCN via the optic nerves. When light from the sun or other bright light source shines in the eyes, nerve pathways to the SCN switch the clock to the "off" phase, turning off melatonin production by the pineal gland. As ocular light inputs decrease, the body's clock turns "on" and the pineal gland recommences melatonin production, which is then released into the bloodstream to reach all body cells.[4]

VOLUME 10 • NUMBER 9 • SEPTEMBER 2007 • PAGES 97-108

Melatonin and Cardiovascular Health

The cardiovascular system has a distinct daily activity cycle entrained by the SCN at least in part via the effects of melatonin. At nighttime, the heart rate slows and BP drops an average of about 10% of the daytime systolic and diastolic BP levels (normal "dipper" profile [DIP]). BP and pulse rate reach the low point of the 24-hour cycle at the same time melatonin levels peak around 02:00-03:00. At the cellular level, the calcium pump becomes more active at this time.

With the dawn, heart rate increases, BP rises, and calcium levels build up within the cells. While these changes prepare for the activity of the day, they also increase the risk that a heart attack or stroke will occur during this time period. Muller et al have noted that the highest vulnerability for a cardiac emergency occurs between the hours of 06:00 and 12:00, with the greatest risk occurring around 09:00. This "heart attack vulnerability period" occurs around the time melatonin levels reach a daytime low.[5]

Normal daily rhythmicity in BP, e.g., higher BP levels during the daytime and a decrease during the nighttime, represents an anticipatory adaptation to higher demands during an active phase of a daily cycle. This regular cycle of BP is important especially in hypertensive patients because nocturnal hypertension (mean nighttime systolic BP greater than 125 mmHg) is an independent risk factor for cardiovascular morbidity and mortality.[6,7]

A study by Bruegger et al linked melatonin levels to heart health. They compared nighttime melatonin levels from a group of 10 healthy volunteers and 15 patients with established coronary artery disease that were matched for age and sex. The healthy patients produced five times as much nocturnal melatonin as those with heart disease.[8]

Blood Pressure Profile: Dipper vs. Non-dipper

A "non-dipper" (NDIP) BP profile refers to patients whose nocturnal decrease of mean BP is less than 10% of the mean daytime blood pressure level. Such patients with impaired nocturnal BP reduction have a higher risk of renal, cardiac, cerebral, and vascular tissue damage.[9,10]

A blunting of the fall in nocturnal BP is the most consistent change associated with incipient diabetic neuropathy, defined by microalbuminuria in normotensive adults with Type 1 diabetes mellitus. However, this type of NDIP profile may also occur in normotensive young adults with Type 1 diabetes in the absence of microalbuminuria, suggesting that the circadian BP abnormality can precede renal disease and overt hypertension.[11]

Although most hypertensive patients can be readily categorized as DIP or NDIP, nearly 30% show fluctuation between the two.[12]

Jonas et al studied 16 elderly patients (mean age 68 years) with essential hypertension, most of whom were treated with one or more antihypertensives including calcium channel blockers, ACE inhibitors, beta blockers, and diuretics.[13] These patients were defined as DIP or NDIP according to ABPM results. Levels of the main melatonin metabolite, 6-sulfatoxymelatonin (6-STM), were determined by ELISA in two separate urine collections, one in the daytime and one during the night. During the night, mean arterial pressure decreased by 10.3 mmHg in the DIP group and increased by 7.5 mmHg in the NDIP group. Although daytime urinary 6-STM levels were comparable between the DIP and NDIP patients, nocturnal urinary 6-STM levels of the NDIP patients were not significantly different from the daytime levels.

Thus, it appears that diminished nocturnal melatonin secretion, as seen with the NDIP profile, attenuates nocturnal BP reduction in hypertensive patients.

Melatonin: The Chemical Signal for Darkness, Rest, and Recuperation

Melatonin is produced by the pineal gland from the essential amino acid tryptophan and is chemically known as N-acetyl-5 methoxytryptamine. Intrapineal tryptophan is initially converted to serotonin, which is subsequently modified enzymatically into the regulatory hormone melatonin.

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
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MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Melatonin has been found in every animal and plant from humans to one-celled algae. In all of these living organisms, it is identical in both its molecular structure and the circadian rhythm of its production cycle. Humans produce 5-10 times more melatonin at night than during the day, a cycle that is found in diurnal animals as well. In a healthy adult, daytime melatonin values average around 10 ng/mL, whereas they peak at nighttime to average values of 60 ng/mL. Exposure to light at night is a powerful suppressant of melatonin production.[14,15]

Serum melatonin has a short half-life and is rapidly metabolized, primarily via hepatic pathways. Measurement of 6-STM excreted in urine reflects pineal function. Urinary 6-STM levels are highly correlated with plasma melatonin levels. In particular, peak plasma nocturnal melatonin levels have correlated well with morning levels of urinary melatonin.[16,17]

Melatonin and its metabolites are powerful antioxidants and free radical scavengers. Because melatonin is fat- and water-soluble, it can penetrate the blood-brain barrier. This property likely contributes to its salutary cardiovascular and cerebrovascular benefits.[18,19]

Proposed Mechanisms of Melatonin's Antihypertensive Effect

The effect of melatonin on diurnal BP changes may be explained by its effects on the sympathetic nervous system. During non-REM sleep, BP usually decreases due to reduced sympathetic activity and a reciprocal increase in vagal tone, which leads to a reduction in cardiac output and peripheral resistance.[20] Hojo et al and Kohara et al demonstrated that patients with an NDIP profile had impaired cardiovascular relaxation with altered sympathetic-vagal balance, resulting in reduced nocturnal sympathetic suppression and sustained adrenergic tone during sleep.[21,22] Oral melatonin suppresses sympathetic activity.[23] Therefore, if administered prior to bedtime, it is possible that melatonin may contribute to nocturnal suppression of the sympathetic nervous system, a factor which underlies the nocturnal BP dip.

Melatonin may also have a direct effect on peripheral arteries, causing vasodilation and a decrease in BP, since melatonin receptors have been found in arteries of rodents,[24] and melatonin has been shown to modulate rat vascular smooth muscle tone.[25] Two melatonin receptor subtypes, Mel 1a and Mel 1b, have been identified in humans. Mel 1a is primarily found in the SCN and the pituitary and cerebral vasculature, whereas Mel 1b is found in the retina. Outside the central nervous system, melatonin binding has been demonstrated in tissues including the coronary vasculature.[26]

Executive Summary

• Melatonin is an important regulatory hormone and a potent antioxidant; with receptors in the retina, pituitary, and cerebral and coronary vasculature, it has wide ranging effects in the body and may be useful as a therapeutic tool in the treatment of hypertension.

• Ambulatory blood pressure monitoring has identified a subset of diurnal "non-dipper" hypertensive patients who do not exhibit the typical 10% or greater decline in nocturnal blood pressure from daytime blood pressure. Such patients are at greater risk for adverse cerebrovascular and cardiovascular events in the morning.

• The non-dipper profile is a marker for altered circadian rhythm as reflected by decreased melatonin secretion with impaired cardiovascular relaxation and increased sympathetic tone during sleep. Although long-term intake of melatonin has not yet been safely established, adjustments in lifestyle to promote (maximize) endogenous melatonin secretion include: 1) increased daily dietary intake of melatonin- (and its precursor tryptophan) containing foods, 2) avoidance of caffeine and alcohol, especially at night, and 3) separation from bedtime by at least 8 hours of medications known to suppress melatonin secretion such as aspirin, beta blockers, and calcium channel blockers.

Human Clinical Studies of the Effect of Melatonin on Blood Pressure

Cagnacci et al, in a small placebo-controlled study of 17 young, healthy, early follicular phase women, demonstrated that a single 1 mg oral dose of melatonin administered between 14:00-18:00 significantly decreased systolic (-9.5 ± 2.8 mmHg; $P < 0.01$), diastolic (-7.5 ± 1.4 mmHg; $P < 0.01$), and mean (-7.4 ± 1.5 mmHg; $P < 0.01$) BP, and standing norepinephrine levels (-105.1 ± 43.5 pg/mL, $P < 0.02$) within 90 minutes compared to placebo.[23]

Scheer et al performed a randomized, double-blind, placebo-controlled, crossover trial in 16 men with untreated essential hypertension to investigate the influence of acute and repeated (daily for three weeks) oral melatonin on 24-hour ABPM. One hour prior to bedtime, melatonin was taken in a dose of 2.5 mg.

Repeated, but not acute, melatonin intake reduced systolic and diastolic BP during sleep by 6 mmHg and 4 mmHg, respectively. No change in heart rate was observed.[27]

Studies done thus far on the effects of melatonin on BP profiles of hypertensive patients have the drawback of being very small and short term, with the longest study lasting only four weeks.

It is also not clear how melatonin interacts with other antihypertensives. Table 1 lists some common drugs that affect melatonin levels.[28-37] Of note is the fact that certain antihypertensives, specifically beta blockers and calcium channel blockers, suppress melatonin. The closer to bedtime these medications are taken, the more likely they are to suppress melatonin secretion and affect nocturnal BP.[28] Therefore, taking the necessary antihypertensives early in the morning would minimize effects on the circadian rhythm of BP mediated by melatonin.

Table 1

Substances affecting melatonin levels

Augment Melatonin Levels	Suppress Melatonin Levels
MAO inhibitors[28]	Alcohol[29]
Norpramine[28]	Tobacco[28,30]
Luvox[28]	Aspirin, NSAIDS[31]
Lithium[28]	Caffeine (tea, coffee, dark chocolate, sodas)[32]
St. John's wort[28]	Prozac[28,33]
	Sedative-hypnotics[34]
	Calcium channel blockers[35]
	Beta blockers[36]
	Steroids (dexamethasone)[28,37]

Adapted from: Reiter R, Robinson J. *Melatonin: Your Body's Natural Wonder Drug.* New York: Bantam Books; 1995:134, 135, 181-191.

Concomitant Use of Melatonin and Conventional Antihypertensives

Lusardi et al performed a double-blind, randomized, placebo-controlled, crossover study of 50 mild-to-moderate essential hypertensive outpatients aged 38-65 (44% female).[38] All patients had been stabilized on nifedipine GITS (gastrointestinal transport system) monotherapy with well-controlled BP (< 140/90 mmHg) for three months prior to the study. Patients received 5 mg of immediate-release melatonin or placebo at bedtime for four weeks and then were crossed over. ABPM at the end of each treatment revealed that this dose of melatonin induced a significant *increase* in systolic and diastolic BP of +6.5 mmHg ($P < 0.001$) and +4.9 mmHg ($P < 0.01$), respectively throughout the 24-hour period.

On the other hand, Zeman et al studied 190 patients with primary hypertension previously treated for a minimum of three months with a variety of antihypertensives, including ACE inhibitors, calcium channel blockers, beta blockers, and diuretics.[39] NDIPs comprised 36% of the study population. All were monitored via ABPM. In a subgroup of 61 patients, plasma melatonin concentrations were measured in the middle of the dark (02:00) and light (14:00) time periods. Although there were no significant differences in daytime BP between DIPs and NDIPs, nighttime systolic, diastolic, and mean arterial BP measurements were higher in NDIPs than in DIPs (P values of 0.05, 0.001, and 0.001, respectively.) Similarly, daytime melatonin concentrations were low in all patients and did not differ between DIPs and NDIPs. However, there was a lower ratio of night/day melatonin concentrations for hypertensive patients that exhibited the NDIP profile.

Melatonin Dosage for Hypertension

Although generally regarded to be safe for short-term use, melatonin is a hormone with wide-ranging effects in the body, and long-term safety has not been established. Most melatonin supplements are synthetic but chemically identical to the melatonin produced in the body. Melatonin extracted from animal glands is a concern for potential infection with the prion responsible for mad cow disease (bovine spongiform encephalopathy) and variant Creutzfeld-Jakob disease in humans. Supplement companies are required to list the source of the melatonin if plant- or animal-based.

The optimal dose of melatonin is not clear, although it has been used in studies for BP control in the range of 0.5-5 mg/d. It is available in controlled- and immediate-release forms. The 2.0 mg controlled-release form has been taken for up to four weeks without adverse effects. Up to 5 mg of the immediate-release form has been taken in clinical studies for 1-4 weeks with some patients reporting side effects of headache, lightheadedness, drowsiness, and weakness.[40]

Dietary Melatonin Sources

Tart cherries and walnuts are excellent dietary sources of melatonin. Montmorency cherries, which account for the majority of tart cherries produced in the United States, contain 13.5 ng of melatonin per gram of fruit,[41] and are available all year in frozen, dried, or juice form. Serving sizes are 1 cup of frozen cherries

(134 g), ½ cup dried cherries (60 g), or 8 fluid ounces of juice (240 mL).[42] Walnuts provide 2.5-4.5 ng of melatonin per gram of nuts consumed.[43] Reiter and colleagues found that feeding chicks a melatonin-rich plant diet increased blood levels of melatonin, indicating that dietary melatonin is absorbed and enters the general circulation, after which it can bind to sites in the brain and other tissues.[44]

Because tryptophan is an essential amino acid from which melatonin is derived, theoretically another way to boost melatonin levels is to eat foods rich in tryptophan. However, clinical studies demonstrating a beneficial effect on BP from dietary tryptophan intake do not exist. Table 2 lists some foods rich in tryptophan.[45]

L-Tryptophan supplements were banned from public sale in 1989 due to an outbreak of eosinophilia-myalgia syndrome, which was traced to a contaminated product from a single manufacturer. However, 5-hydroxy-L-tryptophan (5-HTP), the immediate precursor in serotonin biosynthesis, has been available as a dietary supplement for almost 20 years and thus far no definitive cases of toxicity have emerged despite world-wide usage.[46]

Adverse Effects

Melatonin reduces fertility in women by suppression of the mid-cycle surge of luteinizing hormone secretion and subsequent inhibition of ovulation.[47] In clinical studies, morning drowsiness and overall weakness were more frequently reported by patients on melatonin than placebo. Therefore, melatonin should not be used by persons who will drive or operate heavy machinery, it should not be taken during the day in daytime active people, and it should not be used concomitantly with other sedating medications.

Patients with autoimmune disease may respond differently to melatonin and such patients should be carefully monitored. Reiter et al, however, report that melatonin can modulate the immune system in a beneficial way by enhancing natural killer cell activity, inhibiting cytokine production and decreasing inflammation.[48] There has been a report of a possible association between melatonin use and exacerbation of Crohn's disease, but the variable natural history of Crohn's disease in any given patient complicates assessment of this potential adverse effect.[49]

Because melatonin has not been tested in pregnant women and small amounts of melatonin are transmitted through breast milk and might adversely affect infant brain development, it should not be used by pregnant mothers or those who are breastfeeding.[40] The use of melatonin in conjunction with calcium channel blockers may cause BP elevation.[38] Certain medications such as calcium channel blockers, beta blockers, and aspirin are, however, important for patients with cardiac disease. Taking them early in the day may not only minimize their inhibitory effects on the production of melatonin (which occurs at night), but also may help offset early morning increases in BP and coagulability.[50]

Table 2

Foods rich in tryptophan

Food	Tryptophan Content (mg/200 calories)
Spinach (frozen, chopped, or raw)	1,051
Spirulina seaweed (dried)	738
Halibut (cooked, with skin)	592
Turkey breast, roasted	507
Cottage cheese (nonfat)	452

Adapted from: Nutrition Data: Nutrition Facts and Calorie Counter: 999 Foods Highest in Tryptophan. Available at: www.nutritiondata.com/foods-00007900000000000000-5. Accessed June 3, 2007.

Conclusion

The lack of nocturnal decline in BP is clinically important because the prognosis for NDIP hypertensive patients is worse than for those with the DIP profile. NDIP and DIP hypertensives differ from each other in their hemodynamic response during sleep and in their physiological response to darkness, as judged by the differential pattern of nocturnal melatonin secretion and autonomic regulation.

The use of melatonin may be a potentially important new strategy for the treatment of primary hypertension with few adverse side effects and possibly several additional benefits. The 5-10 mmHg decline in BP seen with melatonin administered at bedtime is of relevance because a similar decrease in diastolic BP in hypertensive patients is associated with a 20% reduction in cardiovascular mortality.[51] However, larger and longer-term trials are necessary to establish which patients would benefit most from the use of melatonin. It will also be important to definitively establish the specific types of antihypertensives with which it can be used.

Recommendation

Larger and longer-term studies are needed to determine whether melatonin can be used, and how much can

safely be ingested on a chronic basis, and for how long, to treat essential hypertension. Potential subgroups of hypertensive patients with a NDIP profile as determined by ABPM may especially benefit from the risk reduction offered by treatment of their circadian dysregulation. Lifestyle modifications, such as taking potentially melatonin-suppressing essential medications early in the day and limitation of alcohol and caffeine intake, particularly in the hours prior to bed, may alleviate suppression of endogenous melatonin secretion and improve BP control. ❖

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Tai Chi to Prevent Falls Among the Elderly

By Dónal P. O'Mathúna, PhD

PART 2 OF A SERIES ON TAI CHI: RISK OF FALLING AS OUTCOME

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TAI CHI IS INCREASINGLY BEING USED IN FALL PREVENTION programs, especially with the elderly. Part 1 of this article described tai chi in some detail and reviewed research studies involving the practice where the incidence of falls was the primary outcome. The review found a relatively small number of studies, which were generally supportive of tai chi as a program to reduce falls in those living in the community. Another group of studies have measured outcomes regarded as indicators of a person's risk of falling. These studies will be the focus of this article.

Fear of Falling

In addition to physical injury, falls can lead the elderly to become afraid of falling. Approximately half of the elderly living in the community experience such fear of falling, although it can have a variety of sources.[1] This fear can lead to a debilitating spiral of loss of confidence,

reduced physical activity and social involvement, more falls, further frailty, and loss of independence. Tai chi is one of several interventions that has been evaluated to determine if it reduces fear of falling, which may be taken as a predictor of reduced falling. A 2007 systematic review of these interventions identified 12 high-quality randomized controlled trials (RCTs), of which three evaluated tai chi.[1]

Two of these studies also measured the number of falls and were reviewed in more detail in Part 1.[2,3] Both were carried out with older people living in the community. The number of falls, and the fear of falling, was reduced significantly in both. A third study in this area randomly assigned 49 people, older than age 60 who lived in the community, to either a tai chi or control group.[4] Those assigned to the control group were asked to make no changes in their physical activity and did not meet together except when outcomes were being measured. Tai chi was practiced as a group for one hour daily for eight weeks. If participants could not attend the group session they were asked to conduct a 30-minute session at home. On average, subjects participated in 35 hours of tai chi over the eight weeks. Using the Falls Efficacy Scale, those in the tai chi group had significant improvements in their fear of falling compared to the control group ($P = 0.006$). The authors noted that their study design did not allow determination of whether the benefit may have arisen at least in part from the regular social interaction in the tai chi group.

Balance

Impaired balance has been identified as a major intrinsic factor contributing to falls among the elderly.[5] Beginning in the 1990s, a number of cross-sectional studies showed that tai chi practitioners exhibited less swaying and had better balance than matched controls who did not practice tai chi.[6] However, many of these studies were conducted using younger and middle-aged adults, not older adults.[7] Also, since these were cross-sectional studies, differences could have existed prior to training in tai chi.

One trial found no correlation between balance performance and number of years of tai chi experience.[5] Therefore, an RCT was conducted with 49 community-dwelling older people (average age 69 years) who had no experience with tai chi.[5] Those in the intervention group undertook 90 minutes of tai chi together, six days a week for eight weeks. Those in the control group met together for a general education program that lasted the same length of time. Using two validated balance measures, the tai chi group had significantly better balance at four weeks, eight weeks, and four weeks after the intervention stopped. Their scores on these tests were similar to those recorded by experienced tai chi practitioners, suggesting that the benefits of tai chi for balance can be achieved within four weeks.

Executive Summary

- *Available evidence supports the use of tai chi to reduce the risk of falling.*
- *Tai chi is a safe practice for older community dwellers provided the usual precautions regarding exercise are followed.*
- *Further research is needed in this area before robust clinical recommendations can be offered.*

One of the studies reviewed in Part 1 found fewer falls after tai chi training than with exercise training, and also showed improved balance.[3] Regression analysis found that those participants who improved their balance were also significantly less likely to fall in the subsequent six months. In addition, the study of fear of falling in 49 older community dwellers described above found significant improvements in one-leg balancing among those in the tai chi group ($P < 0.001$).[4] Another RCT involved 49 elderly men with osteopenia or osteoporosis.[8] The community-dwelling men (aged 60-82 years) were randomly assigned to a non-intervention control or 18 weeks of tai chi practiced for 45 minutes, twice a week. Significant improvements in balance were found for the tai chi group while no changes were found in the control group.

In contrast, another study randomly assigned 180 community-dwelling elderly people (aged 65-74 years) to one of three groups.[9] One group engaged in tai chi, another performed resistance exercises, and the third had no intervention. The exercise sessions were conducted three times per week for one year. No significant differences were found between the groups with respect to balance, flexibility, muscle strength, or number of falls. Among women in the study, those in the tai chi and exercise groups had significantly less loss of bone mineral density than women in the control group ($P < 0.05$).

Yet another study showed that after one hour of tai chi, three times weekly for 12 weeks, 39 older people (average age 65 years) had improvements on a battery of tests measuring balance, muscle strength, endurance,

and flexibility.[10] However, no control group was used in this particular study.

Two of the RCTs described above that found a reduced incidence of falls also measured physical functioning. The earlier RCT involved 200 participants and conducted several measurements of muscle strength, flexibility, cardiovascular endurance, and body composition.[2] Few statistically significant differences were found, except that those in the tai chi group had less loss of grip strength and greater lower extremity range of motion than the control group. The other RCT found significantly greater improvements in trunk flexibility among those in the tai chi group compared to the control group ($P < 0.001$).

A quasi-controlled study randomly assigned two long-term care facilities to be either the tai chi or control site.[11] A total of 68 residents participated. Tai chi classes were taught three times per week for 35 minutes for 12 weeks at one site, while the control site received no exercise intervention. The number of falls did not differ between the sites, but outcomes for muscle strength, flexibility, balance, and mobility were significantly better in the tai chi group compared to control ($P < 0.001$).

Adverse Effects

No adverse effects of tai chi were reported in the studies reviewed here.

Conclusion

The first part of this review examined the small number of existing studies evaluating tai chi in the elderly, and generally found tai chi reduced the incidence of falls among community-dwelling adults. The studies examined here of risk factors for falls lend further support to the conclusion that tai chi is beneficial. The total number of studies remains small, however, and much heterogeneity exists in study design and outcomes measured. Much variety exists in the tai chi protocols and frequency of practice, with little consensus regarding the schedule needed for beneficial or optimal effects. Further research is needed before firm recommendations can be offered, but the indications are that tai chi is useful in helping to reduce falls and risk of falls.

Recommendation

Tai chi training may be of benefit in helping prevent falls in elderly people living in the community. Less evidence is available to support the use of tai chi for

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

36. Which of the following medications can suppress melatonin secretion?
a. Beta blockers
b. Aspirin
c. Sedative-hypnotics
d. All of the above

37. The "non-dipper" blood pressure profile is a risk factor for poor cardiovascular outcomes.
a. True
b. False

38. The risk of falling is believed to be impacted by:
a. fear of falling.
b. ability to balance oneself.
c. physical functioning ability.
d. All of the above

39. Older people thinking of starting tai chi should be cautioned about:
a. the high incidence of serious adverse effects with tai chi.
b. the increased risk of falling with tai chi.
c. the considerations involved with any program that includes physical activity.
d. All of the above

Answers: 36. d, 37. a, 38. d, 39. c.

those who are more frail or reside in nursing homes.

Tai chi programs vary considerably in duration and rigor; therefore, they should be approached carefully and the intensity increased gradually. As with any exercise program, individualized medical advice should be sought before commencing, and any changes carefully monitored.

People should remain alert to any symptoms that indicate overexertion. Keeping such cautions in mind, regular practice of tai chi may help improve balance and physical functioning, and thus contribute to reducing the incidence of falls and fear of falling. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Pro vs. Anti: Diarrhea with Antibiotics

Source: Hickson M, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: Randomized double blind placebo controlled trial. *BMJ* 2007;335:80. Epub 2007 Jun 29.

Goal: To determine whether ingestion of a commercially available probiotic drink protects against antibiotic-associated diarrhea (AAD) in older hospitalized patients.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Subjects: Older hospitalized patients (n = 135, mean age = 74 years) recruited from three London hospitals and taking antibiotics (data analyzed on 113 subjects).

Methods: Subjects were divided into two groups: Those randomized to the placebo intervention received a long-life sterile milkshake (Yazoo), while those in the active group consumed a yogurt drink (Actimel®) containing *Lactobacillus casei*, *L. bulgaricus*, and *Streptococcus thermophilus*. The drinks were ingested twice a day beginning within 48 hours of initiation of antibiotic therapy (oral or intravenous) and continued for one week past completion of the course. The primary outcome was occurrence of diarrhea; secondary outcome measures focused on diarrhea due to *Clostridium difficile* and presence of its toxin (A, B, or both) in a stool sample. Final follow-up was five weeks after completion of antibiotic therapy. *Lactobacillus* counts were carried out on probiotic drink samples to ensure the presence of viable organisms, baseline stools samples were screened for *C. difficile*, and subjects' compliance was assessed.

Results: Subjects in the probiotic group developed AAD at a lesser rate than those in the placebo group (12% vs. 34%, odds ratio of 0.25 for use of the probiotic). The absolute risk reduction with probiotic use was 22%. While 17% of subjects in the placebo group had diarrhea due to *C. difficile*, no one in the active group did (absolute risk reduction with probiotic use = 17%). No adverse events related to study drinks were reported.

Conclusion: Consumption of a specific commercially available probiotic drink

reduces the incidence of AAD and *C. difficile* diarrhea in older hospitalized patients receiving antibiotic therapy.

Study strengths: Close follow-up of subjects who were discharged from the hospital; checking for viability of microbes; use of commercially available drinks; intention-to-treat analysis; screening for *C. difficile*.

Study weaknesses: Significant problems with recruitment; possible (albeit unlikely) bias through unblinding; incomplete data on 16% of initial participants; compliance (only 75% in the probiotic group, reported to be mainly due to delivery and distribution failures).

Of note: A total of 1,760 patients were screened with only 135 subjects taking part in the trial; the most common reason for exclusion was likelihood of diarrhea from causes unrelated to antibiotic therapy; patients and researchers were blind to the study drinks, and individual hospital pharmacies were in charge of dispensing; for purposes of this trial, diarrhea was defined as two or more liquid stools/day for three or more days; subjects were mainly on orthopedic, "elderly care," and general medical wards; 40% of subjects were receiving more than one antibiotic; Yazoo is an "ultra high temperature treated product and has no bacterial count"; exclusion criteria included antibiotic use within the prior four weeks, history of valvular heart disease, and bowel surgery; partway through the trial researchers received approval to recruit patients with cognitive impairment (total of seven, with three in the active group); low albumin and low sodium levels were also associated with an increased risk of diarrhea; estimated cost for a 17-day course of Actimel is $20; estimated costs for treating *C. difficile* diarrhea run to $3,700, mainly due to use of vancomycin and the requisite increase in duration of hospitalization.

We knew that: Probiotics are defined as live microorganisms which, upon ingestion by a host in sufficient amounts, exert health benefits beyond basic nutrition; multiple studies suggest that probiotic therapy is effective at preventing AAD and is safe; diarrhea associated with antibiotic use is a common complication occurring in 5-25% of patients, with *C. difficile* the causative agent in 15-25% of cases, most often in older patients; *C. difficile* diarrhea typically occurs 2-3 weeks after cessation of antibiotic therapy.

Clinical import: AAD is a cause of significant morbidity for patients at each end of the age spectrum. While a number of studies have examined specific microbes for the prevention of AAD, few trials have been performed in older patients, fewer still using a commercially available probiotic drink. The results of this trial are convincing, and many questions persist.

It is well known that antibiotics can interfere with colonic microflora homeostasis. Probiotic therapy may offer benefits in the setting of antibiotic administration in a number of ways, including stimulation of the host immune response, competition with neighboring pathogens for nutrients and receptor sites, increased mucin production (thereby blocking mucosal adhesion), production of antimicrobial substances, and interference with toxins. Which, if any, of these actions is at work is yet to be agreed upon. The therapy does, however, appear to be successful. It also appears to be safe, though caution is warranted in the immunocompromised (live bacteria do translocate). It seems reasonable to utilize probiotics in the setting of antibiotic administration even while the mechanism of action of probiotic therapy is still being worked out. And yet, which organisms to employ?

The effects of probiotic therapy are strain-specific. As the authors readily point out, it is not possible from the data to determine whether a synergistic interaction between the three microbes helped prevent illness, or if a single microbe was especially effective, or any combination of factors in between. All that can be stated from the trial is that the specific combination of the three microbes in the dosages employed seems effective.

Duration of therapy has also been a question. In this trial, probiotic administration during antibiotic therapy and continued for one week thereafter offered benefit.

The authors intimate that some form of probiotic therapy should be considered routinely for older patients on antibiotics. A wealth of data on probiotics is now on hand, and this recommendation seems more than reasonable, but specific information on recommended strains and dosage is still somewhat haphazard.

What to do with this article: Keep a hard copy in your file cabinet. ❖

Rice is Nice: Red Yeast Rice and Lipids

Source: Huang CF, et al. Efficacy of *Monascus purpureus* Went rice on lowering lipid ratios in hypercholesterolemic patients. *Eur J Cardiovasc Prev Rehab* 2007;14: 438-440.

Goal: To determine the effect of red yeast rice (RYR) on lipid ratios.

Design: Randomized, double-blind, placebo-controlled trial performed over eight weeks in Taiwan.

Subjects: Women and men with hypercholesterolemia aged 23-65 years (n = 79).

Methods: All participants followed an American Heart Association Step I diet program for four weeks as lead-in to the trial. Subjects meeting study criteria were then randomized to receive either RYR 600 mg or a rice powder placebo twice daily. Twelve-hour fasting blood samples were taken at the time of randomization, as well as four and eight weeks into the trial period.

Results: The placebo group did not experience significant improvements in lipid levels or lipid ratios. Those receiving RYR showed a significant improvement over the placebo group in LDL-C levels, as well as total cholesterol (TC)/HDL-C, LDL-C/HDL-C, and Apo B/Apo A-I ratios. After eight weeks, TC decreased by 20%, LDL-C by 26%, and

Apo B by 25%. The active group also saw decreases in the percentage of subjects with TC/HDL-C > 5 (from 64% to 33%), LDL-C/HDL-C > 5 (from 33% to 8%), and Apo B/Apo A-I ≥ 1 (from 67% to 28%).

Conclusion: RYR can effectively lower lipid ratios in patients with dyslipidemia.

Study strength: Consideration of multiple lipid measures.

Study weaknesses: Short duration; no information on adverse events or side effects (if any); no data on HDL-C or triglyceride levels.

Of note: Subjects had to have an LDL-C > 160 mg/dL, TC > 240 mg/dL, and triglycerides < 400 mg/dL to participate; participants received dietary instruction from a registered dietitian during the intervention phase of the trial; data suggest that patients with low LDL-C levels but a high TC/HDL-C ratio have a significantly higher incidence of coronary artery disease than those with similar LDL-C levels, but low TC/HDL-C ratios; the dose employed in the trial is lower than what is commonly recommended (1,200 mg twice daily).

We knew that: Lipid ratios may reflect the proportion of atherogenic to antiatherogenic lipids and lipoproteins; a small number of trials have shown RYR to be effective in improving lipid profiles; prior study suggests that for each 1% decrease in TC/HDL-C there is an associated 1.3% reduced risk for coronary artery disease, and that each unit difference in the same ratio is associated with an 18% reduction in risk for a coronary event; additional data suggest that for each one unit increase in the LDL-C/HDL-C ratio, there is an associated 1.2-fold increase in risk of cardiovascular disease; Apo B/Apo A-I is an indicator of non-HDL particle size divided by HDL particle size; many experts have called for the Apo B/Apo A-I ratio to be included in the standard lipid profile, but recent data call into question whether the ratio is as predictive of cardiovascular risk when evaluated on its own as previously believed.

Clinical import: Most research articles on management of lipid disorders focus on the impact of treatment on specific levels of lipids or lipoproteins. This trial addressed the use of RYR on lipid ratios, parameters that have been growing in popularity among specialists. Most of us are familiar with the TC/HDL-C ratio (optimally < 3.5), and are becoming more familiar with measurements of Apo B (a protein component of LDL-C and VLDL-C), Apo A-I (the major protein fraction of HDL-C), and the Apo B/Apo A-I ratio. This trial suggests that RYR is effective in modifying cardiovascular risk based on its effects on lipid parameters, including specific ratios.

Statin therapy is quite effective for management of most forms of dyslipidemia, but often is associated with untoward side effects on liver and muscle. RYR possesses statin activity at a very low dosage (but enough to solicit a warning letter from the FDA, see www.fda.gov/bbs/topics/NEWS/2007/NEW01678.html for details), yet existing data suggest it to be similarly effective and likely associated with fewer side effects. RYR seems a reasonable option, but relatively little research exists using the supplement and more is necessary. The trial at hand contains significant flaws, but its results are strong.

One challenge for practitioners is that we need to be able to steer patients toward trusted manufacturers of RYR if this therapy is to be employed. It should be kept in mind that elevation of liver enzymes has been seen with RYR, and a similar level of repeat clinical evaluation as warranted with statin therapy would seem prudent. In addition, use of coenzyme Q10 is a consideration, as it is with statins.

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In Future Issues:

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September 2007

ALTERNATIVE MEDICINE ALERT™
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Hypertension: A Patient Handout

HIGH BLOOD PRESSURE INCREASES YOUR CHANCE (OR RISK) FOR GETTING HEART DISEASE and/or kidney disease, and for having a stroke. It is especially dangerous because it often has no warning signs or symptoms. Regardless of race, age, or gender, anyone can develop high blood pressure. It is estimated that one in every four American adults has high blood pressure. Once high blood pressure develops, it usually lasts a lifetime. You can prevent and control high blood pressure by taking action.

Why Is High Blood Pressure Important?

High blood pressure is dangerous because it makes the heart work too hard. It also makes the walls of the arteries hard. High blood pressure increases the risk for heart disease and stroke, the first- and third-leading causes of death for Americans. High blood pressure can also cause other problems, such as heart failure, kidney disease, and blindness.

What Causes High Blood Pressure?

The causes of high blood pressure vary. Causes may include narrowing of the arteries, a greater than normal volume of blood, or the heart beating faster or more forcefully than it should. High blood pressure might also be caused by another medical problem. Most of the time, the cause is not known. Although high blood pressure usually cannot be cured, in most cases it can be prevented and controlled.

Who Can Develop High Blood Pressure?

High blood pressure is common. About 65 million American adults—nearly 1 in 3—have high blood pressure. It is very common in African Americans, who may get it earlier in life and more often than whites. Many Americans tend to develop high blood pressure as they get older, but this is not a part of healthy aging. Middle-aged Americans face a 90% chance of developing high blood pressure during their lives. Others at risk for developing high blood pressure are the overweight, those with a family history of high blood pressure, and those with prehypertension (120-139/80-89 mmHg).

High Blood Pressure Detection

You can find out if you have high blood pressure by having your blood pressure checked regularly. Most doctors will diagnose a person with high blood pressure on the basis of two or more readings, taken on several occasions. A consistent blood pressure reading of 140/90 mmHg or higher is considered hypertension, another term for high blood pressure.

Some people experience high blood pressure only when they visit the doctor's office ("white-coat hypertension"). If your doctor suspects this, you may be asked to monitor your blood pressure at home or asked to wear a device called an ambulatory blood pressure monitor. This device is usually worn for 24 hours and can take blood pressure every 30 minutes.

Tips for Having Your Blood Pressure Taken

- Don't drink coffee or smoke cigarettes 30 minutes before having your blood pressure measured.

- Before the test, sit for five minutes with your back supported and your feet flat on the ground. Rest your arm on a table at the level of your heart.
- Wear short sleeves so your arm is exposed.
- Go to the bathroom prior to the reading. A full bladder can change your blood pressure reading.
- Get two readings, taken at least two minutes apart, and average the results.
- Ask the doctor or nurse to tell you the blood pressure reading in numbers.

Prevention

You can take steps to prevent high blood pressure by adopting a healthy lifestyle. These steps include maintaining a healthy weight; being physically active; following a healthy eating plan that emphasizes fruits, vegetables, and low-fat dairy foods; choosing and preparing foods with less salt and sodium; and, if you drink alcoholic beverages, drinking in moderation.

Healthy Eating. Research has shown that following a healthy eating plan can both reduce the risk of developing high blood pressure and lower an already elevated blood pressure.

For an overall eating plan, consider the DASH eating plan. DASH stands for Dietary Approaches to Stop Hypertension, a clinical study that tested the effects of nutrients in food on blood pressure. Study results indicated that elevated blood pressures were reduced by an eating plan that emphasizes fruits, vegetables, and low-fat dairy foods, and is low in saturated fat, total fat, and cholesterol. The DASH eating plan includes whole grains, poultry, fish, and nuts and has reduced amounts of fats, red meats, sweets, and sugared beverages.

A second clinical study, called DASH-Sodium looked at the effect of a reduced dietary sodium intake on blood pressure as people followed either the DASH eating plan or a typical American diet. Results showed that reducing dietary sodium lowered blood pressure for both the DASH eating plan and the typical American diet. The biggest blood pressure-lowering benefits were for those eating the DASH eating plan at the lowest sodium level (1,500 mg per day).

Reduce Salt and Sodium in Your Diet. A key to healthy eating is choosing foods lower in salt and sodium. Most Americans consume more salt than they need. The current recommendation is to consume less than 2.4 g (2,400 mg) of sodium a day. That equals 6 g (about 1 teaspoon) of table salt a day. The 6 g include all salt and sodium consumed, including that used in cooking and at the table. For someone with high blood pressure, the doctor may advise eating less salt and sodium, as recent research has shown that people consuming diets of 1,500 mg of sodium had even better blood pressure lowering benefits. These lower-sodium diets also can keep blood pressure from rising and help blood pressure medicines work better.

Issues for Women

Three out of four women with high blood pressure know they have it. Yet fewer than one in three are controlling their blood pressure. All women should take steps to control their blood pressure.

Pregnancy. Although many pregnant women with high blood pressure have healthy babies without serious problems, high blood pressure can be dangerous for both the mother and the fetus. Women with pre-existing or chronic high blood pressure are more likely to have certain complications during pregnancy than those with normal blood pressure. However, some women develop high blood pressure while they are pregnant (often called gestational hypertension).

The effects of high blood pressure range from mild to severe. High blood pressure can harm the mother's kidneys and other organs, and it can cause low birth weight and early delivery. In the most serious cases, the mother develops preeclampsia, which can threaten the lives of both the mother and the fetus.

Oral Contraceptives. Women taking oral contraceptives experience a small but detectable increase in both systolic and diastolic blood pressure, usually in the normal range. Women age 35 and older who smoke cigarettes are at even greater risk for heart disease and stroke and are encouraged to quit smoking. If they are unable to quit smoking, they should talk to their doctor about using other forms of contraception.

Hormone Replacement Therapy. A recent study indicated that blood pressure does not increase significantly with hormone replacement therapy in most women with and without high blood pressure. However, a few women may experience a rise in blood pressure attributable to estrogen therapy. Therefore, it is recommended that all women treated with hormone replacement therapy have their blood pressure monitored more frequently after such therapy is started.

Source: National Heart, Lung and Blood Institute. Available at: www.nhlbi.nih.gov/hbp/index.html. Accessed Aug. 16, 2007.