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FALLS

ABSTRACT & COMMENTARY

Tai Chi and Fall Risk

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: Tai chi practice in the older and at-risk population reduces the risk of falls (with the most robust results in the short-term) and may reduce the risk of injury from falls; no effect is seen when measuring time to the first fall.

SOURCE: Lomas-Varga R, Obrero-Gaitan E, Molina-Ortega FJ, Del-Pino-Cassado R. Tai chi for risk of falls. A meta-analysis. *J Am Geriatr Soc* 2017;65:2037-2043.

Falls and fall-related complications hold the dubious honor of ranking first as the primary cause of death via injury in older adults worldwide.[1] It is no wonder that efforts to reduce the incidence of falls and injury from falls are underway. Exercise, environmental modification, and reduction of polypharmacy, especially in cases in which dizziness, sedation, or unsteady gait may occur, are among interventions proposed and studied to address this issue.[2]

Tai chi is a traditional Chinese systemic exercise program known for improving balance, flexibility, and endurance. It is one of several exercise programs that has produced promising preventive data from multiple studies. However, Lomas-Varga et al noted shortcomings and limitations, such as lack of control groups and small sample size, with many of the tai chi studies. Additionally, it is important to note that there are several major styles of tai chi and that practitioners may vary in skill and ability to teach.

This meta-analysis targeted recent randomized, controlled studies that looked at specific outcome points, including the effect of tai chi on the fall rate in general, the rate of injurious fall, and time to the first fall in a homogenous population of older and at-risk adults. Additionally, the effect of tai chi in both the short term (< 12 months) and long term were compiled using data from the appropriate studies.

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Summary Points

- The authors of this meta-analysis presented results from 10 randomized, controlled studies regarding tai chi practice in at-risk and older adults, including more than 2,500 subjects between the ages of 56 and 98.
- The analysis showed high-quality evidence for medium protective effect for rate of falls in the short-term and a weaker protective effect over the long-term (after 12 months.)
- When looking at falls causing injury, there is low-quality evidence of a medium protective effect in the short term and even less of an effect in the long term.
- There is moderate-quality evidence that tai chi practice does not affect time to first fall.

From an initial pool of 891 references, 10 studies met the rigid eligibility criteria to be included in the final meta-analysis. All were randomized, controlled trials (RCT). Four of these studies included data on short-term results only, another four recorded long-term data, and one study contained both short- and long-term outcomes. Participants numbered just under 3,000 older adults between the ages of 56 and 98.

The quality of evidence backing the results of each study was evaluated based on a standard system — the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).[3] Using these guidelines, quality of evidence was placed on a range stemming from very low to low, moderate (needing further research), and high (indicating that further research is unlikely to change confidence in the assessment of impact).

None of the included RCTs documented any adverse effect from the practice of tai chi. All of the studies included about an hour of practice time in each session. The frequency of sessions ranged from one to three times weekly; studies lasting less than 12 months were grouped separately from those continuing longer than one year. Documentation of the type or style of tai chi were not included in the final analysis.

Selected results are presented in Tables 1, 2, and 3. These results point to high-quality evidence (using the GRADE system) that the practice of tai chi may reduce the risk of fall by 43% in the short term, but that this effect is reduced in long-term follow-up to about 13%, although both results are statistically significant. The evidence toward risk of injurious fall reduction is low quality, as per the GRADE system and based on fewer studies. The time to first fall has moderate-quality evidence (GRADE) of no effect from tai chi practice.

■ COMMENTARY

The cost of falls in older adults is considerable and multifaceted. In 2015, direct healthcare costs associated with falls totaled more than $30 billion, while indirect costs due to factors such as disability, loss of independence, and reduced quality of life, magnified the effect of what often appears to be a preventable event.[4] Modifiable risk factors include lower body weakness, deterioration of balance, poor vision, use of medications affecting balance and/or walking, and environmental factors, such as poor footwear and uneven floors.[2,3]

Primary care providers often are well-positioned to address many of these issues with patients at risk. Some of these factors require external modifications, such as changing footwear and/or critically looking at areas of risk within the home. Improving balance and lower body strength — two key areas in preventing falls and potentially reducing injury from falls — seem more suited to specific individual efforts. This meta-analysis points to promoting tai chi practice as a possible fall prevention intervention and gives

Table 1: Incidence of Falls		
	Short-term Results (< 12 months)	**Long-term Results**
Number of studies	5 studies	6 studies
Number of subjects	1,432 subjects	1,546 subjects
Incidence risk ratio	0.57 (95% CI, 0.46-0.70)	0.87 (95% CI, 0.77-0.98)
Quality of evidence	High	High
P value	0.000	0.029
Falls risk reduction	43%	13%

Table 2: Incidence of Injurious Falls		
	Short-term Results (< 12 months)	**Long-term Results**
Number of studies	1 study	1 study
Number of subjects	357 subjects	334 subjects
Incidence risk ratio	0.50 (95% CI, 0.33-0.75)	0.72 (95% CI, 0.54-0.95)
Quality of evidence	Very low	Very low
Risk of bias	Serious	Serious
Injurious fall risk reduction	50%	50%

Table 3: Time to First Fall	
Number of studies	5 studies
Number of subjects	1,320 subjects
Incidence risk ratio	0.98 (95% CI, 0.69-1.32)
Quality of evidence	Moderate
P value	0.883

some hard evidence of efficacy, at least in the short-term, but still leaves some unanswered questions.

There are five major styles of tai chi. The Yang style seems the most popular worldwide, and most likely to be the type of tai chi practiced in larger groups often seen in parks or gatherings. Movements tend to be slow and steady, as opposed to the older Chen style, which includes more energetic and faster movements interspersed with slower movements. The Sun style, on the other hand, concentrates almost entirely on internal movements and stillness.[5] It is unfortunate that most of the studies do not mention or control for style, as the type of tai chi practiced may influence results.

The strength of this meta-analysis was the high number of studies and subjects, which allows the results to be generalized more readily. Only one qualifying study looked at either short- or long-term injurious falls, making these results less meaningful. Hopefully, future investigations of tai chi will focus not just on fall rate but also on the effect of injurious falls.

Although this meta-analysis included an impressive number of subjects, the authors noted that the studies varied in specific details. While statistical analysis controlled for heterogeneity, some of these details may affect clinical adaptation. In particular, a review of the studies in this meta-analysis revealed a range of control groups from "activity as usual" to specific exercise programs. A comprehensive 2017 review (also a meta-analysis) of fall prevention associated with a different exercise intervention (Step Training Program) revealed results similar to those found with tai chi.[5] Notably, however, a 2011 Australian study found tai chi to be the most cost-effective intervention for fall prevention for community-dwelling older adults compared to several other interventions, including other exercise programs. Interestingly, medication review and vitamin D supplementation emerged as most cost-effective for older adults in residential facilities in this same study.[6]

Results of a 2017 Chinese meta-analysis, including 18 studies of tai chi and fall prevention, suggested that the impact of tai chi on fall prevention is more robust with exercise frequency.[7] However, noting significant bias in some of the studies, the authors recommended future direction aimed at reducing bias and eliciting more data regarding length of sessions, number of practices weekly, and overall effect. Additionally, this group noted a variation in response to different types of tai chi and mentions a likelihood that the Yang style of tai chi may be more effective than the Sun style. More studies documenting specific style of tai chi are recommended.

The variability in the types of control groups among the studies, in the frequency of tai chi practice (from one to three times weekly), and unclear documentation of the type or style of tai chi make generalizability of results of this meta-analysis difficult. All of these factors may very well prove to be essential in understanding the effect of tai chi for any individual.

Future studies paying particular attention to these details are needed.

Talking with older adults about fall prevention and recommending specific interventions is a vital component of medical care of the aging population. A 2017 public health study covering older adults in Hawaii suggested that this group tends to "deny their risk of falls before they actually fall" and, in general, view their own risk of falling more optimistically than statistics bear out.[8] Efforts promoting risk reduction seem less relevant if the targeted population is not on board. One proposed solution is to promote the positives, such as "maintain your independence," rather than warn about fall prevention per se.

Prevention of falls often requires a multipronged approach; the integrative provider is on solid ground reviewing both environmental and personal interventions with patients. Noting the positive results from tai chi studies, combined with an understanding of the limitations of these studies, can help shape a fall prevention strategy that suits each individual according to unique needs and circumstances. Developing such a plan with a focus on the positives may help with acceptance and buy-in. As future studies with more rigid criteria and results emerge, these recommendations and interventions can be adjusted accordingly, with the goal of helping our patients maintain a healthy lifestyle throughout the age continuum.

Although suggestive evidence points to best results from practice of the Yang style of tai chi several times weekly, many patients will find a specific choice of tai chi style and frequency, limited by practical considerations (such as community availability and scheduling). Even with specific questions remaining, the potential benefits from tai chi are clear. In the aging population and those at risk of significant health consequences from falls, waiting for results of more definitive studies may prove to be too late. With no identified adverse effects from tai chi and clear potentially devastating adverse health consequences from falls, promoting tai chi should be adopted as part of an overall strategy for fall prevention. ■

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DEPRESSION

ABSTRACT & COMMENTARY

Use of Essential Oils as an Alternative Treatment for Depression

By Erica Benedicto, PA-C, MPH, PYT

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Ms. Benedicto reports no financial relationships relevant to this field of study.

Editor's Note: This review covers numerous human clinical trials and basic science research to begin the process of exploring an interesting treatment modality, essential oils, for an all-too-common condition, depression. As Ms. Benedicto points out, there are some important clinical pearls in this area, even as we in the scientific and clinical community await more scientific rigor in the form of P values, confidence intervals, and large sample sizes. I look at this review for a glimpse into the potential therapeutic efficacy of essential oils, realizing that pilot studies, uncontrolled clinical trials, and case series need to be corroborated with more methodologically sound work. Hopefully, such future research can clarify dosing and treatment protocols that may be lacking in this preliminary review.

SYNOPSIS: The antidepressant effects of essential oils are promising, but more studies in humans beyond preliminary stages are needed.

SOURCE: de Sousa DP, Silva RHN, Silva EFD, Gavioli EC. Essential oils and their constituents: An alternative source for novel antidepressants. *Molecules* 2017; 22:e1290. doi: 10.3390/molecules22081290.

According to the World Health Organization, depression carries the heaviest burden of disability among mental disorders. Globally, the average prevalence for major depression is 4.7% or one out of 20 people.[1] The prevalence is 5.9% in women and 3.8% in men. Depression causes symptoms that affect people of all ages, compromising quality of life and all areas from work to social relationships. The search for effective alternatives to traditional pharmaceuticals is imperative. de Sousa et al studied essential oils, their constituents, mechanism of action, and therapeutic potential for depressive disorders.

Aromatic, medicinal plants have been used for centuries. Essential oils are rich in bioactive compounds. Studies have shown that they enter the blood stream either by inhalation or ingestion to cause psychological effects that complement pharmacological interventions. Examples of studies that have been conducted are in the realm of sleep quality,[2,3] anxiety,[4,5] nicotine craving,[6] and post-traumatic stress disorder.[7] This study was conducted to review essential oils and their constituents for the treatment of depression, since there is evidence that isolated compounds of these essential oils have antidepressant actions.

The authors performed a search of English-language PubMed articles from 1995 to December 2015 about plants and essential oils that have antidepressant activity. Plants were identified by chemical name and the name of their bioactive compounds. The reason for selecting certain plant species was to evaluate the antidepressant activity and to identify the mechanism of action of oils or particular components of the oils.

HUMAN STUDIES

Lavender. The most frequently studied essential oil for mood is lavender, as it has widely recognized anxiolytic effects.[5] Using lavender oil capsules from *Lavandula angustifolia* (Lamiaceae) flowers, Bezerra et al conducted a pilot study as an adjuvant therapy for major depression in eight patients with symptoms of anxiety, insomnia, and psychomotor agitation for three weeks. All three symptoms improved in the participants of this case series.[8]

Diego et al examined the moods of otherwise healthy adult men after acute inhalation of lavender oil. EEG activity, alertness, and mood were assessed and found to increase/improve in the 40 male participants. The researchers found that subjects also performed math calculations more accurately and faster.[9]

Summary Points

- The most studied essential oil for mood states is lavender, particularly well-known for its anxiolytic effects.
- The diverse chemically active constituents in essential oils work via several proposed mechanisms to positively affect depression.
- More studies on essential oils are required to support their use as real options for depression treatment.

In another pilot study, Conrad et al administered lavender and rose in an essential oil blend (*L. angustifolia* and rose) either topically or through inhalation to 28 postpartum women diagnosed with mild-to-moderate depression or anxiety in 15-minute sessions, twice a week for four consecutive weeks. The essential oils significantly relieved both depression and anxiety symptoms with no side effects.[10]

Clary sage (*Salvia sclarea L.*). In a pilot study of 22 menopausal women, Lee et al found that 5-HT serum levels increased from pre- to post-inhalation. Plasma cortisol levels also decreased significantly.[11]

Orange (*Citrus sinensis*). One controlled, randomized clinical pilot trial with men under conventional antidepressant treatment compared men who were treated with orange oil inhalation to those who had no essential oil inhalation. Overall mood improved significantly in the orange oil treatment group. The researchers also found that subjects in the treatment group had normalized neuroendocrine hormone levels and immune function, and that these benefits were better than what is seen with antidepressants.[12]

ANIMAL STUDIES

Wild ginger (*Asarum heterotropoides*) contains methyl eugenol as the main compound. Researchers suspect methyl eugenol is the main mediator of the antidepressant effects based on prior studies on rats with essential oils containing this compound. Immunohistochemistry found the mechanism of action to be increasing corticotrophin-releasing factor and tyrosine hydroxylase-positive cells and a decrease in the 5-HT-positive cells. This led researchers to believe the increased CRF and reduced monoamines to be the reason for antidepressant-like effects of wild ginger oil.

Lemon (*Citrus limon*) reduced immobility time in the forced swimming test (FST) in rats and mice and reduced locomotion and exploration, indicating a sedative effect in acute inhalation.[13] Reduced immobility times is a similar effect that occurs to conventional antidepressant drugs.[13,14] Studies indicate that the mediation by 5-HT and dopamine neurotransmission produces lemon's antidepressant-like effects. The main monoterpenes involved in *C. limon* essential oil were limonene, geranyl acetate, and trans-limonene oxide.

Suriname cherry (*Eugenia uniflora*) was found to contain sesquiterpenes that induced antidepressant-like effects. One of the sesquiterpenes, beta-caryophyllene, acts as a CB2 receptor agonist, which is expressed in the brain and involved in modulation of anxiety and depressive states.[15,16]

Two groups from China have studied the use of Korean perilla (*Perilla frutescens*) for its antidepressant-like effects. Using the chronic unpredictable mild stress (CUMS) model of depression for animals, the researchers showed reversal in behavioral, neurochemical, and immunological changes caused by stress with *P. frutescens* L. Britton.[17,18] Researchers also found reduced sucrose-preference in stressed mice, often related to anhedonia. More evidence is geared toward identifying release of pro-inflammatory cytokines in major depression. Administration of frutescens chronically and dose-dependently decreased the serum levels in CUMS mice. This essential oil also contains limonene and beta-caryophyllene, both studied for their antidepressant-like effects.

Clary sage (*S. sclarea L.*) causes antidepressant-like effects through mediation of the activation of dopamine and 5-HT neurotransmission with linalool and geraniol as the principal constituents involved.

Acute administration of clove (*Syzygium aromaticum*) showed reduced immobility time in mice in FST and tail suspension test (TST), reversed sucrose preference, and reduced eating in an unfamiliar environment. Chronic administration restored brain-derived neurotrophic factor (BDNF) in CUMS rats.[19] Major compounds included eugenol, beta-caryophyllene, and eugenyl acetate, which have been shown to have antidepressant-like actions.[20,21,22]

In acute administration of the essential oil from red cedar (*Toona ciliata* var. yunnanensis), there was an increase in hippocampal 5-HT, noradrenaline, dopamine, and BDNF. Additional studies are needed to isolate the effects of oil compounds found in red cedar.

Indian valerian (*Valeriana wallichii*) oil also decreased immobility time of mice in the FST. There is also evidence that the nitric oxide signaling pathway is involved and causes an acute antidepressant-like effect. Additional studies are needed to identify the effects of isolated compounds of Indian valerian for depression.

BIOCHEMISTRY AND MECHANISMS OF ACTION

Eugenol and linalool are the most studied compounds from essential oils such as the ones discussed above. The most common antidepressant-like actions from these constituents are shown in FST and TST. Eugenol targets the monoamine oxidase (MAO) enzyme, by inhibiting MAOA activity and chronic administration increases BDNF, which is also a MAO shared by antidepressants.[22] Acute administration of linalool, from lavender and clary sage essential oils, shows activation of monoamine 5-HT1A and alpha2-receptors. Relevant to psychological pathology, past research has found an association between pro-inflammatory cytokines and depressive symptoms.

■ COMMENTARY

This article presents a breadth of information regarding the research behind essential oils, specific chemical constituents, and their antidepressant actions. Although this literature review showed promising potential for the use of essential oils for depression, more studies are needed.

Risks involved with certain essential oils that were not mentioned in the review include skin irritation, phototoxicity, interactions with drugs, and toxicity, if ingested. Most of the research presented here was conducted on animals, so more human research is necessary to confirm clinical efficacy of the antidepressant properties described. BDNF and monoamine concentrations are the most noted mechanisms of action mentioned in this review relevant to the antidepressant efficacy of essential oils. More specifically, essential oils that contain the compounds eugenol and linalool, which increase BDNF and extracellular monoamine concentrations, appear to be the most encouraging. Plants that contain these oils are listed in Table 1.

The authors made the intuitive leap that since isolated constituents show a benefit, the diversity of the chemically active parts working together may have a more positive, even synergistic, effect on depression. This review mentioned a possible anti-inflammatory effect of some of the isolated compounds as mediators to the antidepressant actions. There is a growing body of research linking high concentrations of pro-inflammatory cytokines and depression symptoms.[24] Since both human and animal studies have shown the

Table 1: Plants Containing Eugenol and Linalool

Plant Containing Compounds	Eugenol	Linalool
Cilantro, coriander	X	
Basil, sweet basil	X	X
Lavendula, lavender		X
Salvia, sage		X
Cinnamon	X	X
Lemon		X
Oregano		X

positive psychological effects of essential oils, there is a possibility that they may be useful as compliment to pharmaceuticals. Neuroplasticity, which is proven to improve depressive symptoms, is induced by BDNF. BDNF increases with the plant compounds mentioned above and may be beneficial as a complement to pharmacotherapy. Although the data are accumulating about the various mechanisms by which the isolated compounds may have physiological effects and some promising preliminary clinical benefits, the overall clinical application requires more research.

The popularity of aromatherapy has grown as more consumers move away from synthetic compounds and into more natural solutions. For the most part, essential oils may offer a possible alternative or complement to pharmaceuticals in the overall clinical picture of depression. This is particularly important to consider if patients request a more holistic approach. High-quality oils require a large amount of plant material, making the price of some oils expensive, which could be a limiting factor in a clinical setting. As with any dietary supplements, it is important to choose reputable products and companies to avoid concerns about adulteration, contamination, and misrepresentation of label claims, although there is no reason to think that this is a specific problem to essential oils.

The statistics surrounding depression are troubling and continue to rise in all demographics.[23] Since depression is one of the most prevalent mental disorders, the search is on for effective integrative health therapeutics; essential oils might have a role in this regard. Prior to knowing the true safety and benefit profile of essential oils for depression, clinical research needs to expand and provide methodologically sound clarifications to the interesting initial benefits as seen in the human research and basic science reviewed here. ■

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PAIN

SHORT REPORT

Topical Cannabis for Wound Pain: A Case Series

By David Kiefer, MD

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Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: For three people with continued pain despite conventional treatment for pyoderma gangrenosum, topical cannabis led to statistically significant pain relief for two of them.

SOURCE: Maida V, Corban J. Topical medical cannabis: A new treatment for wound pain — three cases of pyoderma gangrenosum. *J Pain Symptom Manage* 2017;54:732-736.

It's not uncommon for methodologically sound clinical trials to trail slightly behind consumer dietary supplement use. One could argue that such is the case with cannabidiol (CBD) oil. CBD is one of the groups of physiologically active compounds extracted from hemp (*Cannabis sativa*), the other being tetrahydrocannabinol (THC). CBD is touted as an effective treatment for pain and for numerous other health conditions, without the psychotropic effects of THC.[1,2,3] There is some interesting evidence surfacing for the anti-inflammatory effects of an interplay between CBD and THC, which Maida and Corban reviewed, pointing to effects on the human endocannabinoid system. It is this mechanism of action that led the authors to use topical cannabis for the difficult-to-treat skin condition pyoderma gangrenosum (PG).

In the article reviewed here, three people with PG confirmed by wound biopsies were treated with topical medical cannabis. The preparations used were created by infusing hemp (*Cannabis sativa*) in sunflower oil. One brand name was Argyle, with a THC content of 5 mg/mL and CBD content 6 mg/mL; (manufacturer Tweed [Canada]). Another was Bedrolite, with a THC content of 7 mg/mL and CBD content 9 mg/mL (manufacturer Bedrocan Inc). Characteristics of the three subjects, their initial medical treatment, and specific topical cannabis treatments are detailed in Table 1.

Patients reported analgesia within three to five minutes of applying the topical treatment. The researchers followed their pain scores on a scale of 0-10, both pre- and post-treatment, for a varying number of weeks as per Table 2. Of note, the mean daily opioid use decreased for the two patients (1 and 2) who were treated with opioid medications. For patient 1, the morphine equivalents decreased to 0.24 mg post-treatment from 26.0 mg pre-treatment. For patient 2, the morphine equivalents decreased to 12.5 mg post-treatment from 27.3 mg pre-treatment.

Summary Point

- Topical cannabis, providing both tetrahydrocannabinol and cannabidiol, had analgesic effects for two of three patients with a painful dermatological condition.

Yes, this is only a case series on three people with a painful skin condition, but the analgesic effects are impressive, both with pain scores and decreases in the use of opioid medications in two of the patients studied (interestingly, those who had higher baseline pain and were taking opioids for that pain). Is it sufficient for clinicians to incorporate this treatment into their clinical practices? By no means, not the least reason of which is because of state and federal laws governing the use of medical marijuana (cannabis). In addition, the results of this study are complicated by the fact that the researchers used a medical cannabis extract, including both phytochemical classes (CBD, THC), complicating the teasing out of clinical response to CBD or THC; we can only say that both

Table 1: Three Study Participants and Wound Treatment, Both Conventional and Related to Topical Medical Cannabis

Demographics	Conventional Treatment	Symptoms	Topical Cannabis Treatment	Response
50-year-old woman; PG x 1 year	Oral and intralesional steroids, oral opioids	Continued "high levels of pain"	1 mL daily (Argyle)	No further steroids needed; other results as per text
76-year-old man; unknown wound duration	Oral and intralesional steroids, oral opioids	Continued "high levels of pain"	0.5 to 1.0 mL Bedrolite twice daily, with 1 to 3 times daily for breakthrough pain	Results as per text
60-year-old woman; "recurrent" wound	Oral steroids, acetaminophen 325 to 650 mg q6 hours prn	"High levels of pain"	0.5 to 1.0 mL Bedrolite twice daily, with 1 to 3 times daily for breakthrough pain	Results as per text

Table 2: Median Pain Scores, on a Scale of 0-10, for Each Patient, Including the Number of Weeks That Data Were Collected

Case	Pre-treatment	Number of Weeks Pre-data Were Collected	Post-treatment (*P* value)	Number of Weeks That Post-data Were Collected
1	8.25	17	2.76 (0.0007)	33
2	8.75	21	2.33 (0.0006)	9
3	4.29	21	1.50 (0.07)	21

groups of compounds together led to the improvements in pain seen. That said, with CBD oil appearing more and more in the marketplace, and on patients' dietary supplement lists, perhaps this study is a first step toward providing clinicians information about how to counsel patients should they express interest in its topical analgesic and anti-inflammatory effects. Hopefully, we'll see larger, more convincing research (double-blind, randomized, controlled trials) into the pain-relieving effects of topical medical cannabis, or its extracts, for all relevant health conditions. ■

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HEADACHE

SHORT REPORT

Low Serum 25-hydroxyvitamin D and Risk of Frequent Headache

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Dr. Merry reports no financial relationships relevant to this field of study.

SUMMARY: Low serum 25-hydroxyvitamin D was associated with a higher risk of frequent headaches in middle-aged/older Finnish men.

SYNOPSIS: Low vitamin D levels are associated with a range of neurovascular diseases, but little data are available on the association between vitamin D levels and headaches. This retrospective, cross-sectional study showed that low serum vitamin D levels were associated with a higher risk of frequent headaches in middle-aged/elderly Finnish men.

Vitamin D insufficiency is emerging as a global public health concern, especially for residents of the Nordic countries who have limited year-round access to ultraviolet B sun exposure.[1] There is increasing evidence linking vitamin D insufficiency to a wide range of neurovascular disorders.[2,3] Studies suggest that the prevalence of headache may increase with increasing latitude, which raises the possibility of a link between vitamin D insufficiency and headaches.[4] However, to date, this is just a biologically plausible hypothesis rather than an evidence-based relationship.

The aim of this study was to investigate the relationship between serum 25-hydroxyvitamin D [25(OH) D] as a marker for vitamin D status and headaches.

This was a retrospective, cross-sectional, population-based cohort study using data from men (aged 42 to 60 years) in the Finnish Kuopio Ischaemic Heart Disease Risk Factor Study cohort. The Kuopio Ischaemic Heart Disease Risk Factor Study is a Finnish-based population study originally designed to evaluate the risk factors for cardiovascular disease, atherosclerosis, and related outcomes in randomly selected men.[5]

The authors of the Kuopio study collected data on 2,682 men 42 to 60 years of age between 1984 and 1989. Data were available on both 25(OH)D and headache for 2,601 of the 2,682 study participants. Consequently, this sub-study evaluated data on 2,601 men.

A diagnosis of frequent headache was defined as the presence of a headache weekly or daily over the previous year. The authors did not comment on the cutoff for low vitamin D level and did not differentiate between vitamin D insufficiency or deficiency. Serum 25(OH)D was measured using a validated high-performance liquid chromatography assay.

The study showed that the average serum 25(OH)D level was 17.4 ng/mL (standard deviation [SD], 7.6 ng/mL; min-max, 3.1-54.4 ng/mL). Of all participants, 67.9% had a serum 25(OH)D < 20 ng/mL, the cutoff for vitamin D insufficiency. In addition, 250 of the study participants (9.6%) reported frequent headaches as defined above. The average 25(OH)D level was statistically significantly lower among those who reported frequent headaches (14.4 ng/mL; SD, 7.5 ng/mL) as compared to those without frequent headaches (17.6 ng/mL; SD, 7.6 ng/mL), even after adjustment for age and month of blood draw ($P < 0.001$). After multivariate adjustment, men in the lowest vs. the highest serum 25(OH)D quartile had a 113% (95% confidence interval, 42; 218%; P for trend 0.001) higher odds ratio for frequent headache.

Summary Point

- Low serum 25-hydroxyvitamin D levels were associated with a higher risk of frequent headaches in middle-aged/older Finnish men.

These are very interesting results, in that they pin a somatic complaint (headache) to a physiological measurement (serum 25(OH)D) that can arguably be improved by supplementation. That said, there are study limitations, such as the fact that the study demographic was limited to middle-aged/older men; there may be minimal generalizability of the results to women and younger men. Furthermore, the diagnosis of headache was based on self-report and did not differentiate between types or severity of headache. Also, this study merely associates headache and low vitamin D levels; there is no inference of causation, nor did the authors comment on the effect of vitamin D supplementation on the frequency or severity of headache in this population. To explore these effects, a well-designed clinical trial would be the logical next step.

In summary, this retrospective, cross-sectional study suggests that low serum 25(OH)D was associated with a higher risk of frequent headaches in the Kuopio study cohort. We can add these results to a growing list of connections between low (or elevated) serum 25(OH)D and health or disease states, not to mention compelling work showing the effect of supplemental vitamin D2 or D3. Does this change our clinical practice? Perhaps not, but for the next patient with frequent headaches, maybe hypovitaminosis D should be added to our differential diagnosis. If a patient with frequent headaches is found to have low serum 25(OH)D, then shared decision-making should explore what to do about it. ■

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SHORT REPORT

Black Seed (*Nigella sativa*) for Asthma: Minimal Effects

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Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: Black seed, crushed, in capsule form, administered to 76 people with asthma in a single-blind, randomized study, showed some minimal improvements in some, but not all, components of spirometry and one serum cytokine after 12 weeks.

SOURCE: Salem AM, Bamosa AO, Qutub HO, et al. Effect of *Nigella sativa* supplementation on lung function and inflammatory mediators in partly controlled asthma: A randomized controlled trial. *Ann Saudi Med* 2017;37:64-71.

Black seed (*Nigella sativa*), also known as black cumin, is a flowering plant native to Asia that is developing a reputation for a variety of health concerns. It is a member of the buttercup family (Ranunculaceae) and is used both orally and topically. The physiological effects center on its volatile oils and fatty acids (saturated and unsaturated), which may explain some studies showing decreased inflammation, lipids, glucose, blood pressure, pain, and anxiety, as well as other cardiovascular effects.[1,2]

Dovetailing from the plant's anti-inflammatory effects, as well as some evidence for bronchodilation, Salem et al randomized people with "partially controlled asthma" into three groups: a placebo (one capsule twice daily) group (n = 24), 500 milligrams of black seed (whole ground seeds in capsules) twice daily (n = 26), or one gram of black seed twice daily (n = 26) for three months and followed their lung function. The study participants' asthma control included inhaled corticosteroids with as-needed use of inhaled beta-agonists; the use of other asthma medications prompted exclusion from this study. This was a single-blind study, in that only the participants were blind to their randomization. At baseline, six weeks, and 12 weeks, the participants underwent an Asthma Control Test (a standardized asthma severity rating) analyses, clinical assessment, spirometry, and laboratory analyses (blood testing for serum total immunoglobulin E [IgE] and cytokines, the latter only at time 0 and 12 weeks).

There was no difference between the three groups with respect to baseline lung function. An intention-to-treat analysis found changes over 12 weeks in the participants (placebo [n = 22], 1 gram of black seed daily [n = 2], and 2 grams of black seed daily [n = 25]) who were able to finish the study. Notably, when compared to the other groups, in the higher-dose black seed group, FEV1% was significantly higher ($P < 0.05$) at 12 weeks, and the FEV1/FVC% and FEF25-75% were higher at six weeks. Interestingly, none of the other spirometry findings were statistically different at any of the time points. With respect to serum cytokines and IgE, only one (IFN-gamma) showed any difference with black seed treatment, a decrease in both doses at 12 weeks when compared to baseline. In the Asthma Control Test scoring, all three groups improved over the course of the 12 weeks, though more so ("significantly higher," no *P* values given in the text) in the black seed groups. No adverse effects were mentioned in the study.

Summary Point

- One or two grams of black seed daily led to minimal changes in spirometry and laboratory analyses in people with mild-moderate persistent asthma.

This is an interesting, ambitious, and multifaceted study, venturing an herbal medicine into the realm of asthma, not a common territory for adjunctive therapies. Yes, this effort might have been improved with stricter methodology (double-blind, greater numbers, etc.), but the quantitative results provided still allow for some commentary. Did this herbal medicine make a significant clinical difference for these people with mild-moderate persistent asthma? It's difficult to say, as most of the spirometry parameters and lab tests

were equivocal between the three groups. It would have been useful to see a justification for the herbal medicine form and dosing chosen in this study. A superficial review of other studies for other conditions reveals a variety of doses and forms, including vapors, oils, and decoctions, so it is possible that insufficient dosing or incorrect plant form is one explanation for the minimal performance of black seed in this trial. Also, before recommending this therapy as an adjunctive treatment, solid safety data should be provided; before exploring this "nudge" toward clinical benefit, as seen in this study, we would need to be assured of a lack of adverse effects. Overall, black seed for asthma may have some slight potential benefit, and it fits with some prior basic science, but this study alone is not sufficient to propel this plant to the top of the asthma treatment list. ■

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CME QUESTIONS

1. **Research data support the practice of tai chi:**
   a. in older adults with preexisting balance problems to prevent deterioration and return to premorbid status.
   b. at least two times weekly to help prevent time to the first fall in the older population.
   c. to reduce the rate of falling in older adults at least for the first year.
   d. All of the above
2. **Neuroplasticity is shown to improve depression symptoms and is induced by which of the following?**
   a. Increasing the action of monoamines in the brain
   b. Causing an anti-inflammatory effect in the brain
   c. Increasing brain-induced neurotrophic factor
   d. Reducing sucrose preference in mice
3. **Which of the following is true regarding the use of topical cannabis for pyoderma gangrenosum?**
   a. It led to a decrease in the use of opioid medications for the two people needing those medications for pain.
   b. It led to an increase in pain scores for all three patients.
   c. It takes about 24 hours for an analgesic effect to be noticed.
   d. An average CBD dose is 50 to 100 mg applied topically twice daily.
4. **Which of the following is true about vitamin D?**
   a. Deficiency is associated with a range of neurovascular diseases.
   b. Serum levels are independent of exposure to UVB.
   c. Insufficiency is not a public health concern in the Nordic countries.
   d. Low levels are not associated with frequent headaches.
5. **Which of the following was seen after 12 weeks of treatment with black seed (*Nigella sativa*) in people with asthma?**
   a. Lower FEV1%
   b. Higher FELV/FVC%
   c. Lower serum IgE
   d. Lower Asthma Control Test results

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- 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.

[IN FUTURE ISSUES]

Nutrition controversies

Plant-based diets and cardiovascular disease

Music therapy in neurological rehabilitation