Cochrane for Clinicians

Putting Evidence into Practice

Vitamin and Mineral Supplementation for Maintaining Cognitive Functioning in Cognitively Healthy Adults

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Clinical Question

Are vitamin and mineral supplements beneficial in preserving cognitive functioning or preventing cognitive decline in cognitively healthy adults 40 years and older?

Evidence-Based Answer

Vitamin and mineral supplementation has little to no beneficial effect on preserving cognitive functioning or preventing dementia in cognitively healthy adults 40 years and older.[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

In 2010, an estimated 35 million people worldwide had dementia, and the prevalence is expected to double by 2030. Modifiable risk factors for dementia include diabetes mellitus, midlife obesity and hypertension, smoking, and physical inactivity. Vitamins and minerals have recognized roles in normal functioning and development, so it has been hypothesized that dietary supplementation may prevent dementia. This Cochrane review sought to evaluate whether vitamin and mineral supplementation preserves cognitive functioning or prevents decline in cognitively healthy adults 40 years and older.[1]

These are summaries of reviews from the Cochrane Library.

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CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 268.

The Cochrane authors identified 28 randomized controlled trials involving more than 83,000 cognitively healthy participants 40 years and older. These trials compared oral vitamin and mineral supplements with either placebo or usual care for at least 12 weeks. The primary outcome was overall cognitive functioning as measured by various accepted and validated scales. Secondary outcomes included subdomain measures (i.e., episodic memory, executive functioning, and cognitive processing speed), incidence of mild cognitive impairment (MCI) or dementia, serious adverse events, and mortality. Most studies did not assess the incidence of dementia specifically or reflect performance of a baseline cognitive assessment. Ten studies had follow-up from five to 10 years, and only one study had follow-up longer than 10 years. The authors pooled study data into five supplement groups based on their theorized mechanisms of action in preventing dementia: antioxidants (vitamin C, vitamin E, and beta carotene), B vitamins, vitamin D, zinc and copper, and selenium. The review also pooled data for any combinations from these different groups.

Fourteen studies (n = 27,882) compared B vitamins (folic acid, vitamin B_6, vitamin B_{12}, or a combination) with placebo and found that, based on low- to moderate-certainty evidence, B vitamins had little to no benefit on measurements of cognitive functioning. These 14 studies evaluated supplementation over varying lengths of time using more than 30 different cognitive function scales, so standardized mean differences (SMDs) were used to describe treatment effect (SMD was defined as the difference between the groups' mean values divided by the pooled standard deviation). SMDs ranged from −0.03 to 0.06 for supplementation from three months to more than 10 years. B vitamin supplementation also did not provide a benefit in any specific subdomains of cognitive functioning, the incidence of MCI or dementia, or mortality.

Eight studies (n = 47,840) assessed antioxidants (vitamin E, vitamin C, beta carotene, or a combination) and had mixed results. Five studies showed that antioxidant supplementation over a mean of 12 months to 8.9 years had no effect on overall cognitive functioning, based on low- to

moderate-certainty evidence. Three studies showed marginal improvements in cognitive functioning that are likely not clinically significant. One study (n = 74) involving adults with type 2 diabetes found that three months of vitamin E supplementation resulted in improved Mini-Mental State Examination (MMSE) scores (maximum score = 30) compared with placebo (mean difference [MD] = 1.4; 95% CI, 1.18 to 1.62). Another study (n = 1,586) found that five to 10 years of vitamin C supplementation in adults with cardiovascular disease resulted in very small improvements in cognitive functioning based on the 41-point Telephone Interview for Cognitive Status (TICS), modeled after the MMSE (MD = 0.46; 95% CI, 0.14 to 0.78).[2] A final study (n = 4,052) demonstrated moderate-certainty evidence of a very small benefit in overall cognitive functioning after a mean of 18 years of treatment with beta carotene, based on improvements in the TICS score (MD = 0.18; 95% CI, 0.01 to 0.35).

Regarding the subdomain of episodic memory, one study (n = 1,583) found that after 8.9 years of vitamin C supplementation, verbal memory scores (a composite score of the immediate and delayed recalls of the 10-word TICS and the East Boston Memory Test, scale not defined) improved slightly (MD = 0.14; 95% CI, 0.06 to 0.22) in women with or at risk of cardiovascular disease.[3] Antioxidants had no effect on executive functioning, speed processing, incidence of dementia, or mortality. Of note, one trial that measured the incidence of dementia in patients taking vitamin E supplements was an ancillary study of a larger trial that demonstrated vitamin E supplementation had a nonsignificant increased risk of prostate cancer (P = .06; relative risk = 1.13; 99% CI, 0.95 to 1.35) after a mean 5.5 years of supplementation (n = 35,533).[4]

Vitamin D does not improve overall cognitive functioning based on the results of one study (n = 4,143) that compared the supplementation of 400 IU of vitamin D_3 with calcium carbonate vs. placebo over an average of 7.8 years. The study found MDs on the modified MMSE as measured at various follow-up times ranging from −0.2 to 0. Vitamin D also did not affect subdomains of cognitive functioning or the incidence of MCI or dementia. Likewise, trials involving zinc and copper (one study, 1,072 participants), selenium (one study, 3,711 participants), or complex multivitamins (combination of B vitamins, antioxidants, and minerals; three studies, 6,306 participants) suggested low-certainty evidence of no effect on cognitive functioning, its subdomains, or the incidence of dementia.

This Cochrane review generally supports the American Academy of Neurology 2018 practice guideline for the prevalence, prognosis, and treatment of MCI. The American Academy of Neurology recommends that patients and families be counseled that there are currently no dietary modalities effective in slowing symptomatic cognitive impairment.[5]

The practice recommendations in this activity are available at http://www.cochrane.org/CD011906.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as the official policy or position of the U.S. Army, the Department of Defense, or the U.S. government.

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Music Therapy for Depression

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Clinical Question

Is music therapy an effective treatment for depression? Are there differences between the various types of music therapy?

Evidence-Based Answer

Moderate-quality evidence shows that music therapy added to standard care is more effective in the first three months than standard care alone for depressive symptoms based on clinician-rated outcomes (standardized mean difference [SMD] = −0.98; 95% CI, −1.69 to −0.27) and patient-reported outcomes (SMD = −0.85; 95% CI, −1.37 to −0.34; three randomized controlled trials [RCTs]; one controlled clinical trial [CCT]; n = 142). There is insufficient evidence to compare active and/or receptive music therapy techniques.[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Depression is a common problem marked by mood changes and loss of interest and pleasure in normal activities. In 2017, an estimated 17.3 million adults (7.1% of all adults) in the United States had at least one major depressive episode.[2] Depression affects more than 300 million people

worldwide and is projected to become a leading cause of disability by 2020.[3] This update of the 2008 systematic review examines more recent, robust evidence to determine if music therapy is an effective treatment for depression and if the effectiveness varies by music type (i.e., active vs. receptive). Music affects a patient's emotional state by increasing dopaminergic activity, downregulating the hypothalamic-pituitary-adrenal axis, and stimulating the parasympathetic nervous system.[4] Active music therapy involves the participant singing or playing an instrument, whereas receptive therapy involves passively listening to music. Both treatments use trained music therapists and may include self-reflection time. Either can be done alone or in a group setting.

This Cochrane review included eight RCTs and one CCT with a total of 421 participants.[1] Data from 411 patients were included in the meta-analysis, which demonstrated an improvement in patient-reported depressive symptoms (SMD = –0.85; 95% CI, –1.37 to –0.34; three RCTs; one CCT; n = 142) and clinician-rated symptoms (SMD = –0.98; 95% CI, –1.69 to –0.27; three RCTs; one CCT; n = 219; moderate evidence) in the short term (up to three months) when music therapy plus standard care was compared with standard care alone. Only one study evaluated effects of the intervention over a longer period of six months. Regarding secondary outcomes, low-quality evidence revealed that music therapy plus standard care resulted in decreased anxiety symptoms (SMD = –0.74; 95% CI, –1.40 to –0.08; two RCTs; one CCT; n = 195) and improved functioning (SMD = 0.51; 95% CI, 0.02 to 1; one RCT; n = 67). Evidence was not sufficient to determine differences between music therapy and standard care or between different types of music therapy for either primary or secondary outcomes. However, one available RCT showed no statistically significant differences in patient-reported depressive symptoms between active and receptive music therapy (SMD = –0.01; 95% CI, –1.33 to 1.30; n = 9).

The studies in the meta-analysis were quite different from one another. Depression was diagnosed using a variety of rating scales and criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.,[5] and outcomes were also reported using various rating scales. The music therapy interventions were heterogeneous in terms of duration and number of sessions, individual vs. group therapy, and type of therapy. Five of the studies recruited participants from mental health service locations, two studies involved geriatric patients, and two others involved high school students. Although only one study reported negative outcomes, it did not demonstrate a difference in adverse events between patients who received therapy and those who did not. There were no differences in the number of individuals who left the study early when comparing those who received standard care plus music therapy with those who received standard care alone (odds ratio = 0.49; 95% CI, 0.14 to 1.70; $P = .26$; five RCTs; one CCT; n = 293).

Current guidelines do not recommend routinely adding music therapy to standard treatment for depressive disorders. Further studies are needed to better characterize aspects of music therapy interventions and determine long-term effects on depression and related conditions. However, this Cochrane review provides low- to moderate-quality evidence that music therapy is a low-cost and low-risk intervention that may be worth adding to standard care for patients with depressive disorders.

The practice recommendations in this activity are available at http://www.cochrane.org/CD004517.

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