**Viscum Album (Mistletoe) for Pancreatic Cancer, Electromagnetic Field Therapy for Osteoarthritis, Homeopathy for Multidrug-Resistant Tuberculosis, Vitamin D for Depression, Acupuncture for Insomnia**

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**Viscum Album Extract May Increase Overall Survival in Adults with Locally Advanced or Metastatic Pancreatic Cancer Not Eligible for Antineoplastic Therapy**

*Level 2 (mid-level) evidence*

Reference: *Eur J Cancer* 2013;49 (18):3788

At least 60% of medications used to treat cancer were originally derived from plants. **1** *Viscum album* (European mistletoe) is widely used in Europe for the treatment of cancer, either alone or in combination with conventional antineoplastic agents. **2** While its mechanism of action is unknown, parenterally administered extracts contain a variety of substances with cytotoxic, apoptotic, and immunostimulatory properties. **3** Nevertheless, in a systematic review of 18 clinical trials (N > 6800), researchers could find no convincing evidence for the benefits of *V. album* in cancer treatment. **4**

In the present study, Serbian researchers randomized 220 adults with locally advanced or metastatic pancreatic cancer to *V. album* extract (0.01 mg starting dose increased to 10 mg) self-administered subcutaneously three times weekly vs. no treatment. **5** All patients were no longer eligible for antineoplastic therapy and received best supportive care at the same oncology center. No patient had brain metastases or life expectancy less than four weeks. Researchers had originally planned to recruit 428 patients but the trial was terminated early after a pre-specified interim analysis found increased overall survival with *V. album*. Comparing *V. album* to no treatment, median overall survival at the end of one year was 4.8 months vs. 2.7 months [hazard ratio = 0.49 (95% CI = 0.36–0.65)]. Findings remained consistent in subgroup analyses by age (≤65 vs. >65), gender, disease stage (III vs. IV), and prognosis (good vs. poor). Adverse events were less common in the treatment group [14.5% vs. 48.2% (P < .05)].

In this open-label trial, parenteral *V. album* was associated with a significant increase in overall survival in patients with end-stage pancreatic cancer who were no longer candidates for conventional antineoplastic therapy. To put the average effect size into perspective, median survival time for 754 untreated patients was 3.9 months (range = 3.1–7.0) in an analysis of 43 chemotherapeutic trials for advanced or metastatic pancreatic cancer. **6** Although the open-label protocol increases the risk of performance bias, the influence of a placebo effect on survival in cancer is likely to be small. **7** The fact that all patients received care at the same location minimizes the chance that patients received different levels of support, another potential source of bias.

**Pulsed Electromagnetic Field Therapy May Decrease Pain in Patients with Osteoarthritis**

*Level 2 (mid-level) evidence*


Nearly one in four U.S. adults has been diagnosed with arthritis, half of whom report activity limitation due to joint pain. **8** Osteoarthritis (OA), by far the most common type, results primarily from a failure of chondrocytes to maintain a balance between synthesis and degradation of the extracellular matrix. **9** Standard non-surgical treatments include physical therapy, oral analgesics and anti-inflammatories, and intra-articular hyaluronic acid and corticosteroids. Pulsed electromagnetic field therapy (PEFT) has garnered some attention as another option for the
Consistent results between systematic reviews have been shown to stimulate chondrocyte proliferation and matrix synthesis. Fields can be non-invasively delivered in two ways: direct electrical stimulation of overlying skin or indirect magnetic induction of an electric current in the target tissues. Results of sham-controlled, randomized trials using pulsed electrical stimulation for OA have been inconsistent.

The authors of the present Cochrane review identified nine randomized trials comparing PEFT (of both types) versus sham for four or more weeks in 636 adults with painful osteoarthritis of the knee (eight trials) and of the knee or cervical spine (one trial). All trials had unknown risk of selective reporting, and eight trials had one or more additional limitations: unclear or no allocation concealment, unclear or no blinding, high dropout rate. PEFT was associated with a reduction in pain [weighted mean difference (WMD) = 15.1 points (on a 0–100 scale, 0 = no pain), 95% confidence interval (CI) = 9.08–21.13] in an analysis of six trials with 434 patients. Results were limited by moderate heterogeneity. No significant differences, however, were found for physical function (analysis of three trials with 197 patients), or quality of life (analysis of two trials with 139 patients). Adverse event rates did differ between groups (analysis of four trials with 288 patients).

The findings of this review suggest that PEFT can moderately improve pain in patients with osteoarthritis without generating more adverse effects than sham. Since 87% of patients were treated for knee pain only, the results probably should not be extrapolated to OA of the cervical spine. Clinical utility is limited by variations in field devise settings and duration of treatment among trials. While this study did not find PEFT effective for improvements in function or quality of life, the authors a previous review analyzing nine trials with 483 patients arrived at essentially the opposite conclusion: a significant benefit for function, but not pain.

One possible explanation for inconsistent results between systematic reviews is the use of mean differences in continuous measures of pain and function. This approach may not be the best expression of outcomes when substantial subgroups of patients experience significant benefit.

**ADDITION OF INDIVIDUALIZED HOMEOPATHIC TREATMENT DOES NOT IMPROVE CULTURE CONVERSION, CURE RATE OR SYMPTOM SCORE COMPARED WITH STANDARD TREATMENT REGIMEN ALONE IN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS**

*Level 2 (mid-level) evidence*

**Reference:** *Homeopathy* 2014;103(2):97–107

One-third of the world’s population is infected with *Mycobacterium tuberculosis* (TB). Approximately 10% of these people are at risk for developing active TB at some time in their lives, and those co-infected with HIV have roughly 30 times the risk. Infections that do not respond to two first-line anti-microbial agents–isoniazid and rifampicin–are considered multidrug-resistant (MDR-TB). More than half of the 480,000 annual cases of MDR-TB occur in India, China, and the Russian Federation.

Homeopathy is a highly individualized system of care in which ultra-dilute medications are prescribed based on comprehensive assessments of patient symptomology. Despite the absence of a plausible scientific explanation for its observed health effects, homeopathy remains popular in many parts of the world, including India.

In the present study, Indian researchers randomized 120 patients (aged 11–63 years) being treated for MDR-TB to homeopathy vs. placebo for 24 months. All patients received standard MDR-TB treatment with six drugs (kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol, and cycloserine) for a six to nine month intensive phase, followed by four drugs (levofloxacin, ethionamide, ethambutol, and cycloserine) for an 18-month continuation phase. Experienced practitioners selected individualized homeopathic interventions from a set of 15 predefined medicines of variable potencies. Clinical symptoms were assessed every 15 days, sputum cultures obtained every three months, and chest x-rays performed every six months. Overall, 32% of the patients had culture-negative MDR-TB (persistent symptoms despite treatment) at baseline.

In an intention-to-treat analysis, there were no significant differences between groups for culture or smear conversion (positive to negative or visa-versa), or for changes in symptom score. In a subgroup analysis of culture positive patients, there were no significant differences in cure rate (five or more consecutive negative sputum cultures in the previous 12–15 months) or symptom score. However, a statistically significant improvement was seen in the chest x-rays of patients receiving standard therapy (ST) plus homeopathy compared to controls [mean difference = 28.4% of patients, 95% confidence interval (CI) = 11.1–45.4]. Trial radiologists (who were blinded according to the published protocol) assessed chest x-rays using a numerical grading scale based on changes they observed in five domains: infiltration, fibrosis, compensatory emphysema, and the number and size of cavitary lesions. Although total scores could range between +5 and −5, the authors did not report outcomes as a continuous variable. Changes were reported as better, absent, or worse. This could be misleading since scores indicating a minimal change (e.g., ±1 or −1) could take on statistical significance without being clinically relevant.

This carefully designed trial failed to demonstrate an effect for the addition of individualized homeopathy on culture conversion, cure rate or symptomatic improvement—the three most clinically meaningful outcomes—in patients treated for MDR-TB. The researchers’ methodology answers a frequent criticism leveled against homeopathy trials, most of which ignore its individualized nature by giving standardized treatments to all patients in the treatment group irrespective of their homeopathic diagnosis. At this point, the best evidence does not demonstrate a clear effect of adjuvant homeopathy for MDR-TB.
THERE IS CURRENTLY INSUFFICIENT EVIDENCE TO DETERMINE THE EFFECTIVENESS OF VITAMIN D SUPPLEMENTATION FOR DEPRESSION

Level 2 (mid-level) evidence


Roughly 5% of the world’s population reports at least one depressive episode in the previous year, and major depression is the leading cause of morbidity among women. While the underlying pathophysiology of this complex disorder remains unknown, recent attention has turned to vitamin D deficiency as a biologically plausible contributing factor. With receptors present throughout the brain, vitamin D is involved in modulation of neuroimmunity, regulation of neurotrophic factors, neuroplasticity, and neurodevelopment.

Seasonal affective disorder may be due in part to a relative deficiency in vitamin D during the winter months. Over two-thirds of North American populations have suboptimal levels of vitamin D. A systematic review including 10 cross-sectional one case-control and three cohort studies (N = 31,424) found low vitamin D levels to be associated with depression. The present systematic review examines the effect of vitamin D supplementation on depressive symptoms in clinical trials.

Researchers identified seven randomized controlled trials including 3191 participants (aged 18–79 years). Only two of these trials included patients diagnosed with depression and only three included subjects with deficient vitamin D levels (<50 nmol) at baseline. All but one study used vitamin D3 (cholecalciferol) as a supplement. The route, frequency and dose of vitamin D supplementation varied considerably across studies. Doses ranged from 400 International Units (IU) orally per day to a single 300,000 IU intramuscular injection. Recommended dietary allowance of vitamin D is 600 IU daily for adults 18–70 and 800 IU daily for adults >70. One study allowed participants to take up to 1000 IU daily outside the protocol. Researchers did not examine post-intervention vitamin D levels.

Overall, the reduction in depressive symptoms with vitamin D supplementation was variable and non-significant [standard mean difference (SMD) = −0.14, 95% confidence interval (CI) = −0.33 to 0.05]. In a subgroup analysis of the two trials with 149 depressed patients, vitamin D supplementation was associated with a greater reduction in depressive symptoms than placebo (SMD = −0.60, 95% CI = −1.19 to −0.01). In contrast, subgroup analyses of the five trials with non-depressed patients showed no significant effect. This was also true of trials involving subjects with either sufficient or insufficient baseline levels of vitamin D (four trials with 2754 patients and three trials with 437 patients, respectively). Patients in the trial showing the largest effect were also taking fluoxetine, raising the possibility that vitamin D supplementation may potentiate the response to antidepressants.

Based on this review, there is currently insufficient evidence to support significant benefit of vitamin D supplementation for depressive symptoms. Of the two trials showing an effect in clinically depressed patients, only one included patients with an average baseline vitamin D level <50 nmol. Supplementation in this trial was with a single injection of up to 300,000 IU with no placebo control. Sorting out if there is any role for vitamin D in the treatment of depression will require large randomized, placebo-controlled trials that (1) enroll only depressed patients deficient in vitamin D, (2) administer standardized oral doses (e.g., 1000 IU) of cholecalciferol, and (3) measure post-treatment vitamin D levels. Until such studies show a favorable effect, there is no evidence-based indication for vitamin D supplementation in the management of depression.

ACUPUNCTURE IMPROVES SLEEP QUALITY AND DAYTIME FUNCTION MORE THAN ESTAZOLAM OR SHAM

ACUPUNCTURE IN PRIMARY INSOMNIA

Level 1 (likely reliable) evidence


Primary insomnia affects up to one-fourth of the U.S. population, and the prevalence may be even higher in other countries. In the West, insomnia that fails to respond to simple sleep hygiene measures is usually treated with hypnotic medications (particularly benzodiazepine receptor agonists) and a wide variety of cognitive-behavior interventions. In the East, acupuncture is often added to this list. An overview of 10 systematic reviews investigating acupuncture for insomnia, however, could not draw firm conclusions due to methodological limitations.

Previous acupuncture trials mostly focus on sleep quality and largely disregard daytime functioning as an outcome of interest.

In the present trial, researchers randomized 180 adult patients with primary insomnia for four or more weeks into three equal groups: true acupuncture plus placebo tablet, sham acupuncture plus estazolam 1 mg (a benzodiazepine sedative-hypnotic), and sham acupuncture plus placebo tablet. None of the patients used acupuncture in the past 12 months for any indication or ever for insomnia. All patients received true or sham acupuncture treatments every other day for six weeks, and took their assigned tablet 30 minutes prior to bedtime on days they did not receive acupuncture. Patients and researchers were blinded, but acupuncturists were not. True acupuncture points were standardized and chosen based on the researchers’ previous study, a literature review, and expert judgment. Deep needle manipulation elicited a de qi sensation (a sign of treatment adequacy) in 85% of patients. Sham points were not used to treat insomnia according to traditional Chinese medical practice, and were needled superficially (with no de qi sensation in > 80% of patients). A modified Pittsburg Sleep Quality Index (PSQI) was employed to measure overall sleep quality. The PSQI consists of seven component scores, six of which were used in the trial: subjective sleep quality, sleep-onset latency, total sleep time, habitual sleep efficiency, sleep disturbances (dyssomnia), and daytime dysfunction. In addition, the Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness.

Compared to sham, true acupuncture was significantly more effective for overall sleep quality and daytime sleepiness at six weeks (P < 0.05). This difference persisted at two months post-treatment follow-up.
for daytime sleepiness only. True acupunctu
worse than both sham and estazolam for vitality (as measured by the Short-From 36 Health Survey) at both six weeks and two months follow-up (P < .002). All analyses were intention-to-treat. Adverse
effects were mild and included hematoma, headache, dizziness and muscle convulsions in all groups (statistical comparisons not provided).

In this carefully designed trial, acupuncture was superior to sham and at least as effective as a benzodiazepine hypnotic for the treatment of primary insomnia. Researchers minimized the risk of bias by treating all groups with both oral tablets and some form of acupuncture. Like virtually all acupuncture trials, however, they did not entirely eliminate the risk of performance bias since practitioner blinding was not attempted. Although drug therapy is more convenient and less expensive, acupuncture is likely to be safer than both sham and estazolam. Although drug therapy is more convenient and less expensive, acupuncture is likely to be safer than both sham and estazolam for treating osteoarthritis. (Cochrane Database Syst Rev. 2013;12:CD003523.)

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