POEMs

Patient-Oriented Evidence that Matters

This month's POEMs provide good evidence that antioxidants are not effective in preventing heart disease, that paroxetine is useful for menopausal flushes (menopausal flashes just doesn't sound right to an antipodean) and they hammer another nail into the coffin of long-term HRT. We have also included a POEM, with not quite the same high level of evidence, on treating tinnitus with ginkgo. This is included to complement the CME paper on tinnitus in this issue. Editor.

Clinical question

Are antioxidants effective in preventing heart disease?

Bottom line

Beta-carotene and vitamin E offer no protection against all-cause mortality, cardiovascular mortality, or stroke in either high risk or low risk patients. (LOE = 1a-)

Reference

Vivekananthan DP, Penn MS, Sapp SK, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet 2003; 361:2017–23.

Study design

Meta-analysis (randomised controlled trials)

Setting

Various (meta-analysis)

Synopsis

Many years ago, Victor Herbert pointed out, among other things, that the term antioxidants was misleading since the purported agents have to oxidize one substrate to reduce another (Am J Clin Nutr 1994; 60:157–8). After discovering that the name is problematic, it's no small wonder that folks have wondered whether we got the function right, not to mention the effect. In this study, the authors searched MEDLINE to identify randomised trials of vitamin E and beta-carotene in primary and secondary prevention of heart disease. They don't describe searching for unpublished data. To minimise the effect of publication bias, they excluded trials with fewer than 1000 subjects. They also only included studies from developed countries to reduce the potential effects of nutrient-poor diets. Two investigators independently determined study eligibility but they don't describe the data extraction methods or their method of resolving conflict, and they don't report the rate of concordance between reviewers.

They identified 12 studies; eight used beta-carotene and seven used vitamin E. Of the 12 studies, seven were for primary prevention and five for secondary prevention. More than 130 000 patients participated in the studies of beta-carotene where all-cause mortality was 7.4% in the actively treated patients and 7% in the control group (P=.003; number needed to kill [NNK]=250). There was a similarly small but significant increase in cardiovascular mortality among patients receiving carotene (3.4% vs 3.1%; NNK=334; P=.003). Carotene had absolutely no effect on stroke events (2.3% for treated and controls). The data were homogeneous across studies for these end points. More than 81 000 patients participated in studies of vitamin E. All-cause mortality was the same in treated and control patients. The event rate was also the same for cardiovascular mortality in treated and control patients and for stroke rate. Finally, to see if the best possible face could be placed on this, they combined all end points and found that the end point of any bad thing was identical in patients receiving vitamin E or placebo. These data were also homogeneous across studies.

** Patient-Oriented Evidence that Matters. See editorial (NZFP 2003; 30:150)*

Clinical question

Is paroxetine useful in the treatment of menopausal hot flashes?

Bottom line

Paroxetine (Paxil) may be a useful alternative to hormone replacement therapy (HRT) for menopausal women with significant hot flashes. Other selective serotonin reuptake inhibitors are likely to be similarly effective. There was minimal difference in response between the 12.5mg per day dose and the 25mg per day dose. (LOE = 1b-)

Reference

Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes. A randomized controlled trial. JAMA 2003; 289:2827–34.

Study design

Randomised controlled trial (double-blinded)

Setting

Outpatient (any)

Synopsis

Many women – and their clinicians – are now reluctant to use HRT. As a result, other effective alternative treatments for menopausal symptoms, especially hot flashes, are needed. A total of 165 menopausal women, 18 years or older, experiencing significant hot flashes were enrolled. After a one-week placebo run-in phase to screen out high-placebo responders, participants were randomised (uncertain concealment of allocation assignment) to receive 12.5mg per day or 25mg per day of paroxetine controlled release or placebo for six weeks. Study subjects were blinded to their treatment group assignment and recorded hot flashes daily in a diary. No patients were lost to follow-up at six weeks, but five were not included in the efficacy analysis because of protocol nonadherence. Mean daily hot flash frequency decreased from 7.1 to 3.9 (mean reduction=3.3) and from 6.4 to 3.2 (mean reduction=3.2) for patients in the 12.5mg per day and 25mg per day paroxetine group, respectively, compared with a decrease from 6.6 to 4.8 (mean reduction=1.8) for those in the placebo group. Women taking paroxetine were more likely to report at least a 50% or more reduction in hot flash frequency and severity (58.3% for those receiving 12.5 mg/day and 62.5% for those receiving 25 mg/day) compared with those taking placebo (42.9%; P=.02 compared with 25mg/day dose; number needed to treat=5). Improvements in hot flash symptoms were independent of any significant changes in mood or anxiety symptoms. Adverse events were mild. Other studies using fluoxetine and venlafaxine have shown similar results.

Clinical question

Does combined hormone replacement therapy decrease the risk of dementia in postmenopausal women aged 65 years or older?

Bottom line

Combined hormone replacement therapy (HRT) with estrogen and progesterone does not decrease – and may slightly increase – the risk of dementia in healthy postmenopausal women aged 65 years or older. This further supports the conclusion from the Women's Health Initiative (WHI) study that combined HRT should be limited only to women in the first four to five years of menopause with low risk of heart disease and breast cancer, and who have a significant risk of osteoporosis or significant menopausal symptoms. (LOE = 1b)

Reference

Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003; 289:2651–62.

Study design

Randomised controlled trial (double-blinded)

Setting

Outpatient (any)

Synopsis

Studies of the effects of estrogen therapy on Alzheimer disease for postmenopausal women have been inconsistent. As part of the Women's Health Initiative Memory Study (WHIMS), an ancillary study to the larger Wom-

en's Health Initiative (WHI) study, a total of 4532 consenting, healthy women aged 65 years or older were enrolled. Participants were randomised in a double-blind fashion (concealed allocation assignment) to take either estrogen 0.625mg and medroxyprogesterone 2.5mg daily (PremPro) or matching placebo. Outcomes were assessed by individuals blinded to treatment group assignment. Follow-up was complete for a mean of four years. Using intention-to-treat analysis, 61 women were diagnosed with probable dementia, 40 (66%) in the HRT group and 21 (34%) in the placebo group (hazard ratio=2.05; 95% CI, 1.21-3.48; P=.01). This increased risk is equal to an additional 23 cases of dementia per 10 000 women per year using HRT compared with placebo. A subgroup analysis showed that the increased risk was greatest in women older than 75 years of age.

Clinical question

Is ginkgo biloba an effective treatment for tinnitus?

Bottom line

This systematic review provides cautious support for a trial of ginkgo biloba 120 to 160mg daily in patients with chronic tinnitus. A large well-designed trial of a 50mg dose that was not included in this systematic review failed to show a benefit. (LOE = 2a)

Reference

Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. Clin Otolaryngol 1999; 24:164–7.

Study design

Systematic review

Setting

Various (meta-analysis)

Synopsis

Ginkgo biloba has a variety of physiologic effects, some good and some bad, and has been advocated for the treatment of dementia, intermittent claudication, and a host of other conditions. The authors of this thorough systematic review did a careful review of the literature and identified five randomised controlled trials, of which four were published and one was unpublished. They varied in quality; the Jadad scores were 0, 2, 4, and 5 for the four published studies, on a scale where 5 is best. Three studies included approximately 100 patients; the study with the weakest methodology had the most patients (n=259) and the unpublished study included 60 patients. Most of the enrolled patients had chronic tinnitus for one year or longer. Four of five studies demonstrated a clinically significant benefit in the ginkgo group over the control group. The one negative study used a smaller dose than the studies showing benefit (29.2mg daily vs 120 to 160mg daily). Outcomes and study designs were too different to combine results, so the outcomes are reported qualitatively. A more recent randomised trial (BMJ 2001; 322:73) did not show any benefit with a 50mg dose, so the jury is still out.