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New Medical Research Round Up

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MODAFINIL INEFFECTIVE FOR MS-RELATED FATIGUE

A previous issue of the Newsletter reviewed the therapeutic use of modafinil.¹ New evidence has emerged which disputes the effectiveness of modafinil for the treatment of fatigue associated with multiple sclerosis (MS).

Fatigue is a well recognized, but difficult to manage symptom observed in patients with multiple sclerosis (MS) and is experienced by as many as 78% of patients.² Unfortunately, available pharmacologic treatments, including pemoline, amantidine, and modafinil are not strongly supported in the literature.

Stankoff et al, reported the results of a randomized, placebo-controlled, double-blind, multicenter trial of 115 patients with relapsing remitting or progressive MS and chronic fatigue for at least 6 months.³ Patients were randomized to modafinil 200mg daily as a divided dose, or placebo. Doses were increased by 100mg a week for 3 weeks, to a maximum dose of 400mg daily. The primary outcome was the change in the Modified Fatigue Impact Scale (MFIS), a validated metric developed by the US National Multiple Sclerosis Society. Outcomes were analyzed on both an intent-to-treat and a per protocol basis. In total, 56 patients were randomized to modafinil, 59 patients to placebo and followed for 5 weeks. There were no significant differences in any demographic or clinical characteristics (disability, fatigue, depression, sleepiness) between modafinil and placebo patients. At study termination, there were no significant differences in MFIS changes, or in any of the MFIS sub-scales (physical, cognitive, or psychosocial). The proportion of patients with a 15 MFIS point improvement, determined a priori to be clinically significant, was 35.6% for modafinil and 42.8% for placebo group.

The results of this study are significant in that they represent the only placebo-controlled, blinded randomized clinical trial of modafinil for MS-related fatigue. The large placebo effect observed in both arms showed significant improvement, which demonstrates the importance of blinding. Previous research either lacked a control group or adequate blinding to sufficiently safeguard from bias. The use of modafinil for MS-related fatigue should be reevaluated in light of these new data and the expense of this drug (\$216/month). Amantidine, which has consistently been shown to have a modest effect in several randomized clinical trials, is another option available for this condition.²

VALUE OF VITAMIN E IN QUESTION

The anti-oxidant vitamin E, long touted for the prevention of everything from cardiovascular (CV) disease to dementia, has recently been subject to increased scientific scrutiny. While, the benefits of vitamin E supplementation have been questioned in the past, new data also suggest the possibility of adverse effects.

Miller et al conducted a meta-analysis of over 130,000 subjects, from 19 randomized placebo controlled trials of vitamin E of 1 year or longer, evaluating the relationship of dose to all-cause mortality.⁴ Of the 11 trials evaluating high dose vitamin E (\geq 400 IU/d), the risk of death was significantly higher in subjects on

vitamin E compared to placebo (RR=1.04; 95% CI 1.01 – 1.07). A dose-response analysis of all 19 trial showed that mortality progressively increased with the dose of vitamin E for doses greater than 150 IU/d and achieved statistical significance with doses greater than 900 IU/d.

Initial results indicating no beneficial effect of vitamin E in patients at high risk for cardiovascular disease from the Heart Outcomes Prevention Evaluation (HOPE) have been previously reported.⁵ The impact of long-term vitamin E supplementation on the risk of cancer and cardiovascular outcomes was assessed in 7030 subjects from 174 of the original 267 study centers. The subjects were continued on the original randomized product for an additional 3 years.⁶

After an average total follow-up of 7.5 years, vitamin E again was found to have no significant effect on the incidence of cancer (RR=0.94; 95% CI 0.84 – 1.06) cancer death (RR=0.88; 95% CI 0.71 – 1.09), major CV events (RR=1.04; 95% CI 0.96 – 1.14), or all cause mortality (RR=1.00; 95% CI 0.91 – 1.10). The incidence of heart failure (RR=1.13; 95% CI 1.01-1.26) and hospital admissions for heart failure (RR=1.21; 95% CI 1.00-1.47) were significantly increased in subjects randomized to vitamin E. This finding was consistent among all subgroups and independent of all evaluated covariates.

Vitamin E is also purported to slow deterioration in patients with moderate Alzheimer's Disease (AD).^{7, 8} Although the studies that suggest this are controversial, many have speculated about the role of vitamin E in preventing or delaying the diagnosis of AD.^{9, 10}

To test this hypothesis, Peterson RC et al, recently reported the results of a randomized placebo-controlled double-blind trial of vitamin E (2000 IU/d) and the cholinesterase inhibitor donepezil, for patients with mild cognitive impairment. This condition is known to be a transition state to diagnosable AD.¹¹ A total 790 patients were randomly assigned to 2000 IU/d vitamin E, 10 mg per day donepezil, or placebo for 3 years. The primary outcome of this study was the development of AD.

Overall, there were no significant differences in the risk of progression to AD between Vitamin E and placebo (RR=1.02; 95% CI 0.74 – 1.41) or donepezil and placebo (RR=0.80; 95% CI 0.74-1.41). Donepezil did provide a modest reduction in the probability of progression to AD during the first 12 months, an effect that disappeared by month 36. Vitamin E had no apparent effect on AD progression at any time during the trial.

Finally, Bairati et al published the results of an investigation of Vitamin E for the purposes of preventing second primary cancers in patients undergoing radiation treatment for head and neck cancer.¹² In this placebo-controlled trial 540 subjects were randomized to a daily antioxidant supplement containing 30 mg beta-carotene and 400 IU vitamin E during radiation therapy and for three years following. Beta-carotene was later removed from the treatment arm after another study showed increased incidence of lung cancer.¹³ The investigators presented results for all

subjects (n=540) and for those enrolled after beta-carotene was removed from the supplement (n=384).

The effect of supplementation on the primary endpoint, incidence of second primary cancer, varied over time, thus follow-up was partitioned to during and after the supplementation period. For all subjects randomized, the incidence of second primary cancers in the supplement group was statistically significantly higher (60.1 cancers/1000 person-years) compared to the placebo arm (25.1 cancers/1000 person-years, HR=2.42; 95% CI 1.45 – 4.04) during supplementation period (from randomization to year 3.5). Among those enrolled after the removal of beta-carotene, the risk was even higher (HR=2.88; 95% CI 1.56-5.31). However, after supplementation was discontinued, supplement users (both combined and vitamin E alone) had a lower risk of second primary cancers (vitamin E alone HR=0.41; 95% CI 0.16-1.03). Similar findings were observed with the outcome of recurrence of original tumor or second primary cancer.

While extrapolation to the general population is difficult, the data from this trial suggest that vitamin E has no role for chemoprevention in patients at high risk for cancer (e.g. squamous cell carcinoma of head and neck) and may in fact, increase the risk for a reoccurrence.

In summary, epidemiologic and in vitro data have supported the hypothesis that the antioxidant vitamin E may have a role for everything from reducing the risk for CV disease to preventing cancer. However, evidence to-date from large, randomized, placebo-controlled outcome studies has consistently demonstrated no benefit. Yet, use of this product has persisted. Recently published research again concludes that vitamin E has no role in the prevention of cardiovascular disease, has limited and controversial efficacy in treating and preventing AD, and may not be helpful for preventing cancers. Furthermore, the widely accepted safety profile of vitamin E has been called into question by data suggesting that use is associated with an increased risk of heart failure, cancer, and death for patients taking higher doses. Aside from a few select conditions (ESRD, macular degeneration), there is now a wide body of literature that has failed to find any beneficial effect of vitamin E and some suggestion of adverse effects.

GASTROINTESTINAL SAFETY OF CLOPIDOGREL

Despite well-established benefits on CV outcomes, the benefits of aspirin are sometimes limited by gastrointestinal (GI) toxicity. Acid suppression therapy with a proton pump inhibitor (PPI) has been shown to lower the risk of GI complications in high risk patients (previous GI ulcer or bleed) on aspirin therapy.¹⁶

The American College of Cardiology / American Heart Association recommends clopidogrel as an antiplatelet alternative for patients with acute coronary syndrome who have gastrointestinal intolerance to aspirin.¹⁴ However, studies to date comparing aspirin to clopidogrel have either been under powered or not designed to properly examine this adverse event.¹⁵

A recent study published by Chan et al examined the risk of GI complications for patients with a previous aspirin-induced ulcer.¹⁷ A total of 320 with subjects on low dose aspirin (\leq 325 mg daily) recently treated for upper GI bleeding were randomized in a

double-blinded fashion to receive either 75 mg clopidogrel or 80 mg aspirin daily plus 20 mg esomeprazole twice daily for 12 months.

The incidence of recurrent bleeding was 8.6% in the clopidogrel arm compared to 0.7% in patients receiving aspirin and a PPI (RR=12.3; 95% CI 1.7 –97.0, p=0.001). Nearly 72% of recurrent ulcers in the clopidogrel arm occurred in the same location of the originally healed lesion. There was no difference in the incidence of lower GI bleeding between the two arms. This study was designed to be a non-inferiority trial intended to demonstrate equivalence between arms. The results were unexpected and suggest clopidogrel may have some ulcerogenic properties. At the very least, these data stress the importance of acid suppression prophylaxis to prevent reoccurrence of GI bleeding.

In summary, this study suggests that in patients with GI toxicity due to aspirin, the combination of aspirin and a PPI is safer than switching to clopidogrel. In addition, selecting a low cost PPI such as Prilosec OTC, which is less than \$20 a month, makes this therapy significantly less expensive than clopidogrel (\$120).

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