hypercalcemia and hypervitaminosis D after receiving 400 IU per day of vitamin D3 plus 1600 IU per day of vitamin D2 for 3 months. The patients required between 6 weeks and 6 months for normalization of serum calcium, with time to resolution of hypercalcemia related to age and peak serum calcium level, but not to peak 25(OH)D level.

Comment: A small subset of the population appears to have an increased susceptibility to vitamin D toxicity. This increased susceptibility appears to be due to at least in part to a mutation in the gene that encodes for the enzyme 25-hydroxyvitamin D 24-hydroxylase (CYP24A1), which is involved in the degradation of 1,25-dihydroxyvitamin D. In the 1950s, there were about 200 reported cases of infantile hypercalcemia in Britain during a period of high vitamin D supplementation (up to 4000 IU per day) in fortified milk products. Manifestations included failure to thrive, vomiting, dehydration, fever, and nephrocalcinosis. While most children have no adverse effects from standard doses of vitamin D, clinicians prescribing vitamin D should be aware of the potential for toxicity.

Vanstone MB et al. Hypercalcemia in children receiving pharmacologic doses of vitamin D. *Pediatrics*. 2012;129:e1060–e1063.

Proton Pump Inhibitors and Magnesium Deficiency

The association between serum magnesium levels and use of proton pump inhibitors (PPIs) was examined in a cross-sectional study of 487 patients over 50 years of age who were hospitalized at a community hospital in Ohio. The mean serum magnesium concentration was significantly lower among the 207 PPI users than among the 280 nonusers (1.91 vs. 2.00 mg/dl; $p = 0.004$). The prevalence of hypomagnesemia (< 1.7 mg/dl) was significantly higher in PPI users than in nonusers (23.2% vs. 10.8%). After adjustment for potential confounding variables, the risk of developing hypomagnesemia was 2.5 times higher among PPI users than among nonusers. Both standard-dose and high-dose PPI use was associated with hypomagnesemia.

Comment: There have been rare case reports of severe hypomagnesemia occurring in patients receiving PPIs. The results of the present study suggest that mild-to-moderate magnesium deficiency occurs relatively frequently as a result of PPI use. PPIs have been associated with multiple adverse effects, and in many situations natural alternatives (such as dietary modifications or supplementation with deglycyrrhizinated licorice) are preferable. When a PPI must be prescribed, concomitant administration of a magnesium supplement would seem appropriate in most cases.

Gau JT et al. Uses of proton pump inhibitors and hypomagnesemia. *Pharmacoepidemiol Drug Saf*. 2012;21:553–559.

Coenzyme Q10 and Fibromyalgia

Mean concentrations of coenzyme Q10 (CoQ10), adenosine triphosphate (ATP), and catalase (an antioxidant enzyme) in blood mononuclear cells were significantly lower, and the mean concentration of lipid peroxides in blood mononuclear cells was significantly higher, in 20 patients (mean age, 46.6 years) with fibromyalgia than in age-matched healthy controls. Ten patients with fibromyalgia received 100 mg of CoQ10 3 times per day for 3 months, in open-label fashion. CoQ10 treatment resulted in significant improvements in the biochemical markers, a 35% decrease in the mean number of tender points ($p < 0.001$), a 39% improvement in the Headache Impact Test-6 score ($p < 0.001$), and a 49% improvement in the Fibromyalgia Impact Questionnaire score ($p < 0.001$).

Comment: In this study, fibromyalgia patients demonstrated biochemical evidence of mitochondrial dysfunction and increased oxidative stress, and CoQ10 supplementation improved both the biochemical markers and clinical symptoms. Magnesium is another nutrient that has been shown both to improve mitochondrial function and to ameliorate symptoms of fibromyalgia. Other nutrients that may enhance mitochondrial function include niacinamide, riboflavin, and carnitine; these nutrients have not been studied as potential treatments for fibromyalgia.

Cordero MD et al. Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q10 effect on clinical improvement. *PLoS One*. 2012;7(4):e35677.

N-Acetylcysteine for Depression Associated with Bipolar Disorder

One hundred forty-nine patients with bipolar disorder 1, bipolar disorder 2, or bipolar disorder not otherwise specified who were experiencing moderate depression received 1 g of N-acetylcysteine (NAC) twice a day for 8 weeks as adjunctive therapy, during the open-label phase of a double-blind placebo-controlled trial of NAC as maintenance treatment for bipolar disorder. All patients had been on stable medical therapy for at least 1 month. After 8 weeks, the mean score on the Bipolar Depression Rating Scale decreased significantly from 19.7 at baseline to 11.1 (44% improvement; $p < 0.001$). Similar improvements were seen in functioning and quality of life.

Comment: Both depression and bipolar disorder are associated with glutathione depletion. NAC is a glutathione precursor that can replenish brain glutathione. The results of the present study suggest that NAC is beneficial as adjunctive therapy in the treatment of depressive symptoms associated with bipolar disorder.

Berk M et al. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. *J Affect Disord*. 2011;135:389–394.

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