# What Is the Evidence that Riboflavin Can Be Used for Migraine Prophylaxis?

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**ABSTRACT**

Individuals with migraine often have recurrent, painful symptoms, and symptomatic treatments have detrimental side effects and do not prevent further attacks. Studies indicate that riboflavin can be used to decrease headache frequency and lessen the need for symptomatic treatment. Mitochondrial dysfunction may play a role in migraine pathogenesis by interfering with oxygen metabolism. Daily doses of riboflavin, vitamin B2, may improve mitochondrial function by increasing the reserve of brain mitochondrial energy, and there are minimal side effects with daily treatment. However, there is a need for further randomized, double-blind controlled studies to determine the effective dose. Although riboflavin may not fully eliminate migraine nor take effect for several months, riboflavin is a promising prophylactic agent with minimal adverse effects that may significantly reduce the frequency of migraine.

## INTRODUCTION

### Importance Of Prophylactic Treatment For Migraine

No perfect treatment exists for many individuals with migraine, who often have recurring, long-lasting, painful symptoms. With a prevalence of 18% in women and 6% in men in the United States, migraine is extremely common (Lipton and Stewart 1993; Bianchi et al. 2004; Boehnke et al. 2004). The use of frequent symptomatic treatment without effective prophylactic medications may lead to more-frequent headaches and medication-overuse headache, which can significantly affect the quality of life. Symptomatic medication for migraine includes triptans, NSAIDs, and ergotamine (Bianchi et al. 2004). Preventive medications include beta blockers, topiramate, flunarizine, tricyclic antidepressants, and valproic acid (Bianchi et al. 2004; Schurks et al. 2008). However, many of these treatments have significant side effects that may limit use. Lifestyle changes, including improved sleep hygiene, more exercise, decreased stress, and minimizing foods that trigger migraine, may also play a noteworthy role in migraine management (Schurks et al. 2008; Sun-Edelstein and Mauskop 2009).

While symptomatic treatments may alleviate acute episodes, they typically do not alter the disease course or decrease the frequency of future episodes. Riboflavin is just one of a bevy of "natural" treatments or herbal remedies used for migraine prophylaxis that may include magnesium, feverfew, petasites hybridus, coenzyme Q10, alpha lipoic acid, valerian root, ginger, eicosapentaenoic acid, and acupuncture (Maizels et al. 2004; Sun-Edelstein and Mauskop 2009). If patients want to use a "natural" treatment for migraine prophylaxis with potential benefits and few risks, they should be encouraged to use a treatment that is sufficiently studied in terms of safety and efficacy; some treatments may be less represented in the literature. This review was performed in order to evaluate the efficacy of riboflavin as a prophylactic treatment for migraine as reported in the literature.

### Pathophysiology: Migraine, Mitochondria, And Riboflavin

Although the pathogenesis of migraine has not been fully elucidated, two pathways by which migraine may evolve are through mitochondrial dysfunction and through abnormal cortical information processing, both leading to activation of a hyperexcitable trigeminovascular system (Sandor et al. 2000). Mitochondrial dysfunction may play a role in migraine pathogenesis by altering oxygen metabolism. Research has indicated that individuals with migraine have decreased mitochondrial phosphorylation potential interictally (Bianchi et al. 2004).

Daily doses of riboflavin may improve mitochondrial function by increasing the reserve of brain mitochondrial energy (Sandor et al. 2000; Maizels et al. 2004). Riboflavin is a precursor for substances important for cell energy and stability, such as flavin mononucleotides and flavin adenine dinucleotide involved in oxidation-reduction reactions (MacLennan et al. 2008; Sun-Edelstein and Mauskop 2009). Riboflavin, at 100 mg/day, has also been used in treatment of mitochondrial disorders including MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and other mitochondrial myopathies (Silberstein and Goadsby 2002; MacLennan et al. 2008).

In a study of 64 patients given 400 mg of riboflavin daily for four months, each individual was genotyped for mitochondrial DNA haplotypes. The different haplogroups seem to have some distinct characteristics, especially with regard to metabolic activity. Specificially, haplotype

**Table 1**

| Study | Year | Placebo-controlled | Age | Number of patients | Riboflavin dose | Treatment duration | Outcome measure | Findings |
|---|---|---|---|---|---|---|---|---|
| **Schoenen et al.** | 1998 | Yes | Age range: 18 to 65 | 55 | 400 mg/day | 3 months | Decrease in attack frequency | NNT= 2.3;statistically significant |
| | | | | | | | Decrease in headache days | NNT=2.8; statistically significant |
| | | | | | | | Reduction in headache intensity | Not statistically significant |
| **Boehnke et al.** | 2004 | No | Average age 52 | 23 | 400 mg/day | 3 to 6 months | Reduction in migraine frequency | NNT = 3.1; From 4 to 2 days/month; statistically significant |
| | | | | | | | Decreased use of "abortive drugs" | From 7 to 4.5 units/month; statistically significant |
| | | | | | | | Reduction in # of headache hours | Decreased by 44%; Not statistically significant |
| | | | | | | | Reduction in headache intensity | Not statistically significant |
| **Maizels et al.** | 2004 | No | Average age 47 | 49 | 25 mg/day | 3 months | 50% or greater reduction in migraine | Statistically significant |
| | | | | | | | 50% or greater reduction in migraine days | Statistically significant |
| | | | | | | | 50% or greater decrease in migraine index | Statistically significant |
| **MacLennan et al.** | 2008 | Yes | Average age 11 | 48 | 200 mg/day | 12 weeks | 50% or greater reduction in the number of migraine attacks per 4 weeks | Not significant |
| | | | | | | | 50% or greater reduction in migraine frequency | Not significant |

H may be more metabolically active and exhibit a higher level of mitochondrial oxidative phosphorylation than non-H haplotypes (Di Lorenzo et al. 2009). Individuals in the non-H haplotype group responded to riboflavin better than those in the H haplotype group (77% responder rate vs. 44.8%) in terms of decreasing attack frequency, and this difference was significant. The difference in metabolic activity between the haplotypes may contribute to the varying response to riboflavin (Di Lorenzo et al. 2009). Specifically, it has been hypothesized that the higher metabolic activity in the H haplogroup may be protective against migraine at baseline, while the non-H haplogroup may be more susceptible to migraine and may, in turn, benefit more from the riboflavin treatment (Di Lorenzo et al. 2009).

## METHODS

A search was performed using the terms "riboflavin" and "migraine" in PubMed. All search terms were limited to the English language. Studies included in this review consisted of prospective clinical trials using riboflavin prophylaxis in humans. Studies involving ribo-

flavin combined with other prophylactic agents were excluded, as were studies that were not accessible. Four studies met inclusion criteria.

In a randomized trial by Schoenen et al. of 55 patients given 400 mg of riboflavin per day for three months, attack frequency and headache days were significantly reduced compared to placebo, with the number needed to treat reported as 2.3 for headache days and 2.8 for attack frequency (Schoenen et al. 1998). In an open-label study of 23 migraineurs treated with riboflavin (400 mg for three to six months), migraine frequency was significantly reduced, from four to two days per month. Additionally, the use of "abortive drugs" decreased from seven to four units per month. Although the number of headache hours decreased by 44%, this was not statistically significant. Furthermore, no change in headache intensity was found (Boehnke et al. 2004).

In a randomized, double-blind study of 49 patients given a daily compound of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg versus a "placebo" of 25 mg riboflavin for three months, there was no difference between the groups for reduction of migraine frequency, decrease in migraine days, migraine index, or triptan doses. Rather, both groups, the combination compound and the riboflavin 25 mg that was intended to serve as the placebo, experienced significant decrease in migraine, migraine days, and migraine index. The response exhibited by the "placebo" of riboflavin 25mg is a greater response than has been typically shown by placebo in previous migraine studies, which may indicate that this lower dose of riboflavin is protective against migraine (Maizels et al. 2004). However, a true placebo was not used.

Riboflavin has been studied in children, with conflicting results. Some retrospective studies showed significant decreases in frequency and intensity of attacks, but fewer randomized studies exist (Condo et al. 2009). A randomized, double-blind study of 48 patients evaluating efficacy of riboflavin (200 mg/day for 12 weeks) in migraine prophylaxis in children showed less-than-promising results. There were no significant differences in the primary outcome or the number of patients achieving a 50% or greater reduction in the number of migraine attacks, nor was there a significant difference in any of the secondary outcomes, such as migraine severity or migraine duration (MacLennan et al. 2008). The results of this study indicate that riboflavin may not be appropriate prophylaxis for children with migraine.

## DISCUSSION

There has been only one placebo-controlled study of riboflavin in adults with migraine, which found that riboflavin decreased attack frequency and number of headache days (Schoenen et al. 1998).

There are many advantages to riboflavin, which include water solubility, good tolerability, and no long-term toxicity . Negative aspects of the treatment include daily medication, questionable efficacy, potential yellow/orange urine discoloration, and possible nausea, diarrhea, and polyuria (MacLennan et al. 2008; Sun-Edelstein and Mauskop 2009).

In the future, further randomized, double-blind controlled studies should be done, specifically with varied dosing to provide evidence for dose dependence, a larger number of patients in order to provide for higher power, studies of longer length in order to determine the durability of the response, and inclusion of patients with a wide age range. In addition, riboflavin should be compared head-to-head with other preventive medications. While prophylaxis with riboflavin may not completely ameliorate migraine and may take several months to achieve results, this is a low-risk, low-cost option with minimal side effects that may be able to improve the quality of life for some patients by reducing the frequency of migraine.

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