**Title**
Riboflavin: An Alternative Approach to Managing Migrane Attacks in the Adult Population



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## Introduction:

As of 2008, epidemiological studies have claimed that over 10% of adults residing in countries within the Western hemisphere experience migraines.[1] Similar studies have estimated that, in just the United States, up to 28 million people currently suffer from migraine attacks.[1] However, despite the prevalence of this syndrome, considerable debate continues to remain over its pathophysiology. As a result of the great degree of uncertainty regarding the true, underlying nature of the disease, no single treatment modality or management practice has been established as a "magic bullet" solution to this heterogeneous disorder.[2]

Contemporary treatments tailor to the individual needs of the patient, with a combination of prescription drugs and lifestyle modifications being utilized to manage migraine attacks. Unfortunately, according to Sun-Edelstein et al., drugs have rarely imposed a great reduction in either migraine frequency or intensity.[2] Further compounding the problem is that many of the prescriptions for reducing migraine attacks have a considerable list of accompanying adverse effects.[3] Thus, due to the low efficacy offered by prescriptions and the negative consequences resulting from their use, recent research has focused more on the role that lifestyle modifications can take. Such modifications (e.g. dietary changes) have demonstrated a greater degree of success.[2]

To that end, this review article will focus on the effects of riboflavin (Vitamin $B_2$) supplements on reducing migraine symptoms and their frequency. Riboflavin has been studied because of its importance in the electron transport chain (ETC), which has been theorized as a potential source for migraines. Sparaco et al. posit that mitochondrial defects and/or dysfunction lower the threshold required to experience a migraine attack.[4] Some possible mechanisms to explain this phenomena include, but are not limited to: a) Oxidative metabolism defect, specifically in the trigeminal nerve nucleus and/or the brainstem, that impairs somatosensory information processing, thus allowing neurons to be hypersensitive to stimulation and b) Mitochondrial defects in the walls of meningeal blood vessels that increase their sensitivity to migraine-inducing substances such as nitric oxide.[4]

As a precursor to the flavin mononucleotide and flavin adenine dinucleotide, both of which are compounds critical for activating the flavoenzymes involved in the ETC, riboflavin supplements have significant potential to rectify mitochondrial defects and, by extension, treat migraine attacks.[5] Although mitochondrial defects cannot explain migraine incidence in all patients, treatments such as riboflavin may prove useful and cost-effective for some migraine patients. Thus, riboflavin's efficacy in treating migraines will be discussed in this review.

## Methods:

All research literature studying the effects of riboflavin among patients with migraines were obtained through Pubmed and GoogleScholar. A Pubmed keyword search of "migraine" and "riboflavin" yielded 55 search results, all of which were restricted to research conducted on human subjects. Inclusion criteria were both open-label and randomized, controlled trials that primarily observed riboflavin's efficacy in reducing either the frequency or intensity of migraine attacks. Furthermore, in an attempt to observe what the most recent studies had found with relation to riboflavin, studies were restricted to those that had been published within the last twenty years. Exclusion criteria were review papers, studies that were irrelevant or beyond the scope of the paper, non-English references, and results that were not studies (e.g letters to the editor, commentaries). Fifty papers were eliminated this way; one paper by Condo et al. was excluded because the experiment tested for the difference in efficacy between 200 and 400 mg/day of riboflavin.

A similar search was run on GoogleScholar, yielding 28 results, one of which was a new result that had not been found through Pubmed. However, this article was not included in the study because it had been written in 1946. No animal studies were found through both searches and thus, were not

included in this review.

Results:

In total, four clinical trials fully met the search and inclusion criteria. All studies defined "migraines" as that which qualifies under the guidelines set by the International Headache Society (IHS); migraines with or without auras were not differentiated.

The first two studies were open-labeled trials that studied the basic effects of riboflavin. Schoenen et al. enrolled 44 patients and orally administered 400 mg of riboflavin for a period of at least 3 months; 23 patients received an additional 75 mg of aspirin.[6] The drug's effects were evaluated at the end of the 3-5 month treatment period, with patients being asked to rank the severity of their migraines on a scale of 1-10. The results showed a mean total improvement in severity of 68.2%, although the response was not different between the riboflavin and riboflavin + aspirin groups. Among the patients treated with just riboflavin, 80% exhibited a 50% or greater reduction in the number of monthly migraine days.[6]

Boehnke et al. attempted a similar study, enrolling 23 patients from an outpatient clinic affiliated with the Humboldt University of Berlin.[7] Inclusion criteria were patients aged 20-65 who experienced 2-8 migraine attacks per month. Patients were prohibited from taking other medications three months prior to and throughout the study. After a four-week baseline period, patients were instructed to consume 400 mg of riboflavin capsules every day and to record the frequency, length, and severity of their attacks. After three months of treatment, riboflavin ingestion was discontinued unless the patient desired to extend the trial for three more months.

The results demonstrated a reduction in median attack frequency (four attacks in baseline vs. two attacks after three months; $p < 0.001$) and migraine duration (50 hours in baseline vs. 22-28 hours after 3 months; $p = 0.098$). The use of abortive anti-migraine tablets (seven tablets/month in baseline vs. 4.5 tablets/month at three months; $p = 0.016$) also decreased; this decrease was even sharper in the six month trial group (four tablets/month; $p = 0.006$). Headache intensity did not change significantly, with a p value of 0.3.[7]

The second two studies were placebo-controlled, double-blinded trials that compared the effects of riboflavin to placebo. For reasons unspecified, one study (Maclennan et al.) failed to disclose the contents of the placebo tablets; the other (Schoenen et al.) used a combination of Avicel and beta-carotene for the placebo. MacLennan et al. recruited 48 patients, aged 5-15, into a randomized, double-blinded trial.[8] Patients had a migraine history greater than three months, with 2-8 migraine attacks per month. Those that had organic or psychiatric diseases, had previously used riboflavin, or had used prophylactic methods for 3 months prior to the study were excluded from the study. Through the biased coin technique, patients were randomized to receive either placebo or daily oral administration of 200 mg riboflavin for 12 weeks. Eventually, 27 and 21 patients were allocated to the riboflavin and treatment groups, respectively. Patients were instructed to keep a diary detailing the type, frequency, severity, duration, etc. of migraines as well as any adverse effects encountered during the trial.[8]

Fourteen out of twenty-one (66.6%) patients in the placebo group and twelve out of twenty-seven (44.4%; $p = 0.125$) in the riboflavin group exhibited a 50% or greater reduction in the number of migraine attacks. Thus, based on this data found in both groups, the attack frequency appears to have drastically decreased in approximately half of the total sample population. The "response rate" and mean severity difference between the two groups were insignificant. The mean duration was unable to be calculated because of many patients' failure to consistently record the onset and offset times of their attacks. Within the data that was retrieved, duration increased with the use of riboflavin (259-316 minutes in placebo vs. 275-315 minutes in riboflavin group). Furthermore, the days accompanied by vomiting or nausea increased from 25-27 in the placebo group to 35-38 in the riboflavin group.

Schoenen et al. recruited 54 patients, aged 18-65 from six centers in Belgium and the Grand

Duchy of Luxemburg.[5] Patients enrolled had migraines for at least a year and a frequency of 2-8 attacks/month. Patients with serious organic and/or psychiatric diseases were not considered. Enrolled patients were randomly chosen to receive placebo or 400 mg of daily riboflavin; all patients received placebo for a one-month "baseline" treatment and were allocated for randomization if they had at least one migraine attack during the month preceding that. 28 patients were recruited to the riboflavin group while 26 were placed in the placebo group. The study was blinded, with all investigators dispensing random drug tablets, the contents of which only the supplying pharmaceutical company knew.[5]

Patients were instructed to rank the severity of each attack ("3" being severe, "0" being "no pain), the presence of nausea or vomiting, and headache duration. These diaries were cross-checked by the investigator and patient during each visit. When the experimenters compared the response seen in the placebo group vs. the riboflavin group, several important patterns emerged. The attack frequency decreased to two fewer attacks in the Riboflavin group ($p=0.0001$) but the frequency remained the same in the placebo group. The number of migraine days decreased in the riboflavin group by 3 days ($p=0.0001$), but increased in the placebo group by 0.50 days. Migraine severity remained at the baseline level for the riboflavin group ($p=0.031$) but increased by 0.05 in the placebo group. Migraine duration decreased by 1.30 hours/day ($p=0.018$) in the riboflavin group but increased by 0.23 hours/day in the placebo group. Lastly, more patients in the riboflavin group exhibited a 50% or greater response rate, meaning a 50% or greater improvement in a particular variable. With respect to the variable "attack frequency," for example, 19% of placebo patients were "responders" while 56% of riboflavin patients were responders ($p=0.01$); in the variable "number of migraine days," 15% of placebo patients and 59% of riboflavin patients were responders ($p=0.002$).[5]

Discussion:

Of the four selected studies, only two were randomized, controlled clinical trials; one of those clinical trials (Maclennan et al.) diverged from the others with respect to its methodology, as that particular study applied a much smaller dose – 200 mg/day – of riboflavin and the goal was to observe the effects of riboflavin specifically within the pediatric population.

Among the three studies conducted on the adult population, the two open-label studies suggest that riboflavin has a positive effect on controlling migraine attacks. Boehnke et al. found that 400 mg of riboflavin per day markedly reduced the frequency of attacks as well as the use of abortive anti-migraine medications such as triptan.[7] Adverse effects appeared to be mild, with only three out of twenty-three (13%) patients experiencing diarrhea, facial erythema, or upper abdominal pain. However, changes in migraine duration decreased but were not statistically significant, with a p value of 0.098; furthermore, there appeared to be no effects on the severity of the attacks. Similarly, Schoenen et al. found evidence in support of riboflavin's efficacy, primarily with respect to two findings: a) 80% of patients in the riboflavin-only group experienced a 50% or greater reduction in the number of migraine days per month and b) global improvement in migraine severity/intensity was a drastic 68.2%.[6]

By virtue of being open-label trials with no control group, both the Schoenen and Boehnke studies are subject to tremendous bias and thus, are not ideal for making substantive conclusions on the utility of riboflavin. Nevertheless, despite the concerns with using the open-label trials, the single clinical trial (Schoenen et al, 1998) done on the adult population lent support to the evidence derived from those two studies.

Much like the open-label trials, the results of the second Schoenen study conducted in 1998 reflected positively on the prophylactic use of riboflavin. In addition to showing significant reductions in attack frequency, migraine severity, migraine duration, and a significantly higher 50% responder rate when compared to placebo, the Schoenen study observed further reductions in the number of migraine days.[5] Within the riboflavin group, attack frequency and headache days decreased even further as more months in the trial passed, with p values all below 0.05. Alternatively, within the placebo group, no

significant changes were noted in any outcome variables. Thus, the conclusions from this study corroborate the conclusions drawn from the open-label trials, with riboflavin proving valuable as a treatment modality to migraines. Using the generated data, Schoenen et al. (1998) calculated the number-needed-to-treat (NNT) values for headache days (2.3), attack frequency (2.8), migraine index (3.1). The observed NNT for adverse effects was a high 33.3, which suggests that riboflavin could potentially hold an advantage over other commonly used prophylactic drugs. Valproate, for example, has a slightly better NTT ratio than riboflavin, at 1.6. However, its NNT for adverse effects is 2.4, indicating that 2.4 patients must be treated before an adverse reaction occurs. Due its better "efficacy:side effect" profile, riboflavin may thus provide a safer alternative to other treatments for migraines.[5]

In contrast, the single study (MacLennan et al.) conducted on the pediatric population did not substantiate the findings from the adult population. Riboflavin was not significantly more effective than placebo in reducing either migraine frequency or severity. The ability of riboflavin to decrease attack frequency by 50% or greater in 44.4% of patients in the treatment group was matched and surpassed by the response in the placebo group.

Through this review, several limitations in riboflavin research were highlighted. The primary roadblock involves the sheer lack of studies that have addressed riboflavin use and its effects on the reduction in migraine frequency/severity. Secondly, the few studies that were used for this review were often plagued with non-ideal recruitment policies. Recruitment was achieved via advertisements made in school newsletters, thus introducing the possibility of sample bias (e.g. only those patients living in the area of circulation would have been able to enroll into the study). Furthermore, several of the studies demonstrated an unequal demographic distribution between the treatment and control groups. Boehnke's trial, for example, consisted largely of female patients (83%). In the Maclennan trial, more patients were allocated to the riboflavin group (twenty-seven) than the placebo group (twenty-one), and 56% of the patients in the riboflavin group were male while 43% of patients in the placebo group were male. To some degree, this may just have been a failure of the randomization process, as an ideal randomization should equalize both the treatment and control groups along multiple dimensions. Thus, future studies must make a greater effort in including patients with diverse backgrounds from multiple centers around the world.

Once the effects of riboflavin compared to placebo have been observed, it may be further helpful to observe riboflavin's efficacy based on DNA genotypes. Some studies have observed variance in responses to riboflavin among patients with particular mitochondrial haplotypes. Based on recent research suggesting that reduced mitochondrial metabolism lowered the efficacy of riboflavin, Di Lorenzo et al. hypothesized that mitochondrial haplotype variations could account for this phenonema. On a trial run on sixty-four patients with migraines, they found that the response to riboflavin was much higher among patients who had a non-H haplotype as opposed to the H haplotype. Although the exact mechanism for this was unexplained, the findings suggest that therapeutic response to riboflavin may differ based on mitochondrial genotypes; thus, conducting future riboflavin vs. placebo response trials that also correlate with mtDNA genotypes can potentially explain why riboflavin was effective for some but not for others.[9] The results may help explain the discrepancies between the MacLennan and Schoenen studies, as the patient population in MacLennan could have been largely "non-H" patients while those in the Schoenen study could have been "H" patients.

## Conclusion:

In summary, based on the single randomized, placebo-controlled trial published at a dose of 400 mg/day, 400 mg of orally administered riboflavin appears to both increase the 50% responder rate and decrease migraine frequency, intensity, and duration in the adult population, all within statistical significance. Similar effects were found in the open-label trials. The fact that such statistically

significant results were derived from studies with small sample sizes (usually less than fifty patients) is extremely encouraging; however, conducting more trials may shed some light on why riboflavin does not appear to have a statistically significant effect on treating migraines within the pediatric population. This discrepancy may be a factor inherent to the fact that children and adults often process drugs differently, or it may simply reflect factors such as the different doses of riboflavin used. Furthermore, conducting more trials on the adult population may provide further support to the conclusions drawn in this review.

Regardless, based on this review, 400 mg of riboflavin appears to offer relief in the management of migraines in adults. While this dose considerably exceeds the recommendation for health given by the National Academy of Sciences, which reports the Dietary Reference Intake (DRI) of riboflavin as 1.1 mg/day for males aged 19-70 and 0.9 for women aged 19-70, very few harmful effects of the high dose of 400 mg have been reported and an upper limit has not yet been determined.[10] At the very least, riboflavin appears to have very few side effects: not only were there few cases of adverse reactions to the supplement during the trials, the NNT for adverse effects in riboflavin was higher compared to other currently-used drugs.

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**Table 1. Study Summary**

| | Sample | Design | Duration | Intervention | Attack Frequency | Use of Abortive meds/treatment | Duration | Intensity/Severity | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Boehnke et al. (2004)** | n=23<br><br>Age: 20-65 | Open-label study with intention-to-treat analysis<br><br>Pts kept a headache diary | 4-week baseline + 3-month treatment; outcomes were measured at end of the treatment period<br><br>Treatment could be extended by 3 more months | 400 mg Riboflavin, administered daily + orally | 4 attacks/month (baseline)<br><br>2 attacks/month ($p<0.001$) after 3rd month<br><br>2 attacks/month ($p=0.005$) after 6th month | 7 tablets/month (baseline)<br><br>4.5 tablets/month ($p=0.016$) after 3rd month<br><br>4 tablets/month ($p=0.006$) after 6th month | 50 hrs (baseline)<br><br>22-28 hrs ($p=0.098$) after 3rd month | Scale of 0 (no pain) to 5 (unbearable)<br><br>3.3/5 (baseline)<br><br>3/5 ($p=0.296$) after 3rd and 6th months | 3 pts had diarrhea, upper abdominal pain, or facial erythema |
| **Schoenen et al. (1994)** | Riboflavin (n=25)<br><br>Riboflavin + aspirin (n=23)<br><br>Age: not given | Open-label study<br><br>Pts kept a headache diary for 1 month before enrollment and throughout study | 3-5 months | 400 mg Riboflavin, administered daily + orally<br><br>75 mg Aspirin for 23 patients | 80% of pts in the riboflavin-only group had ≥50% reduction in the number of migraine days per month | Not assessed | Not assessed | Severity was defined as the "arithmetic mean" between the pt's perceived severity (scale of 1-10) and the # of monthly migraine days.<br><br>Global improvement of 68.2% ($p=0.01$); this response did not differ (in a statistically significant manner) between the riboflavin vs. riboflavin + aspirin groups. | One pt withdrew from the riboflavin + aspirin group due to gastric upset. |
| **Schoenen et al. (1998)** | Riboflavin (n=28)<br><br>Placebo (n=26)<br><br>Age: 18-65 | Double-blinded, placebo-controlled, randomized trial<br><br>Pts kept a headache diary | Baseline month (on placebo) + 3 months (trial) | 400 mg Riboflavin vs. 400 mg placebo (Avicel + beta-carotene); administered daily + orally | Number of Attacks: -2.00; $p=0.0001$ (Riboflavin), 0 (Placebo)<br><br>Number of Migraine Days (Total): -3.00;$p=0.0001$ (Riboflavin), 0.50 (Placebo)<br><br>50% Responder (i.e ≥50% reduction) in Number of Attacks: 56%; $p=0.01$ (Riboflavin), 19% (Placebo)<br><br>50% Responder (i.e ≥50% reduction) in Migraine Days: 59%; $p=0.002$ (Riboflavin), 15% (Placebo) | Treatment use, per migraine day<br><br>0; $p=0.369$ (Riboflavin)<br><br>0 (Placebo) | -1.30 hrs/day; $p=0.018$ (Riboflavin)<br><br>0.23 (Placebo) | Scale of 0 (no pain) to 3 (severe)<br><br>0.00; $p=0.031$ (Riboflavin) 0.05 (Placebo) | Days w/ nausea or vomiting:<br><br>0; $p=0.016$ (Riboflavin)<br><br>0 (Placebo) |
| **Maclennan et al. (2008)** | Riboflavin (n=27)<br><br>Placebo (n=21)<br><br>Age: 5-15 | Double-blinded, placebo-controlled, randomized trial<br><br>Parents/families kept a headache diary | 12 weeks | 200 mg Riboflavin vs. 200 mg placebo; administered daily + orally | Number of pts with ≥50% reduction in migraine attacks: 14/21 (66.6%) in placebo, 12/27 (44.4%; $p=0.125$) in riboflavin | Mean number of attacks treated with analgesics decreased in both groups (no p value) | Not calculated for majority of subjects | Scale of A (mild) to C (severe)<br><br>No change in migraine severity for either group (no p value) | Tension headaches in one child (riboflavin group), diarrhea in one child (placebo group) |