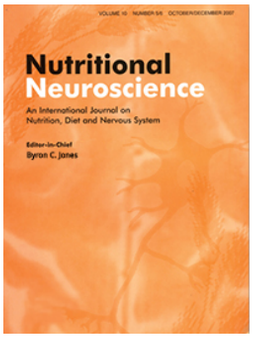

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# Effect of Vitamin B2 supplementation on migraine prophylaxis: a systematic review and meta-analysis

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**ABSTRACT**

**Objective:** Migraine is a common disease worldwide and migraine prevention is primarily currently based on pharmaceuticals. The mechanism of Vitamin B2 may positively contribute to migraine. This systematic review and meta-analysis aimed to evaluate the impact of Vitamin B2 supplementation on the days, duration, frequency, and pain score of the migraine attack.

**Methods:** : The PRISMA guideline was used for the studying process. Five electronic databases, PubMed, Embase, Cochrane, CINAHL, and CEPS were searched from 1990 to March 2019. The search terms were Vitamin B2, migraine, and prophylactic. A meta-analysis was performed using Comprehensive Meta-Analysis (CMA) version.

**Results:** : Nine articles were included in systemic review and finally meta-analysis. Eight randomized controlled trials and one controlled clinical trial with 673 subjects were analyzed using meta-analysis. Vitamin B2 supplementation significantly decreased migraine days ($p = .005$, $I^2 = 89\%$), duration ($p = .003$, $I^2 = 0$), frequency ($p = .001$, $I^2 = 65\%$), and pain score ($p = .015$, $I^2 = 84\%$).

**Conclusions:** A pooled analysis of available randomized controlled clinical trials demonstrated that Vitamin B2 400 mg/day for three months supplementation had significant effect on days, duration, frequency, and pain score of migraine attacks.

**KEYWORDS**
Systematic review; meta-analysis; migraine; vitamin B2; prophylaxis; headache; non-pharmacotherapy; pain

## Introduction

Migraine is a common neurological disease and is usually unilateral, but bilateral migraines sometimes occur. Migraine patients are sensitive to environmental and noise stimulation and often have accompanying symptoms such as nausea, vomiting, photophobia, and phonophobia [1,2]. The World Health Organization (WHO) has listed migraine as one of the top ten diseases and recommend periodic consultation and control [3]. Note that 10% of the global population suffers from migraine, particularly women, students, and urban residents in which the incidence is high. Moreover, migraine has a high prevalence in Central and South America [4,5]. Although migraine does not pose an immediate threat to life, it results in 3% of global disabilities [6] and indirecAtly affects patients' life quality. Migraine treatment guidelines recommend that the aim of migraine prophylaxis is to decrease its frequency, duration, and severity, improve drug responses and efficacy during acute attacks, improve daily function, and decrease disability [7–10]. Currently, around 38% of migraine patients require prophylaxis but only 3%–13% receive it [11].

Headache is a chronic debilitating disease, but its pathogenesis is still unclear. However, a study reported that migraine may be associated with vasoactive peptides [12]; nevertheless, another study reported that mitochondrial dysfunction may decrease the threshold for migraine attacks while simultaneously increasing neuron excitability and trigger excessive migraine responses [13–15]. Drugs are used in migraine prophylaxis in clinical practice; however, this is often accompanied by side effects, which decreases drug compliance in patients. Therefore, optimal efficacy for migraine prophylaxis cannot be achieved, migraine attacks cannot be reduced, patients' quality of life cannot be improved, and the possibility of disability cannot be decreased. Vitamin B2 is an important factor in oxidative metabolism that can improve energy metabolism in the brain and may decrease susceptibility to migraines [15].

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In this study, we performed a systematic review and meta-analysis to examine the efficacy of vitamin B2 in alleviating and preventing migraine. In this study, the number of migraine days, duration, frequency, and pain score were used to compare the alleviation effects of vitamin B2. Furthermore, we compared the efficacy of vitamin B2 and other common migraine prophylactic drugs in migraine prophylaxis.

## Methods

### Protocol

The systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [16].

### Search strategy

The primary aim of this study is to examine the preventive effects of vitamin B2 supplementation on migraine. We searched for studies in five databases (PubMed, Embase, Cochrane Library, CINAHL, and Airiti Library). The search period was from 1990 to March 2019; the keywords used were acute migraine/headache; vitamin G; vitamin B2; riboflavin; and prevent, recurrent. Boolean logic combinations of key words and controlled vocabulary. Finally, two researchers screened all paper with the titles and abstracts then included. The search strategy is shown in Figure 1.

### Eligibility criteria

All included studies must discuss the migraine alleviation or prevention effects of vitamin B2, including the number of migraine days, migraine duration, frequency, or pain score. Papers were selected based on the study objective, and the inclusion criteria were as follows: (1) Study subjects are adult migraine patients, with or without aura; (2) Clinical controlled experiments, randomized controlled trials; (3) Vitamin B2 alone or vitamin complex (containing vitamin B2) was used as the intervention; and (4) Migraine prophylaxis results were assessed in the paper (including the number of migraine days, duration, frequency, and pain score). The exclusion criteria were as follows: (1) non- systematic reviews; (2) non- randomized clinical controlled trials.

### Data extraction and assessment for study quality

Each paper was carefully read. First, two researchers independently assessed each paper. After the scores given by the two researchers were compared, the two researchers and a third researcher jointly discussed and determined the quality of a paper if there were opinion-related differences. The Cochrane risk of bias tool was used to assess clinical trial studies. The risk of bias, indirectness, inconsistency, result accuracy, and publication bias were used to assess the risk of bias for every study. The authors, year, study design, study samples, intervention measures, presence of a control group, and study results were extracted from these studies (Table 1).

### Statistical analysis

Literature result analysis was divided into both primary and secondary results. Primary results were whether there was a reduction in the number of migraine days, migraine duration, frequency, and pain score after vitamin B2 intervention. Secondary results were comparison with other migraine prophylaxis medication such as 80 mg of propranolol, 500 mg of sodium valproate, 200 mg of metoprolol, or 10 mg of bisoprolol and 75 mg of aspirin. The collated study results were used to compare efficacy in migraine prophylaxis. Finally, data from randomized controlled trials were used for meta-analysis on the number of migraine days, migraine duration, frequency, and pain score. As each study was on different parent populations, different doses of vitamin B2 were used, and different results were examined, the random effect model was used for the statistical analysis of the results. Subsequently, subgroup analysis was performed on the effects of the number of migraine days, migraine duration, frequency, and pain score. Sensitivity analysis was performed when heterogeneity was high, and unsuitable papers were excluded to assess whether there are significant differences in migraine prophylaxis. The comprehensive meta-analysis (CMA) version 3 was used for meta-analysis.

## Results

### Search results

Seven hundred thirty-three studies were selected based on the screening criteria, and 160 repeated studies were excluded. The title and abstracts of the remaining studies were examined. There were 500 studies whose title and content did not match the screening criteria, 37 studies were not randomized controlled trials and systematic reviews, full text was not available for two

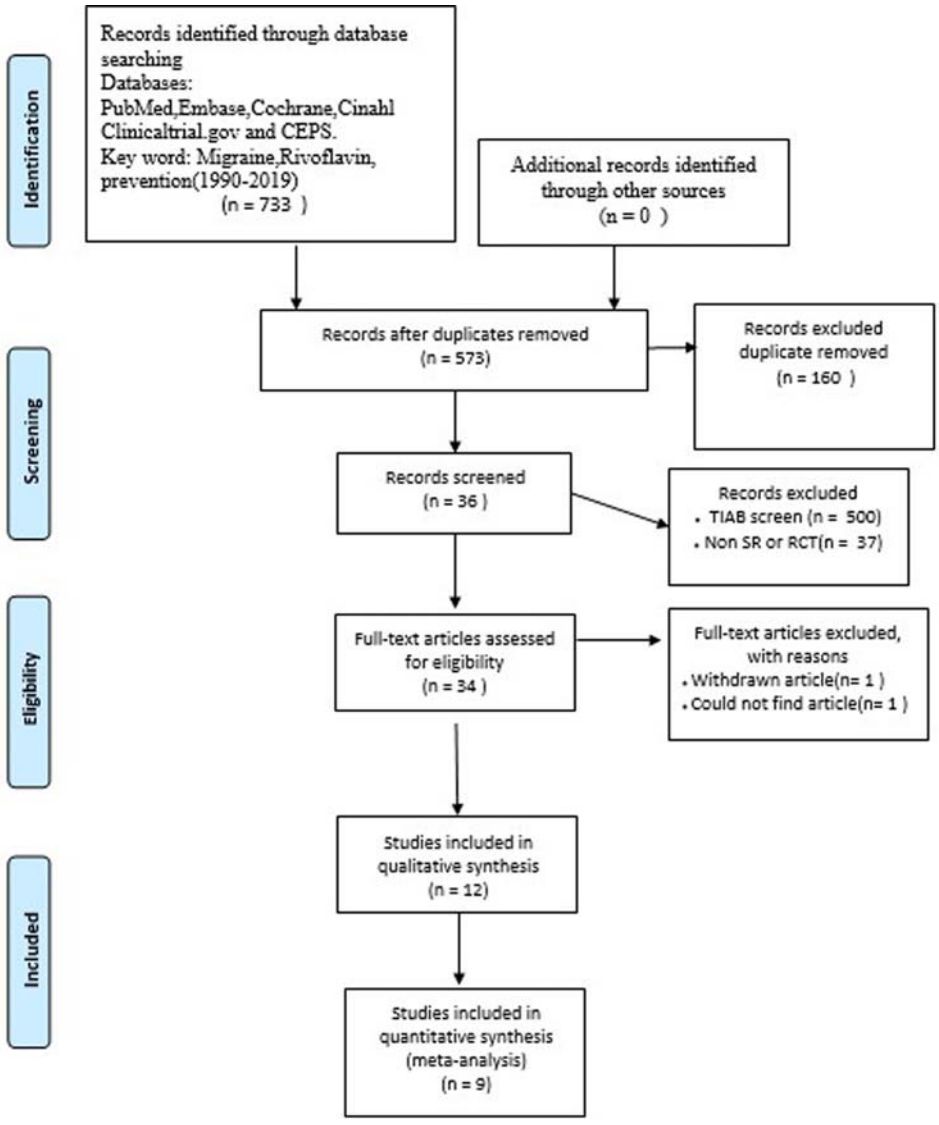


**Figure 1.** PRISMA flow diagram.

papers, and 25 studies did not meet the inclusion criteria. All the aforementioned studies were excluded, and 12 English studies were included, it contains 3 systematic review articles [17–19]. Finally, we included nine articles in the study analysis. Of these studies, 8 were randomized controlled trials [20–27], 1 was a clinically controlled experiment [28].

### *Study characteristics*

The eight randomized controlled trials [20–27] contained both the experimental and control group. Six studies [20–24,26] complied with randomization and blinding principles. The sample sizes of studies ranged from 26 to 130 subjects, and all study subjects were adults. In five research studies [24–28] subjects took 400 mg of vitamin B2 every day. In 1 research paper [23], subjects took 100 mg vitamin of B2 every day. In two research papers [22,23], subjects took vitamin complex (containing 400 mg vitamin B2) every day. The follow-up period of these studies was 1–6 months. In terms of control group, three studies used placebo [20,24,26], 1 study used 25 mg vitamin B2 (to mimic urine color due to vitamin B2 supplementation as required by blinding principle) [22], and four studies compared vitamin B2 with other migraine prophylactics, which were 80 mg of propranolol [23], 500 mg of sodium valproate [24], 200 mg of metoprolol or 10 mg of bisoprolol [25] and 75 mg of aspirin [27].

In this study, the risk of bias (ROB) tool was used to assess study quality. Selection bias, performance bias, and attrition bias were nearly 50%, which was low ROB. Detection bias was >80%, which was low ROB and reporting bias and other biases were all 100%, which were low ROB. The recommendation for effective prevention of

**Table 1.** Characteristics of studies included in the systematic review.

| No. of studies | Author/Year/ Countary | Purposes/Design | Subjective/ Sample size | Interventions (per day) | | Results |
|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | |
| 1 | C. Boehnke et.al/ 2004/Germany | Efficacy for the prevention of migraine/ Open label study | Migraine/23 | Riboflavin 400 mg | No | 1. Significantly decrease frequency ($p < .05$). 2. Significantly decrease the use of abortive drugs ($p < .05$) |
| 2 | J.Schoenen et.al/ 1998/Germany | Efficacy for the prevention of migraine/ RCT | Migraine/55 | Riboflavin 400 mg | Placebo | 1. Significantly decrease frequency ($p = .005$) and days ($p = .012$) |
| 3 | Charly Gaul et. al/2015/ Germany | Efficacy for the prevention of migraine / RCT | Migraine/ 130 | Combination (Rivoflavin 400 mg Magnesium 600 mg Coenzyme Q10 150 mg) | Placebo | 1. Significantly reduce the intensity ($p = .03$) and pain score ($p = .01$). 2. Combination (contain Rivoflavin 400 mg) can prophylaxis of migraine. |
| 4 | Nambiar et al./ 2011/India | Efficacy of riboflavin and propranolol of prevent migraine /RCT | Migraine/ 100 | Riboflavin 100 mg | Propranolol 80 mg | 1. Both study groups showed a reduction of migraine frequency, duration, and severity of headache. 2. No significant difference was seen between the two study groups in most of the measures. 3. Side effects were significantly less in the Riboflavin group ($p = .035$). |
| 5 | Morris Maizels et. al/2004/ America | Efficacy for the prevention migraine of combination/ RCT | Migraine /120 | Combination vitamins (Riboflavin 400 mg Magnesium 300 mg and Feverfew 100 mg) | Riboflavin 25 mg | 1. No significant difference was seen between the two study groups ($p = 0.87$). 2. Efficacy of the Rivoflavin 25 mg compare with the combination for prophylasis migraine. |
| 6 | Abolghasem Rahimdel et.al/2015/Iran | To compare the efficacy of Vitamine B2 and Sodium Valproate of prevent migraine/ RCT | Migraine /90 | Riboflavin 400 mg/ per day | Sodium Valproate 500 mg | 1. No significant difference was seen between the two study groups ($p > .05$), but Riboflavin significant fewer side effect (=.005). 2. Riboflavin 400 mg/ per day can prophylaxis of migraine. |
| 7 | Schoenen J et.al/ 2003/America | Efficacy for the prevention migraine of combination/ RCT | Migraine /80 | Riboflavin 400 mg/ per day | Placebo | 1. Significantly reduce the frequency, days, and pain score of migraine ($p < .01$, $p < .012$ and $p < .012$). 2. No significantly change in Placebo group Riboflavin 400 mg/ per day can prophylaxis of Migraine and to be safe and to have relatively few adverse effects. |
| 8 | Peter S et.al /2000/Belgium | The influence of different pharmacological treatments on the intensity dependence of auditory evoked cortical potentials/ RCT | Migraine /26 | Riboflavin 400 mg/ per day | Metoprolol 200 mg and Bisprolol 10 mg | 1. Beta block group significantly reduce intensity ($p = .02$), but Riboflavin group no significant change ($p = .39$). |
| 9 | Schoenen J/ 1994/ Belgium | Efficacy with prevention of migraine/RCT | Migraine /54 | Riboflavin 400 mg/ per day | Aspirin 75 mg | |

(*Continued*)

**Table 1.** Continued.

| No. of studies | Author/Year/ Countary | Purposes/Design | Subjective/ Sample size | Interventions (per day) Intervention | Comparison | Results |
|---|---|---|---|---|---|---|
| | | | | | | 1 No significant difference was seen between the two study groups. ($p > 0.05$).<br>2 Riboflavin 400 mg/ per day can prophylaxis of migraine and low-cost. |

migraine is taking 400 mg of vitamin B2 (riboflavin) every day for three continuous months.

## *Primary outcome of migraine prevention*

### *Effects of Vitamin B2 supplementation on the number of migraine days*

Five out of the nine randomized controlled trials [20–22,26,27] discussed the number of migraine days, and all showed that taking vitamin B2 can effectively decrease the number of migraine days. Schoenen [26] conducted a four-month follow-up on subjects who took 400 mg of vitamin B2 daily for three continuous months. Their results found that this could decrease the number of migraine days by 3 days/month, and this difference was statistically significant. Gaul [26] performed a three-month follow-up on subjects who took vitamin complex containing 400 mg of vitamin B2 for three continuous months. They reported that the number of migraine days decreased by 1.2, 1.4, and 1.8 days/month on Months 1, 2, and 3, respectively. Maizels [22] conducted a three-month follow-up on subjects who took vitamin complex containing 400 mg of vitamin B2 continuously for 1 month. They reported that this decreased the number of migraine days by 2.04 days/month. Breen [20] conducted a three-month follow-up on subjects who took 400 mg of vitamin B2 daily for three continuous months. The results showed that this significantly decreased the number of migraine days ($p = 0.012$). Schoenen [27] conducted a six-month follow-up upon subjects who took 400 mg of vitamin B2 daily for three continuous months. Their results reported that the number of migraine days initially decreased from $8.7 \pm 1.5$ days/month to $2.9 \pm 1.2$ days/month. In summary, taking 400 mg vitamin B2 daily can effectively decrease the number of migraine days by an average of two days/month.

Meta-analysis was performed on some of the five studies, and four studies [21,22,26,27] included six datasets. One study did not available for data analysis. The random effect model results demonstrated that the difference between the vitamin B2 group and placebo group was significant ($p = .005$), but the heterogeneity was high ($I^2 = 89\%$). However, the random effect model result was not significant when subgroup analysis on different months was carried out ($p = .106$) (Figure 2).

### *Effect of Vitamin B2 supplementation on the duration of migraine*

Five out of the nine randomized controlled trials [20,23,24,26,28] discussed migraine duration, and 80% demonstrated that taking vitamin B2 can effectively decrease migraine duration [20,23,24,26]. Boehnke [28] performed a six-month follow-up on subjects who took 400 mg vitamin B2 daily for three continuous months. The study results showed that vitamin B2 did not decrease migraine duration ($p = 0.098$). The results of Schoenen (1998) demonstrated that vitamin B12 can decrease duration by 1.3 h/attack. Nambiar [23] conducted a six-month follow-up on subjects who took 100 mg vitamin B2 daily for three continuous months. Migraine duration was initially $2.8 \pm 1.0$ hand was maintained at $2.8 \pm 1.0$ h (unchanged) at Month 1. Migraine duration decreased to $2.4 \pm 0.6$ and $2.1 \pm 0.7$ h on Months 2 and 3, respectively. On Month 6, migraine duration did not decrease but slightly increased to $2.6 \pm 0.8$ h (overall decrease of $\sim 0.2 \pm 0.2$ h). Rahimdel [24] conducted a three-month follow-up on subjects who took 400 mg vitamin B2 daily for three continuous months, and migraine duration decreased from $15.1 \pm 7.1$ h to $4.2 \pm 2.6$ h/month (overall decrease of $\sim 10.9 \pm 4.5$ h). The results of Schoenen (2003) demonstrated that vitamin B12 can decrease migraine duration ($p = 0.018$). In summary, vitamin B2 could decrease migraine duration by 0.4–10 h.

Meta-analysis was performed on four studies [23,24,26,28] that included 7 datasets. The random effect model results demonstrated that the difference between the vitamin B2 group and placebo group was significant ($p = .003$), and the heterogeneity was low ($I^2 = 0$). However, differences between random effect model results were significant when subgroup analysis on different months was performed ($p = .042$). There

| Subgroup within study | | Study name | Effective number of samples: Experimental group | Effective number of samples: Control group | Statics for each study: Lower limit | Statics for each study: Upper limit | Statics for each study: p-Value |
|---|---|---|---|---|---|---|---|
| 1m | 1m | Gaul, 2015 | 55/57 | | -0.514 | 0.228 | 0.449 |
| 1m | | | | | -0.514 | 0.228 | 0.449 |
| 2m | 2m | Gaul, 2015 | 55/57 | | -0.515 | 0.227 | 0.448 |
| 2m | | | | | -0.515 | 0.227 | 0.448 |
| 3m | 3m | Gaul, 2015 | 55/57 | | -0.555 | 0.187 | 0.331 |
| 3m | 3m | Maizels, 2004 | 29/28 | | -0.695 | 0.426 | 0.639 |
| 3m | 3m | Schoenen, 1994 | 25/23 | | -5.452 | -2.986 | 0.000 |
| 3m | | | | | -2.943 | 0.212 | 0.090 |
| 4m | 4m | Schoenen, 1998 | 27/27 | | -1.724 | -0.572 | 0.000 |
| 4m | | | | | -1.724 | -0.572 | 0.000 |
| Overall | | | | | -0.575 | -0.103 | 0.005 |

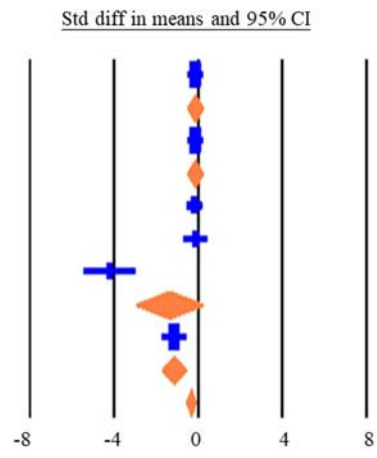


**Figure 2.** Forest plot: primary outcome on days with migraine.

was no significant difference in Months 1, 2, and 6 ($p$ = 1.0; $p$ = .57; $p$ = .298); however, significant differences were present between Months 3 and 4 ($p$ = .01; $p$ = .017) (Figure 3).

### *Effect of Vitamin B2 supplementation on the frequency of migraine*

Seven out of the nine randomized controlled trials [20,22–26,28] discussed migraine frequency; all demonstrated that taking vitamin B2 can effectively decrease migraine frequency. The results of Boehnke (2004) demonstrated that migraine frequency decreased from four attacks/month to two attacks/month (a decrease of two attacks/month). The results of Schoenen (1998) demonstrated that vitamin B12 can decrease migraine frequency by two attacks/month. The results of Nambiar (2011) showed that headache frequency was initially 4.0 ± 1.0 attacks/month, which decreased to 2.3 ± 0.7 attacks/month (a decrease of 1.7 ± 0.3 attacks/month). However, this decrease did not continue until Month 6 but slightly increased to 2.9 ± 0.7 attacks/month (0.1 ± 0.3 attacks/month). The results of Maizels (2004) demonstrated that migraine frequency decreased from 5.0 attacks/month initially to 3.2 attacks/month, which was a reduction of 1.8 attacks/month. The results of Rahimdel (2015) demonstrated that headache frequency initially decreased from 9.2 ± 6.2 attacks/month to 2.4 ± 1.6 attacks/month (a decrease of around 2.2–11 attacks/month). The results of Schoenen (2003) demonstrated that vitamin B12 can decrease migraine frequency ($p$ = 0.005). The results of Peter (2000) demonstrated that taking vitamin B2 daily can initially

| Subgroup within study | | Author years | Effective number of samples: Experimental group | Effective number of samples: Control group | Statistics study: Lower limit | Statistics study: Upper limit | Statistics study: p-Value |
|---|---|---|---|---|---|---|---|
| 1m | 1m | Nambiar,2011 | 50/50 | | -0.392 | 0.392 | 1.000 |
| 1m | | | | | -0.392 | 0.392 | 1.000 |
| 2m | 2m | Nambiar,2011 | 50/50 | | -0.506 | 0.279 | 0.570 |
| 2m | | | | | -0.506 | 0.279 | 0.570 |
| 3m | 3m | Boehnke,2004 | 23/- | | -0.782 | 0.061 | 0.094 |
| 3m | 3m | Nambiar,2011 | 50/50 | | -0.615 | 0.172 | 0.269 |
| 3m | 3m | Rahimdel,2015 | 45/45 | | -0.779 | 0.059 | 0.091 |
| 3m | | | | | -0.551 | -0.073 | 0.010 |
| 4m | 4m | Schoenen,1998 | 28/26 | | -1.214 | -0.117 | 0.017 |
| | | | | | -1.214 | -0.117 | 0.017 |
| 6m | 6m | Nambiar,2011 | 50/50 | | -0.602 | 0.185 | 0.298 |
| | | | | | -0.602 | 0.185 | 0.298 |
| Overall | | | | | -0.400 | -0.085 | 0.003 |

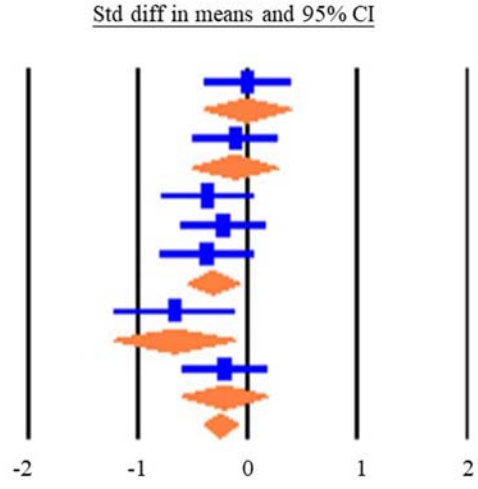


**Figure 3.** Forest plot: primary outcome on duration with migraine.

| Subgroup within study | | Study name | Effective number of samples | | Statics for each study | | |
|---|---|---|---|---|---|---|---|
| | | | Experimental group | Control group | Lower limit | Upper limit | P-Value |
| 1m | 1m | Nambiar,2011 | 50/50 | | -1.092 | -0.285 | 0.001 |
| 1m | | | | | -1.092 | -0.285 | 0.001 |
| 2m | 2m | Nambiar,2011 | 50/50 | | -0.507 | 0.278 | 0.567 |
| 2m | | | | | -0.507 | 0.278 | 0.567 |
| 3m | 3m | Boehnke,2004 | 23/- | | -1.259 | -0.322 | 0.001 |
| 3m | 3m | Rahimdel,2015 | 45/45 | | -0.392 | -0.392 | 1.000 |
| 3m | 3m | Nambiar,2011 | 50/50 | | -0.977 | -0.392 | 0.002 |
| 3m | | | | | -0.644 | -0.111 | 0.002 |
| 4m | 4m | Schoenen,1998 | 28/26 | | -1.724 | -0.150 | 0.000 |
| 4m | | | | | -1.724 | -0.572 | 0.000 |
| 6m | 6m | Boehnke,2004 | 23/- | | -1.100 | -0.201 | 0.005 |
| 6m | 6m | Nambiar,2011 | 50/50 | | -0.514 | 0.271 | 0.545 |
| 6m | | | | | -0.645 | -0.054 | 0.020 |
| Overall | | | | | -0.587 | -0.284 | 0.000 |

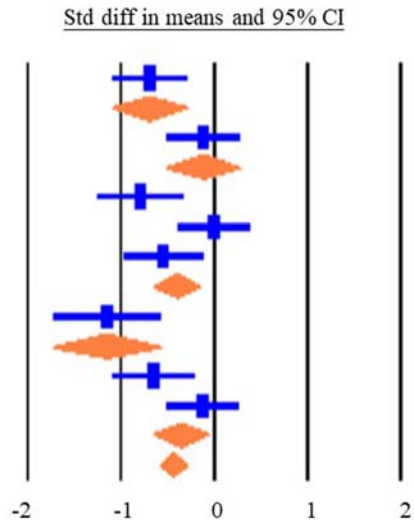


**Figure 4.** Forest plot: primary outcome on frequency with migraine.

decrease headache frequency from 3.1 ± 1.5 attacks/month to 1.7 ± 1.7 attacks/month (a decrease of ~1.2–1.6 attacks/month). To summarize, considering vitamin B2 can effectively decrease migraine frequency by two attacks/month.

Meta-analysis was performed on four studies [22–24,26] that included eight datasets. The random effect model results showed that the difference between the vitamin B2 group and placebo group was significant ($p = .000$), but the heterogeneity was high ($I^2 = 65\%$). However, differences between random effect model results were significant when subgroup analysis on different months was performed ($p = .008$). There was no significant difference in Months 1, 2, 3, and 6 ($p = .081$, $p = .769$, $p = .063$, $p = .183$) and significant difference was only seen in Month 4 ($p = .001$) (Figure 4).

### *Effect of Vitamin B2 supplementation on the pain score of migraine*

Nine out of the nine randomized controlled trials [20–28] discussed headache severity, and 78% [20–24,26,27] demonstrated that considering vitamin B2 can effectively decrease migraine severity. The results of Boehnke (2004) demonstrated that migraine frequency decreased from four attacks/month to two attacks/month (a decrease of two attacks/month). The results of Schoenen (1998) demonstrated that vitamin B12 can decrease migraine frequency by two attacks/month. The results of Nambiar (2011) demonstrated that headache frequency was initially 4.0 ± 1.0 attacks/month, which decreased to 2.3 ± 0.7 attacks/month (a decrease of 1.7 ± 0.3 attacks/month). However, this decrease did not continue until Month 6 but slightly increased to 2.9 ± 0.7 attacks/month (0.1 ± 0.3 attacks/month). The results of Maizels (2004) demonstrated that migraine frequency decreased from 5.0 attacks/month initially to 3.2 attacks/month, which was a reduction of 1.8 attacks/month. The results of Rahimdel (2015) demonstrated that headache frequency decreased from 9.2 ± 6.2 attacks/month to 2.4 ± 1.6 attacks/month (a decrease of around 2.2–11 attacks/month). The results of Schoenen (2003) demonstrated that vitamin B12 can decrease migraine frequency ($p = 0.005$). The results of Peter (2000) showed that taking vitamin B2 daily can decrease headache frequency from 3.1 ± 1.5 attacks/month initially to 1.7 ± 1.7 attacks/month (a decrease of around 1.2–1.6 attacks/month). To summarize, taking vitamin B2 can effectively decrease migraine frequency by two attacks/month.

Meta-analysis was performed on five papers [21,22,24,26,27] that included eight datasets. The random effect model results demonstrated that the difference between the vitamin B2 group and placebo group was significant ($p = .015$), but the heterogeneity was high ($I^2 = 84\%$). However, the differences between random effect model results were not significant when subgroup analysis on different months was performed ($p = .109$). Significant difference was only found in Month 3 ($p = .031$) and there were no significant differences in Months 1, 2, 4, and 6 ($p = 1.0$, $p = .847$, $p = .516$, and $p = .772$) (Figure 5).

| Subgroup within study | | Study name | Effective number of samples | | Statics for each study | | |
|---|---|---|---|---|---|---|---|
| | | | Experimental group | Control group | Lower limit | Upper Limit | P-Value |
| 1m | 1m | Nambiar, 2011 | 50/50 | | -0.392 | 0.392 | 1.000 |
| 1m | | | | | -0.392 | 0.392 | 1.000 |
| 2m | 2m | Nambiar, 2011 | 50/50 | | -0.568 | 0.217 | 0.380 |
| 2m | | | | | -0.568 | 0.217 | 0.380 |
| 3m | 3m | Gaul, 2015 | 55/57 | | -0.872 | -0.119 | 0.010 |
| 3m | 3m | Maizels, 2004 | 24/25 | | -1.150 | -0.007 | 0.047 |
| 3m | 3m | Nambiar, 2011 | 50/50 | | -0.392 | 0.392 | 1.000 |
| 3m | 3m | Schoenen,1994 | 25/23 | | -4.630 | -2.503 | 0.000 |
| 3m | | | | | -1.939 | -0.091 | 0.031 |
| 4m | 4m | Schoenen,1998 | 28/26 | | -1.150 | -0.058 | 0.030 |
| 4m | | | | | -1.150 | -0.058 | 0.030 |
| 6m | 6m | Nambiar,2011 | 50/50 | | -0.657 | 0.130 | 0.189 |
| 6m | | | | | -0.657 | 0.130 | 0.189 |
| Overall | | | | | -0.457 | -0.048 | 0.015 |

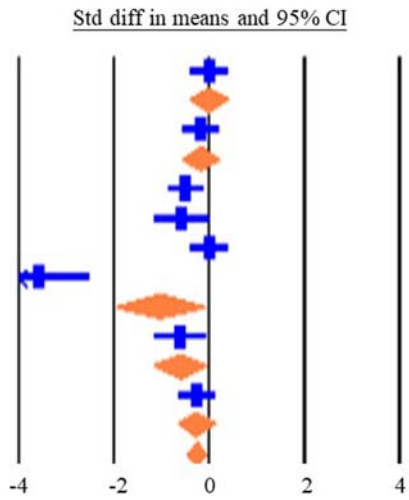


**Figure 5.** Forest plot: primary outcome on pain score with migraine.

### *Secondary outcome*

Effectiveness of Vitamin B2 compare with preventive pharmaceuticals. Four randomized controlled trials [23–25,27] compared vitamin B2 with other migraine prophylactics, which were 80 mg of propranolol [23], 500 mg of sodium valproate [24], 200 mg of metoprolol or 10 mg of bisoprolol [25] and 75 mg of aspirin [27]. In the study of Rahimdel (2015), subjects in the experimental group took 400 mg of riboflavin daily while subjects in the control group took 500 mg of sodium valproate daily. In the study of Schoenen (1994), subjects in the experimental group took 400 mg of riboflavin daily while subjects in the control group took 400 mg of riboflavin and 75 mg of aspirin daily. The results of these studies demonstrated that there were no significant differences between these two groups. In the study of Natashu [23], subjects in the experimental group took 80 mg of propranolol daily while subjects in the control group took 100 mg of riboflavin daily. Overall, there was no significant difference, but there was a significant difference in headache frequency in Month 1 ($p < 0.001$) and in severity in Month 3 ($p = 0.033$). In the study of Sándor [25], subjects in the experimental group took 200 mg of metoprolol or 10 mg of bisoprolol daily while subjects in the control group took 400 mg of riboflavin daily. Headache severity was significantly decreased in the experimental group ($p = 0.02$) but not in the control group ($p = 0.39$). Overall, both treatments could decrease migraine frequency, but vitamin B2 did not decrease migraine intensity. Table 2 shows a summary for the comparison between Vitamin B2 and pharmaceutical of preventive.

**Table 2.** Comparison of preventive migraine drugs.

| Author/Year | Method design | Experimental group/ control group | Research results |
|---|---|---|---|
| J Natashu et. al/ 2011 | RCT | Rivoflavin 100 mg / Propranolol 80 mg | No significant difference between the two groups. |
| Abolghasem Rahimdel et.al/2015 | RCT | Rivoflavin 400 mg/ Sodium Valproate 500 mg | No significant difference between the two groups. |
| Peter S et.al /2000 | RCT | Beta block (Metoprolol 200 mg and Bisprolol 10 mg qd)/ Riboflavin 400 mg | Both of the two groups can decrease frequency of migraine, but Rivoflavin group could not decrease the intensity. |
| Schoenen J/ 1994 | RCT | Rivoflavin 400 mg/ Rivoflavin 400 mg and Aspirin 75 mg | No significant difference between the two groups. |

### *Sensitivity analysis and publication bias*

As the number of studies included is very less, we could not perform publication bias analysis. Overall, in the eight randomized controlled trials and one clinically controlled experiment, there were significant differences in the number of migraine days ($p = 0.005$), migraine duration ($p = 0.003$), migraine frequency ($p = 0.000$), and migraine pain score ($p = 0.015$). The following section is a description of sensitivity analysis.

### *Number of migraine days*

Overall, there was considerable difference in the number of migraine days ($p = 0.005$), and the heterogeneity was

high ($I^2 = 89.77$). An inspection of studies reported that the standard deviation at Month 3 in Schoenen (1994) was higher than that in other studies. After removing Month 3 results from this study, there was no significant difference overall ($p = 0.084$), but heterogeneity significantly decreased (from $I^2 = 89.77$ to $I^2 = 60.93$).

### Migraine duration

Overall, there was a significant difference in migraine duration ($p = 0.003$), the heterogeneity was low ($I^2 = 0$), and the fixed-effect model was used. Therefore, a special sensitivity analysis was not performed.

### Migraine frequency

Overall, there was a significant difference in migraine frequency ($p = 0.000$), and the heterogeneity was high ($I^2 = 65.83$). Inspection of studies reported that Nambiar [23] performed a six-month follow-up, and headache frequency decreased in Months 1, 2, and 3, but increased in Month 6, which was different from other studies. After removing this study, there were still significant differences ($p = 0.002$), but the heterogeneity did not significantly decrease (from $I^2 = 65.83$ to $I^2 = 59.75$).

### Migraine pain score

Overall, there was a significant difference in the number of migraine pain score ($p = 0.015$), and the heterogeneity was high ($I^2 = 84.15$). Inspection of studies reported that Schoenen (1994) is a non-RCT open pilot study, and results were based on migraine severity. Overall mean severity improved by 68.2%, and the percentage was used as a unit. This was different from other study results. After this study was removed, there was still an overall significant difference ($p = 0.005$) and heterogeneity significantly decreased ($I^2 = 84.15$ to $I^2 = 22.86$).

## Discussion

The results demonstrated that taking 100 mg or 400 mg vitamin B2 or vitamin complex containing 400 mg vitamin B2 daily for three continuous months have significant effects in terms of number of migraine days, migraine duration and frequency; however, there were only a few studies on pain score, and there was no significant effect. A few studies on the experimental group and control group demonstrated that vitamin B2 was better than placebo. Vitamin combinations can still effectively prevent migraine, but there are difficulties in confirming the component responsible for prophylactic efficacy. This may be because many vitamins synergize with each other to result in better efficacy in migraine prophylaxis; this requires further elucidation. In this study, the longest follow-up period found was six months, and related studies with longer follow-up duration are required to validate long-term effects.

Migraine prophylaxis is relatively important, and the main aim of prophylactic drugs is to decrease the number of migraine days, duration, frequency, and severity of migraine, improve drug responses and efficacy during acute attacks, improve daily function, and decrease disability [2,7–9]. The American Academy of Neurology recommends using beta blockers, calcium channel blockers, antiepileptics, and antidepressants as the migraine prophylaxis. These drugs may not be suitable for every patient and may cause certain side effects. In this study, we compared the benefits of vitamin B2 and migraine prophylactic drugs. Four studies [23–25,27] compared the efficacy of migraine prophylaxis, of which the effects of daily administration of 100–400 mg vitamin B2 are comparable to daily administration of 80–240 mg of propranolol, 500 mg of sodium valproate, and 75 mg of aspirin and could prevent migraine [23,24,27]. The four studies showed that vitamin B2 has significantly fewer side effects [23–25,27].

### Relationship between vitamin B2 and migraine

Note that around 75% of migraine patients have a family history of migraine, and migraine may be associated with genes. Migraine may be attributed to certain inducing factors, such as certain types of food, stress, menstrual cycle, changes in sleep patterns, and other factors, or pain may be exacerbated because of light, sound, or sudden head movement. Although a typical migraine lasts for 30 min to 24 h and is often alleviated after sleep [29], some people suffer migraines that last longer than one day, and medication cannot relieve their pain during the migraine attack. As a result, they must be hospitalized to receive medical treatment in advance [30].

Migraine has a tendency to be inherited and is associated with mitochondrial dysfunction. Mitochondrial diseases are a group of inherited diseases that are characterized by defects in oxidative phosphorylation and is caused by gene mutations in nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) [31]. Vitamin B2 or riboflavin, as a non-drug nutrient supplement, is a cofactor in the citric acid cycle and redox reaction in the electron transport chain. Therefore, vitamin B2 plays an important role in energy generation in the mitochondria, and vitamin B2 is used as a potential treatment for mitochondrial diseases affecting energy metabolism [32,33]. Vitamin B2 seems to be a

safe and well-tolerated option to prevent migraine symptoms in adults; however, there is currently insufficient evidence to recommend vitamin B2 as an adjuvant treatment for adults with migraine [17]. In 2020, the pain care guidelines in the Cochrane Taiwan website recommended daily administration of 400 mg vitamin B2 (riboflavin) for three continuous months to prevent migraine in adults. The GRADE level of evidence was 1A (strong recommendation, high level of evidence) [34].

### Relationship between sex, hormones, and migraine

Headache quality and correlation characteristics of migraine in women are higher than in men, e.g. their headache duration and intensity were higher than that in men, and the frequency of nausea was higher than that in men [35]. Mitochondrial defects will decrease migraine threshold and low vitamin B2 may result in mitochondrial dysfunction, thereby causing migraine to occur. A literature review on vitamin B2 supplementation in adults reported that it showed significant differences in decreasing migraine frequency and duration and did not have severe side effects [17].

From the demographic distribution of the enrolled population in that study, most subjects were women and certain studies have 90% female subjects. The mean enrollment age was 35–47 years, and subjects have migraine with/without aura and complex migraine. Most subjects have migraine without aura. The prevalence of migraine is higher in females than in males. The incidence of migraine is 17.5% (in females) and 8.6% (in males), and is 2–3 times more in females than in males. This is particularly true because women of childbearing age have the highest incidence, which is correlated with hormones during the menstrual cycle [35,36].

Calcitonin gene-related peptide (CGRP) has vasodilatory effects on cerebral and dural blood vessels and can transmit pain from the trigeminovascular system from the intracranial blood vessels to the central nervous system, thereby causing neuroinflammation. After the trigeminal nerve is stimulated, it will promote CGRP release, which induces migraine. During the menstrual cycle, CGRP increases in women; however, the CGRP level in female patients with migraine do not change during the menstrual cycle, and the CGRP values measured were high [37]. Moreover, animal studies showed gender differences in CGRP as female rats show specific responses and sensitivity toward CGRP [38]. Female hormones are the primary factor for migraine risk and characteristics, and the possible cause may be associated with hormones such as testosterone, estradiol, and progesterone [39].

### Relationship between the hippocampus and migraine

The hippocampus often participates in memory consolidation, spatial navigation, and stress response. Because migraine attacks may be a source of repeated stress, changes in hippocampal function and structure may play an important role in migraine pathophysiology. High-resolution magnetic resonance imaging was used to compare hippocampal morphological and functional differences in age- and sex-matched patients with high frequency (HF) and low frequency (LF) of acute migraine attacks. The morphological measurement results were compared with age- and sex-matched healthy controls (HC). Compared with the HF and HC groups, bilateral hippocampal volume was larger in the LF group. This demonstrates that dysregulation in brain adaptivity and plasticity may occur as attack frequency increases. In the same hippocampal region, there is functional correlation with greater inactivity to noxious stimuli (LF > HF), which is accompanied by an overall decline in functional connections between the hippocampus and other brain regions involved in pain processing in the HF group. Functional magnetic resonance imaging showed different brain structure changes between the women of childbearing age with migraine and healthy women. Comparison between migraine patients and healthy subjects demonstrated a different brain structure, the total hippocampal volume is lower, and there are stronger hippocampal-cortical connections in migraine patients [40–42]. In clinical practice, there are few routine brain magnetic resonance imaging examinations for tracking among long-term migraine patients. If routine brain magnetic resonance imaging tracking is performed on migraine patients, radiologic tracking of the hippocampal volume can be used to predict the migraine severity or generation of a prediction score. Early drug adjustment based on disease severity is performed to decrease migraine severity and disability in daily life, thereby improving life quality and decreasing the possibility of potential complications.

Migraine tends to occur in women of childbearing age. From the subjects enrolled in studies in the paper, most subjects are women. In Taiwan, there are many working women who require to shoulder the stress of multiple roles; moreover, suffering from migraine makes their life harder. The use of migraine prophylaxis can decrease migraine and disability and improve the

quality of life of patients. Because of conception considerations, most migraine prophylactic drugs are not suitable for women of childbearing age. In view of safety, efficacy, and side effect, vitamin B2 supplementation may be a preferential option for migraine prophylaxis.

Vitamin B2 is not a drug but a nutrient supplement that is inexpensive, it does not require physician's prescription, it is easy to obtain, and has fewer side effects. Hence, it can be considered for widespread use as migraine prophylaxis in future. Moreover, nausea, orange urine, and diarrhea caused by vitamin B2 must be considered. Larger and stringent clinical trials are required to determine the long-term efficacy and duration of vitamin B2, migraine prophylactic effects when vitamin complex and different doses are given. Furthermore, the use of functional magnetic resonance imaging for predicting migraine severity score is still a major challenge in future studies. We hope that more similar studies can be used for verification and prediction to benefit migraine patients.

## Conclusion

Systematic review confirmed that the use of vitamin B2 as migraine prophylaxis can effectively decrease the frequency, duration, and severity of migraine. Compared with other migraine prophylactics, vitamin B2 has comparable effects as most prophylactic drugs. Overall, vitamin B2 is relatively safe, cheap, well-tolerated, and has fewer side effects. Furthermore, the meta-analysis reported that vitamin B2 significantly decreased the number of migraine days, pain duration, pain frequency, and pain score. Migraine prophylaxis must consider differences in patient characteristics, patient preference, and interactions with routine drugs. Based on these systematic reviews and meta-analysis results, 400 mg of vitamin B2 daily can be the priority for migraine prophylaxis.

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