# Mulling migraine medication

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## Will a combination treatment reduce the frequency of severe headaches?

### CLINICAL SCENARIO

A MEMBER of an online GP discussion board recently posted a question about the combination of magnesium, riboflavin and coenzyme Q10 (CoQ10) as prophylaxis to reduce migraine frequency, something that had been recommended by a pharmacist. Curiously, this combination is described in *eTG Complete* (July 2018 edition) with the disclaimer that the "supporting evidence is not strong". So, what is the evidence?

### CLINICAL QUESTION

What is the effect of the combination of oral magnesium, riboflavin and coenzyme Q10 on the frequency and severity of migraine?

**What does the research evidence say?**

**Step 1: The Cochrane Library**

No Cochrane systematic review exists for the question.

**Step 2: TripDatabase**

I conducted a search using the TripDatabase PICO search tool (Participant: "migraine", Intervention: "magnesium", Comparator: "placebo", Outcomes: blank), and searched for riboflavin and CoQ10 in turn. This identified the Gaul et al (2015) study of a proprietary supplement containing these three substances as the main ingredients. Let's have a look at this randomised trial published in the *Journal of Headache and Pain* in detail.[1]

### CRITICAL APPRAISAL

I will use the randomised controlled trial appraisal sheet from the Centre for Evidence-Based Medicine.[2]

**PICO**

**Participants: who was studied?**

The study included 130 otherwise-well adults (aged between 18 and 65), formally diagnosed with migraine with or without aura, with a diagnosis for at least a year, who had experienced at least three migraine attacks per month in the past three months, recruited by neurologists practising in Germany.

Important exclusions: patients who took any migraine preventive treatments (including drugs, psychotherapy and acupuncture) or any antipsychotic or antidepressant medication in the past three months, had medication overuse, and those who had failed to respond to more than two different prophylactic agents in the past.

**Intervention: what was the exposure?**

Intervention group: magnesium 600mg + riboflavin 400mg + CoQ10 150mg per four capsules, taken as two capsules twice daily, for three months. Note: each capsule also contained small doses of vitamins A, C, E, B1, B3, B5, B6, B7, B12, D, folic acid and iron, zinc, manganese, copper, chromium, molybdenum, selenium and bioflavonoids.

**Comparator: what was the control/alternative?**

Placebo group: identical looking placebo capsules.

**Outcomes: what was measured?**

Primary outcome: days with migraine.
Secondary outcomes: maximal pain of migraine headache, and migraine burden as measured using the headache impact test (HIT-6) questionnaire.[3]

**What were the results?**

Primary outcomes – the effect on migraine days per month at three months of treatment, intervention vs placebo:

- -1.8 vs -1.3 days/month, difference = 0.5 days (favouring intervention), p = 0.23
- Interpretation: the magnitude of the difference is very small and not statistically significant.

Secondary outcomes:

- Small difference in maximal pain per migraine day (favours intervention) of unclear clinical importance, 0.17-point difference on three-point scale.
- Small difference in headache impact test (HIT-6 score) (favours intervention) of unclear clinical importance, 2.8-point difference (minimum important difference is 2.3 to 2.7 points).[4]

### DISCUSSION AND CONCLUSION

This paper has some problems. Firstly, it has substantial threats to its internal validity (see box). Although the study was randomised, there are differences between the groups. The participants in the placebo group were more likely to have migraine without aura, had previously tried other prophylaxis, and had more comorbidities – factors that all have a direction of bias towards supporting the intervention.

Secondly, this study's primary outcome is difficult to interpret. A prophylactic is typically considered effective when it achieves a 50% reduction in the migraine frequency for the patient. This study does not report the proportion of participants in each group who achieved this outcome, despite it being an obvious measure that would allow comparisons with other prophylactic treatments.

Thirdly, my impression was that this paper was biased in how it reported and interpreted its results. The paper claimed that the "beneficial efficacy" of the intervention compared to placebo is demonstrated by the statistically significant differences in the HIT-6 scores, a secondary outcome (see StatFacts). This is partially justified with the statement that the minimum important difference (MID) is 1.5 points.

However, the authors cited a study from a primary care population rather than the more appropriate, but much less favourable, MID estimate from clinical trial settings (2.3 to 2.7 points).[4,5]

Furthermore, the actual HIT-6 scores remained high at three months (intervention vs placebo, 57.1 vs 59.9) and migraine continued to have a substantial impact on the average participant's quality of life, regardless of allocated treatment.[6]

The authors also de-emphasised the adverse event rate, which occurred in a third of participants in the intervention group, compared to a tenth of the placebo group. This was a sponsored study and reads like it was written to maximise support for the tested agent. One of the authors was employed by the sponsor.

The evidence for magnesium, riboflavin and CoQ10 is, at best, equivocal for migraine prophylaxis.[7-11] This trial does not provide convincing evidence that their combination is effective, and as such, it should not be recommended routinely.

Patients interested in taking this combination should be informed about the substantial side-effect rate in the shared decision-making process.

References on request

**Stat Facts**

**PRIMARY AND SECONDARY OUTCOME MEASURES**

Clinical trials are designed around the primary outcome measure. In critical appraisal, focus needs to be placed on the primary outcomes. As a rule of thumb, be very sceptical of predictive empirical claims that a hypothesis is true because of supportive secondary outcomes, despite a negative primary outcome. Negative primary outcomes should raise the possibility that positive secondary outcomes may be due to biases or are simply false positives.

**Internal Validity**
**Are the results valid?**

**Randomised patient assignment?**
**Yes.** Randomisation lists were prepared by computer.

**Groups similar at the start?**
**Arguably not.** The placebo group (vs intervention group) had more migraine without aura (64.9% vs 50.9%), fewer participants on no previous prophylactics (63.2% vs 72.7%), with more history of medical disease (57.8% vs 42.1%) and concomitant medications (63.6% vs 36.3%).

**Groups treated equally apart from assigned treatment?**
**Yes.**

**All patients accounted for?**
**Unclear.** The investigators did not undertake an "intention-to-treat" analysis, with about 14% of participants excluded due to "major protocol violation".

**Measures objective? Or patients and clinicians kept blinded?**
**Possibly/probably not.** The participants' self-reports can be subjective. Furthermore, participants might have guessed their allocated treatment due to the effect of riboflavin on urine colour.