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## An alternative multimodal treatment is effective and safe for migraine*

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The objective of the article was to evaluate an alternative approach for migraine. The patients received an alternative multimodal approach (AMA) involving nutraceuticals, melatonin, and dietary changes. Six patients were included in the study. Comorbidities were observed in all patients and included hypertension, depression, anxiety, diabetes, asthma, silicone breast implants, and allergic rhinitis. Sleep disorders were observed in 67 % of the patients. Interestingly, after applying AMA, there was a remarkable improvement in all participants. Vitamin D levels surged significantly, and sleep improved in all patients with sleep disturbances. The number of days with migraine was reduced significantly. An improvement of VAS well-being was observed after AMA, and a reduction of the VAS migraine pain was noted. All migraineurs, except one, suspended the conventional preventive drugs for migraine. An AMA is effective and safe, without any side effects for migraine prevention and therapy.

*Keywords*: migraine, headache, nutraceuticals, pain, vitamin D, melatonin, migraineurs, well-being.

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## Introduction

Migraine is one of the most frequent and disabling types of headache worldwide. World Health Organization ranks migraine as the third globally most prevalent medical condition and the second most disabling neurological disorder. The annual and lifetime frequencies are 18 % and 33 % in women, respectively, and 6 % and 13 % in men [1].

Therapeutical approach in this neurological disorder is separated into two parts: The acute intervention and preventive strategy. Both include drug use that varies from analgesics, non-steroidal anti-inflammatory drugs (NSAID), derivatives of ergots, and (most typically) selective serotonin receptor agonists (triptans) for the first-line therapy depending on the phase of the disease. For long-term preventive purposes the beta-blockers, antidepressants, and calcium antagonists are widely used [1; 2]. These drugs have various side effects and may cause gastritis, gut bleeding, insomnia or excessive sleepiness, cardiovascular events, and analgesic abuse headache [1–3]. Based on these adverse events, new and useful therapeutical options are desired for migraine therapy and prevention. In this line, alternative and complementary medicine are highly desirable to treat cephalalgia. A new trend in the field of migraine treatment is the immunotherapy with various monoclonal antibodies, antagonists of either calcitonin gene-related peptide or its receptor, which is a promising but quite expensive pathway of therapy.

The holistic alternative multimodal approach (AMA) comprises physical exercise, mindfulness, nutraceuticals, vitamin supplementation, and dietary manipulations [4]. However, so far AMA has been rarely used in conventional anti-migraine treatment. The reason probably is a too slow translation of new pathophysiological knowledge into routine medical practice. The most comprehensively studied currently still is a trigeminal-vascular theory of migraine pathogenesis. For a long time, the pathogenesis of migraine was interpreted in the spirit of reductionism, and only one link of pain-sensitive cerebral vasculature distension was emphasized, thus justifying the use of therapy aimed to vasoconstriction [5]. But recently, many new facets of migraine pathophysiology were studied. There is an association of migraines with dysbyosis and production of butirate and some amines/indoles by altered gut microbiota. Lack of gut melatonin may be involved in migraine pathogenesis because of a relative increase in the N-acetylserotonin/melatonin ratio, which results in hyperactive glutamatergic excitatory transmission in migraine [6; 7]. Not surprisingly, migraine can be tightly linked to many autoimmune disorders (also related to microbiota changes and melatonin regulation failure), like celiac disease, Hashimoto's thyroiditis and associated hypothyroidism, rheumatic diseases, and antiphospholipid syndrome [8–10]. Similar metabolic disorders (obesity, hyperinsulinemia, mitochondrial dysfunction, early complicated metabolic syndrome, altered vitamin D metabolism) may accompany both migraine and some above-mentioned autoimmunopathies [6; 9; 11; 12].

There were previous publications on the application of melatonin and nutriceuticals in migraine, but with contradictory results [13; 14]. Therefore, the present study was undertaken to evaluate AMA's efficacy and safety in patients with migraine.

## Patients and methods

### *Patients*

The present retrospective study included six patients, all of them over 18 years old, diagnosed with migraine according to the International Classification of Headache Disorders-3 (ICHD-3) criteria [15], and were followed-up in our outpatient clinic. Both migraineurs with or without aura were included. The follow-up period varied from 1 to 5 years. Demographic data, review of medical charts, presence and types of comorbidities, medications used, as well as frequency and intensity of migraine attacks were recorded. Exclusion criteria were: Stroke, hyperparathyroidism, or the presence of any cancer, temporal arteritis, Horton's cephalalgia, brain tumor, and diagnoses of systemic autoimmune diseases. All patients had routine laboratory analyses done prior to enrollment in the study, and vitamin D, vitamin $B_{12}$, folic acid, homocysteine, and cortisol blood levels were available in their medical charts. All patients had magnetic resonance imaging demonstrating normal cerebral images.

### *Methods*

The Visual Analogue Scale (VAS) for pain evaluation [16] is a 100-mm line on which subjects indicate the degree of pain perceived at the moment. The left end of the scale (0 mm) corresponds to "no pain," and the right end (100 mm) corresponds to "unbearable pain." Patients gave a verbal gradation of pain by choosing a number between 0 to 10, with higher numbers corresponding to higher pain levels. The same scale was used to detect their well-being levels. In this case, 0 was linked to the lower levels of well-being, and 10 was the higher well-being level.

### *Interventions*

Vitamin D and magnesium supplementation were prescribed to all participants, but doses varied depending of their serum levels. Melatonin was offered to those subjects with insomnia or any sleep disorder. Methylating agents were added if the patient had hyperhomocysteinemia or low blood levels of folic acid and/or vitamin $B_{12}$. *Rhodiola rosea* was added to the patients with moderate/severe fatigue and/or low cortisol (optimal range considered: 15 to 25 mcg/dL). Resveratrol and coenzyme $Q_{10}$ were added to patients with fatigue and to the patient (Case 6) at risk of burnout. A gluten-milk-sugar-free diet was suggested to patients with overweight or obese or to those with a history of milk or gluten intolerance. And 5-hydroxytryptophan (5-HTP) was offered to patients with any degree of anxiety. In this pilot study, no change or suggested physical exercises were offered, because $^{2}/_{6}$ already practiced exercises, but the other $^{3}/_{6}$ patients insisted that physical training could trigger a migraine in them.

### *Statistical analysis*

Results are presented as mean ± standard deviation, median (range), or percentage. Statistical analyses were performed using the JASP software version 0.12.2. Shapiro — Wilk was used to detect normal distribution. Mann-Whitney test or Student's t-test were used to comparing medians or means, and a Fisher's exact test was used to compare frequencies. The results were considered to be significant if $p < 0.05$.

## Results

Six patients with migraine were included in this study. The mean age of all migraine patients was 41.7 ± 14.6 years, female/male ratio 4/2, respectively (67 % females), and 100 % were Caucasian. The migraine onset age was 16.5 (12–18) years, and the disease duration was 28.5 ± 18.4 years (Table 1). All patients had a diagnosis of migraine and $^{3}/_{6}$ experienced classical migraine associated with aura. Only one patient (Case 6) presented with an analgesic abuse headache. A set of comorbidities existed in all patients, including arterial hypertension in $^{2}/_{6}$ (33 %), depression in $^{2}/_{6}$ (33 %), anxiety in $^{2}/_{6}$ (33 %), diabetes mellitus type 2 in $^{1}/_{6}$ (17 %), bronchial asthma in $^{1}/_{6}$ (17 %), silicone breast implants in $^{1}/_{6}$ (17 %), and allergic rhinitis in $^{1}/_{6}$ (17 %). Sleep disorders were observed in $^{5}/_{6}$ (83 %). Migraine preventive drugs were used in $^{5}/_{6}$ of participants: duloxetine in $^{3}/_{6}$ (50 %), escitalopram in $^{1}/_{5}$ (20 %), fluoxetine in $^{1}/_{5}$ (20 %), topiramate in $^{2}/_{5}$ (40 %), and amitriptyline in $^{1}/_{5}$ (20 %). One patient used NSAID chronically.

*Table 1.* **Demographics, disease data, drugs of the 6 included patients**

| Patients | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Age | 40 | 41 | 34 | 68 | 43 | 24 |
| Sex | Male | Female | Female | Male | Female | Female |
| Race | Caucasian | Caucasian | Caucasian | Caucasian | Caucasian | Caucasian |
| Disease onset, age (years) | 12 | 16 | 12 | 12 | 17 | 18 |
| Disease duration | 28 | 25 | 22 | 56 | 25 | 6 |
| Comorbidities | Hypertension, sleep apnea | Asthma, depression, anxiety, Hashimoto | Depression | Hypertension, dyslipidemia, diabetes 2, undetermined Chagas | Panic attacks, silicone breast implants, gastritis | Allergic rhinitis |
| Aura | + | + | – | | + | – |
| Medication use | Duloxetine | Escitalopram 20 mg, oral contraceptive, amitriptyline, topiramate 50 mg | Fluoxetine 40 mg/day, topiramate | Duloxetine | Topiramate, duloxetine | NSAID, and Tandrilax (caffeine, carisoprodol diclofenac, paracetamol) |
| Sleep problems | + | + | + | – | – | + (bruxism) |

Table 2 illustrates the various types of therapies used as the elements of AMA in the six patients. All patients used vitamin D in a dose that varied from 10.000IU–25,000IU/day, and one patient received once-monthly intramuscular 600.000IU injections. Four out of six (67 %) patients took melatonin at a dose between 5 to 15 mg/day, vitamin $B_{12}$ in

$^{5}/_{6}$ (83 %), and methyl folate in $^{4}/_{6}$ (67 %). Rhodiola rosea was prescribed in patients with low cortisol levels in $^{3}/_{6}$ (50 %). A dietary change was offered to $^{3}/_{6}$ (50 %).

The changes of migraine manifestations in patients at baseline and after AMA treatment are summarized in Table 3. Interestingly, there was a weight loss after AMA [76.2 ± 18.3 vs. 73.9 ± 18.1 kg, p = 0.009], even in patients to whom a special diet was not suggested. Vitamin D blood levels increased significantly after AMA [26.4 ± 7.0 vs. 36.7 ± 4.3 ng/mL, p = 0.011]. Sleep improved in all patients who complained of sleep disturbances. Homocysteine levels had a non-significant reduction in all cases studied [11.6 (5.1–16.5) vs. 7.8 (5.8–9.5) ng/mL, p = 0.164].

*Table 2.* **Multimodal alternative approaches used in the treatment of 6 included patients**

| Patients | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Vitamin D supplementation, dose/day | 25,000IU | 10.000IU | 10.000IU | 20.000IU | 20.000IU | 600.000IU/ every 4 months |
| Magnesium | 300 mg | 200 mg | 100 mg | 200 mg | 200 mg | 500 mg |
| Folic acid, pyridoxine, and/ or vitamin $B_{12}$ | $B_{12}$ 1 mg, folate 1 mg, $B_6$ 50 mg | | $B_{12}$ 1 mg, $B_6$ 200 mg | $B_{12}$ 0.25 mg, folate 0.5 mg, $B_6$ 50 mg | $B_{12}$ 1 mg, folate 0.5 mg | Folate 5, $B_{12}$ 0.6 mg |
| Maximum melatonin, dose/day | 15 mg | 5 mg | 10 mg | – | – | 10 mg |
| 5–HTP | – | 300 mg | 100 mg | – | 50 mg | 300 mg |
| Rhodiola rosea, dose/day | 400 mg | | – | 400 mg | 400 mg | – |
| Coenzyme Q10 | 150 mg | – | – | 25 mg, via sublingual | 50 mg, via sublingual | 100 mg |
| Resveratrol | 100 mg | – | – | 50 mg, via sublingual | 50 mg, via sublingual | 100 mg |
| Diet change | – | Gluten-milk-sugar-free diet | – | – | Gluten-milk-sugar-free diet | Hypocaloric diet |
| Physical exercise | – | – | – | Kept walking 3x week | – | Kept |

The number of days with migraine per month has substantially reduced [17.6 ± 10.1 vs. 3 ± 0 days, p = 0.003]. The time to achieve clinical response varied from 1–4 months. All patients, except one (Case 6), suspended the conventional preventive drugs taken for migraine. Even the said patient (Case 6) reduced the NSAID capsules count from 33 to 9 capsules/month.

*Table 3.* **Features before and after alternative multimodal approach in the 6 migraineurs**

| Patients | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Vitamin D pre→post ng/dL | 19.8→42.5 | 20.8→33.9 | 36→41 | 19.8→42.5 | 30.1→33 | 27.4→40 |
| Weight, kg | 98.7→95 | 98→96.2 | 75.6 | 65→63 | 55→53 | 65→62 |
| AVS, pain | 8.0→0 | 8.5→3.0 | 8.0→3.0 | | 9.0→5.0 | 8.0→3.0 |
| AVS, wellbeing | 5.0→8.0 | 5.0→7.0 | 4.0→8.0 | | 6.5→8.5 | |
| Sleep improvement | + | + | + | + | + | + |
| Homocysteine, mcmol/L | 10.13→7.79 | 11.6→N/S | 5.1→N/S | 16.5→9.5 | | 7.3→5.8 |
| Frequency with migraine | 2–3 per week→3 days | 2 per week→3 days/month | 2–3 per week→3 days | | 2x week 3 days/month | daily tensional headache→3 days/month |
| Days/month with migraine | 3 | 20/3 | 20/3 | | 20/3 | 30/3 |
| Time of response | 2–3 months | 1 month | 1 month | 3 months | 2 months | 3–4 months |
| Previous drugs | All suspended | All suspended | All suspended | All suspended | All suspended | Reduced Tandrilax 33 capsules 9/month |

An impressive improvement of VAS well-being was observed after AMA [4.9 ± 1.0 vs. 7.9 ± 0.6, p = 0.0007]. A significant reduction of the VAS migraine pain was also noted [8.0 (8.0–9.0) vs. 3.0 (0–5), p < 0.0001].

## Discussion

The present retrospective study demonstrated that an AMA methodology effectively prevents and treats migraines without any noticeable side effects. The study's advantages were that only migraine patients who fulfilled the migraine diagnosis criteria were involved [15] and the same researcher performing all data collection and analysis.

Previous studies reported on the presence of vitamin D deficiency or insufficiency in migraine patients. Intriguingly, when 70 migraine patients were compared to 70 healthy controls, a higher level of serum vitamin D (between 50 to 100 ng/mL) was linked to an 80–83 % lower odds of migraine headache than those with serum levels below 20 ng/mL [17]. More so, a previous study that evaluated 157 subjects with migraine observed a negative association between serum vitamin D levels and migraine frequency [18]. Regarding vitamin D supplementation for migraine, one randomized, double-blinded, placebo-controlled parallel trial, lasting 24 weeks with 48 migraineurs, showed a significant reduction in migraine frequency compared to the placebo group [19].

Melatonin levels are negatively associated with migraines. A randomized, double-blind, placebo-controlled study of 196 participants, randomized to receive placebo, amitriptyline, or melatonin were followed for 3 months. The authors concluded that melatonin is better than a placebo for migraine prevention, more tolerated than amitriptyline, and as effective as amitriptyline 25 mg [20].

Hyperhomocysteinemia is commonly observed in migraine. The pathophysiological mechanism implicating homocysteine in migraine involves activation of NMDA receptor, inhibition of GABA receptor, neurogenic inflammation, and increased oxidative stress. More than 15 cross-sectional studies reported that higher homocysteine levels are linked to migraine [21]. In this line, methylation treatment is desirable in migraine subjects to normalize homocysteine levels. Four studies on folic acid, pyridoxine, and/or vitamin $B_{12}$ administration in migraine patients were reported. All of them showed a marked improvement of migraine in the acute phase, thus, interrupting acute attacks and even migraine frequency and disability along more extended periods [21].

Magnesium has been associated with migraine pathogenesis. This bioelement is pivotal for human functional homeostasis and has a crucial role in health and life maintenance. One of the prominent roles of magnesium is to conserve neurons' electric potential. Studies have demonstrated low levels of this cation in the blood and cerebrospinal fluid of migraine patients [22]. The rationale for magnesium supplementations was confirmed in a meta-analysis, which included 21 studies with 1,737 participants. Intravenous magnesium reduced acute migraine attacks within 15–45 minutes, 120 minutes, 24 hours after the infusion, and oral magnesium alleviates migraine frequency and intensity [23]. Magnesium was successfully combined in migraine treatment with coenzyme $Q_{10}$ and phytotherapy in a prospective observational study [24].

Some studies evaluated serotonin levels in migraine patients and observed reduced serum levels of this neurotransmitter [25]. So, supplement 5-hydroxytryptophan (5-HTP), a serotonin precursor, is highly logical to individuals who suffer migraines. Its efficacy was confirmed in a trial which evaluated, in 124 migraineurs, methysergide versus 5-HTP. A significant improvement in both groups, 75 % in methysergide, and 71 % in the 5-HTP group were observed. Interestingly, the most beneficial effect of 5-HTP was on intensity and duration rather than the frequency of the attacks. Side effects were more frequent in the methysergide group than in the 5-HTP group [26].

The *Rhodiola rosea seu crenulata* was previously used in subjects with the headache associated with mountain sickness, although without significant differences compared to placebo [27]. This plant extract is commonly used for stress-related fatigue treatment and in hypocortisolism [28]. *Rhodiola* (Hong jing tian) is recommended by traditional Chinese medicine to elevate Qi energy, release pulse, and calm down [29]. This phytotherapeutic medication was used in 3 of our patients who had low levels of cortisol. Since migraine is currently interpreted by pathophysiologists as a result of compensatory cerebral hyperperfusion in response to energy production deficit and/or oxidative stress in the brain [30], we also administered to patients coenzyme $Q_{10}$ and antioxidant resveratrol playing a role in fatigue treatment [31; 32] and used in migraine prevention [24; 33]. These components of AMA were given in the present study to those patients who felt fatigued. A gluten-milk-sugar-free diet was used because of migraine association with both celiac disease and hyperinsulinemia [8; 11]. Although only two patients were under a gluten-milk-sugar-free diet, all participants lose weight. One explanation

could be the exclusion of drugs that enhance appetite. A study that evaluated weight gain after taking antidepressants in 362 psychiatric patients reported that 40.6 % of them gained weight, amounting to a 7 % increase, compared to the baseline when escitalopram, duloxetine citalopram, sertraline, paroxetine, venlafaxine, and mirtazapine, but not fluoxetine, were consumed [34]. The presented patients took duloxetine and escitalopram.Regarding amitriptyline, it is known to induce weight gain [35]. On the contrary, topiramate and fluoxetine are classically associated with weight loss, although our patients reduced weight after topiramate and fluoxetine withdrawal. An additional possible explanation for the weight loss is the anxiety and stress reduction following the migraine control because hyperinsulinemia and resulting hyperphagia in stress both are well documented [36; 37].

No side effects with the AMA application were observed in the present retrospective study. It contrasts strongly with patients under preventive pharmacotherapy for migraines that experience several adverse effects such as weight gain, sleep disorders, dizziness, and others. It should be emphasized that substantial efforts are currently being applied to develop new antimigraine compounds since the current ones have relatively low efficacy [38]. Therefore, a tendency of reappraisal of natural medicines and diet compounds in migraine treatment is a global trend [39].

The frequency of headache analgesic abuse ranges from 0.5 % to 2.6 % in the general population, 11–70 % among them with chronic daily headache [37]. This frequent phenomenon is further enhanced by regular polypragmasy and over-the-counter habits, including those evoked by NSAIDs, analgesics, and triptans. For example, one of the women (patient number 6) had an excellent outcome with the AMA approach, resulting in reduced headaches from 33 days to 3 days per month and a decreased NSAID pill count from 30 to 9 per month. Future studies evaluating the AMA mode of non-pharmacological therapy in headache analgesic abuse are highly encouraged.

The limitations of the current study are that it included a relatively small number of patients, and the control group is lacking. However, this is a preliminary, pilot retrospective study. In the future broad and well-designed, prospective, and controlled studied may follow, with many more participants using AMA in migraine, which might reaffirm its safety and efficacy.

In conclusion, this study demonstrated that a multimodal approach using vitamin D, melatonin, methylation agents, magnesium, *Rhodiola rosea,* and 5-HTP supplementations improves migraine symptoms and reduces migraine frequency and intensity attacks in migraineurs. More so, in contrast to polypharmacy intake, the AMA approach can reduce the adverse effects and improve their quality of life.

## Declarations

Conflict of interest: None of the authors has a conflict of interests.

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Ethical statement: The authors declare that the World Medical Association Declaration of Helsinki were followed in this study. Informed consent was obtained from the patients for publication of this study. No face image or other personal identification of them was used.

Contribution of authors: JFC — idea, design, therapeutic treatment, data collection, writing of clinical part, final editing; AL — writing of nutriciological part, consulting in diets; NM — nutriciological and phytotherapeutic treatment, data collection, statistical analysis; LPC — pathophysiological analysis, writing of pathophysiological part, final editing.

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