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Clinical use of omega-3 fatty acids in migraine

A narrative review

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Abstract

Background: Omega-3 fatty acids (FAs) can produce several beneficial effects and are commonly used for the treatment of migraine symptoms. Although current therapeutic measures for migraine included pharmacological therapies, dietary supplements, and herbal ingredients, dietary patterns, acupuncture, relaxation techniques, biofeedback, and psychotherapy, omega-3 FAs therapeutic role seems to be obtained through the inhibition or reduction of the release of inflammatory cytokines. The present review aims to provide updated information about the effects of omega-3 FAs in migraine treatment, investigating their clinical effects alone or in combination with other substances.

Methods: Bibliographic research was conducted by examining scientific literature from January 2000 until January 31, 2020. Ten clinical studies were included in the review. Quality assessment of randomized controlled trials was performed by using the JADAD scale.

Results: Clinical studies methodology is not always of good quality and results show moderate evidence concerning the therapeutic role of omega-3 FAs in migraine.

Conclusion: Further clinical trials are necessary to implement the knowledge concerning the use of omega-3 fatty acids in the treatment of migraine.

Abbreviations: CGRP = calcitonin gene related peptide, COX-2 = cyclooxygenase-2, CRP = C-reactive protein, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = Eicosapentaenoic acid, FAHFAs = fatty acyl esters of hydroxyl fatty acids, FAs = fatty acids, GABA = gamma-Aminobutyric acid, ICAMs = intercellular adhesion molecules, IL = interleukin, iNOS = inducible nitric oxide synthase, NSAIDs = non-steroidal anti-inflammatory drugs, PUFAs = polyunsaturated fatty acids, TNF = tumor necrosis factor, VCAMs = vascular cell adhesion molecules, ω-3 = Omega-3.

Keywords: docosapentaenoic acid, docosahexaenoic acid, eicosapentaenoic acid, headache, migraine, omega-3 fatty acids, pain, polyunsaturated fatty acids

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1. Introduction

Omega-3 (or ω-3) is the name for long-chain polyunsaturated fatty acids (PUFAs).[1] Among PUFAs properties, the most relevant are represented by antioxidant,[2] anti-inflammatory,[3] and neuro-protective effects.[4] FAs are key components of nutrition, play a primary role in the lipid composition of cell membranes,[5] and their metabolites are crucial as cell signaling molecules.[6] The main FAs present in the brain and nervous system are long-chain PUFAs.[7,8] The physiological functions of Omega-3 FAs in the nervous system include the maintenance of membrane fluidity and synapse integrity[9] and endogenous derivatives of Omega-3 FAs, act as anti-inflammatory mediators.[10]

Eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) are the most important long-chain omega-3 FAs, however, their endogenous formation can be not sufficient for physiological necessities.[11] They are structurally and functionally distinct from omega-6 PUFAs, and inflammatory cells contain high proportions of the omega-6 PUFAs and low proportions of omega-3 PUFAs.[1,12,13] In general, lipids derived from omega-6 FAs show pro-nociceptive properties, while mediators derived from omega-3 FAs have anti-nociceptive properties, with some exceptions.[14] Moreover,

omega-3 interferes with the conversion of omega-6 to eicosanoids, thus reducing the production of prostaglandins and leukotrienes.[12,15]

Omega-3 and omega-6 FAs modulate inflammation, and pain-related biochemical pathways,[16] in particular, omega-3 FAs intake have been associated with decreased concentration of C-reactive protein (CRP), pro-inflammatory eicosanoids, cytokines, chemokines, and other inflammatory biomarkers.[17]

In recent years, PUFAs were recommended to treat systemic pathological conditions,[18] and administration of omega-3 PUFAs has been proposed for the treatment neurological diseases such as hyperactive disorder, attention deficit,[19] Alzheimer,[20] depression,[21] neurodegenerative diseases,[22] and spinal cord injury.[23] These FAs mediate numerous physiological functions and have therapeutic potential for neuro-traumatic conditions[24] and omega-3 FAs intake provide relief from neuropathic pain caused by diabetic neuropathy.[25] In addition, patients affected by cervical radiculopathy and thoracic outlet syndrome reported long term significant pain attenuation with high oral doses of omega-3 FAs.[26] More recently, analgesia with omega-3 FAs in chronic headache has also been observed.[27]

1.1. Migraine

Migraine is a common chronic neurological disease, characterized by frequent attacks of disrupting pain, commonly associated with depression, anxiety, hypertension, stroke, and cardiovascular diseases.[28] Even in its episodic form migraine can evolve in a chronic condition.[29] Factors that could contribute to its pathogenesis are menstrual cycle, pregnancy, lifestyle, diet, and chronic stress.[30]

Etiology of migraine is still not completely known, even if genetics and environmental factors could play a central role[31] and current opinion states that neurogenic inflammation contributes to migraine pathogenesis.[32] It is well known that in a neuro-inflammatory condition, increased neuronal activity leads to the release of inflammatory mediators such as the cytokine tumor necrosis factor (TNF)-α.[33] Phases of attack migraine are also frequently associated with higher serum levels of glutamate, magnesium deficiency, monoaminergic pathway and mitochondrial disorders, calcitonin gene related peptide (CGRP) release.[34,35] Cytokines, by increasing membrane permeability and through cell-to-cell interactions, have a significant role in the inflammatory process of the central nervous system (CNS) and generation of pain.[36]

In migraine patients, vascular dysfunction is generated by increased production of adhesion molecules and, during attacks, is sustained by increased concentrations of pro-inflammatory cytokines.[34] Expression of pro-inflammatory cytokines, adhesion molecules, and activation of microglia, contribute to generate and sustain inflammation and neuropathic pain.[37,38] Human and experimental pre-clinical research also highlighted the role of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), confirming that they contribute to sustaining inflammation and neurogenic pain in migraine.[39]

Migraine is a neurovascular disorder[40] affecting approximately 11% of the population worldwide[41] and classified among the 10 most prevalent incapacitating diseases.[42] It is a common disorder even at early ages with the prevalence of 10.6% in children 5 to 15 years old.[43] The mean age of onset of migraine symptoms is about 7 years in boys and approximately 10.9 years in girls.[44] Migraine attacks may have a negatively impact the quality of life of children,[45] moreover, recurrent headaches can worsen daily activities even during adolescence.[46]

1.2. The role of fatty acids in neuroinflammation

Neurogenic inflammation plays a crucial role in the pathogenesis and progression of migraine,[47] and also leads to the sensitization and activation of perivascular meningeal afferent nerves.[48] Moreover, the activated glia is responsible for producing pro-inflammatory cytokines and mediators capable of damaging the blood–brain barrier. FAs modulation of membrane proteins related to ion channels including the transient receptor potential family, could be responsible for omega-3 analgesic properties. Changes in lipid composition in the microenvironment influence the physiological function of membrane proteins related to cellular signaling processes,[49] especially those involving G-proteins.[50] On this basis, membrane-lipid supplementation can also be employed in the prevention or the treatment of many health problems as it is for vascular diseases and cancer pathologies.[51,52]

PUFAs produce self-mediated (i.e., acting as peroxisome proliferator-activated receptor alpha ligands) biological effects and effects mediated by their bioactive metabolites.[53,54] These bioactive compounds are specialized mediators such as epoxides, electrophilic oxo-derivatives, ethanolamines, acylglycerols, acrylamides of amino acids or neurotransmitters, and fatty acyl esters of hydroxyl fatty acids (FAHFAs),[7,55–58] exerting mostly anti-inflammatory effects.[59]

The production of pro-inflammatory proteins, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 in various cell types, including endothelial cells, monocytes, macrophages, and dendritic cells is inhibited by PUFAs.[17] Moreover, PUFAs regulate the severity of inflammatory diseases and reduce neurogenic pain.[60,61] In the light of the concepts expressed above, the authors collected clinical studies carried out with omega-3 FAs, alone or in association, with the aim to evaluate the state of the art of their use in migraine therapy.

2. Materials and methods

The authors collected clinical findings carried out investigating the effects of omega-3 FAs use, alone or in combination with other substances, in the treatment of migraine. The analysis included all articles published in peer-reviewed scientific journals describing clinical trials omega-3 fatty acids (FAs) in the treatment of migraine. Articles were excluded if they did not meet the following inclusion criteria: articles written only in English language, articles published in peer-reviewed scientific journals.

2.1. Search strategy

Bibliographic research was carried out, by examining scientific literature from January 2000 until January 31, 2020, independently by 2 researchers (blinded to the authors and initially on results) in the major scientific databases and search engines of peer-reviewed literature on life sciences and biomedical topics (PubMed, Scopus, Embase, Web of Science, Google Scholar).

The investigators used the following keywords or combination of keywords: "Omega-3 fatty acids," "eicosapentaenoic acid (EPA)," "docosapentaenoic acid (DPA)," "docosahexaenoic acid

(DHA)," and "migraine." All articles published in peer-reviewed scientific journals describing clinical trials and applications of omega-3 FAs in migraine were collected and discussed. Case series, case reports, and human studies were excluded.

2.2. Study selection

The selection review of clinical studies written in English and regarding omega-3 FAs were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[62] (Fig. 1). Only clinical trials were included in the review if they were conducted in subjects of all ages, and, investigated the impact of omega-3 supplement, omega-3 in association with other drugs, or omega-3-enriched diet, on patients suffering for migraine according to the criteria of the International Headache Society.

From the eligible articles, 2 other investigators independently extracted data by using a standard data extraction form. There was not any disagreement between investigators about data extraction. Variables for which data were sought are the therapeutic indication, design of the study, number, sex, and age of subjects included in the studies, endpoints, adverse effects, and outcome.

The JADAD scale was used to assess the risk of bias analysis, evaluating the reported method of randomization, blinding, and loss to follow-up in a clinical trial and assigns a score from 0 to 5, with higher scores (3–5), indicating higher methodological quality and lower scores (0–2) indicating the lower methodological quality of the trial.

This systematic review does not need ethical approval, because it does not utilize the individual patient data.

3. Results

A collection of 29 scientific articles, describing the effects of omega-3 FAs treatment for migraine corresponding to the inclusion criteria were selected from our bibliography research. Seventeen articles were excluded for title and abstract (Fig. 1).

Study selection and characteristics, according to PRISMA guidelines were reported in the relative flow diagram. (Fig. 1).

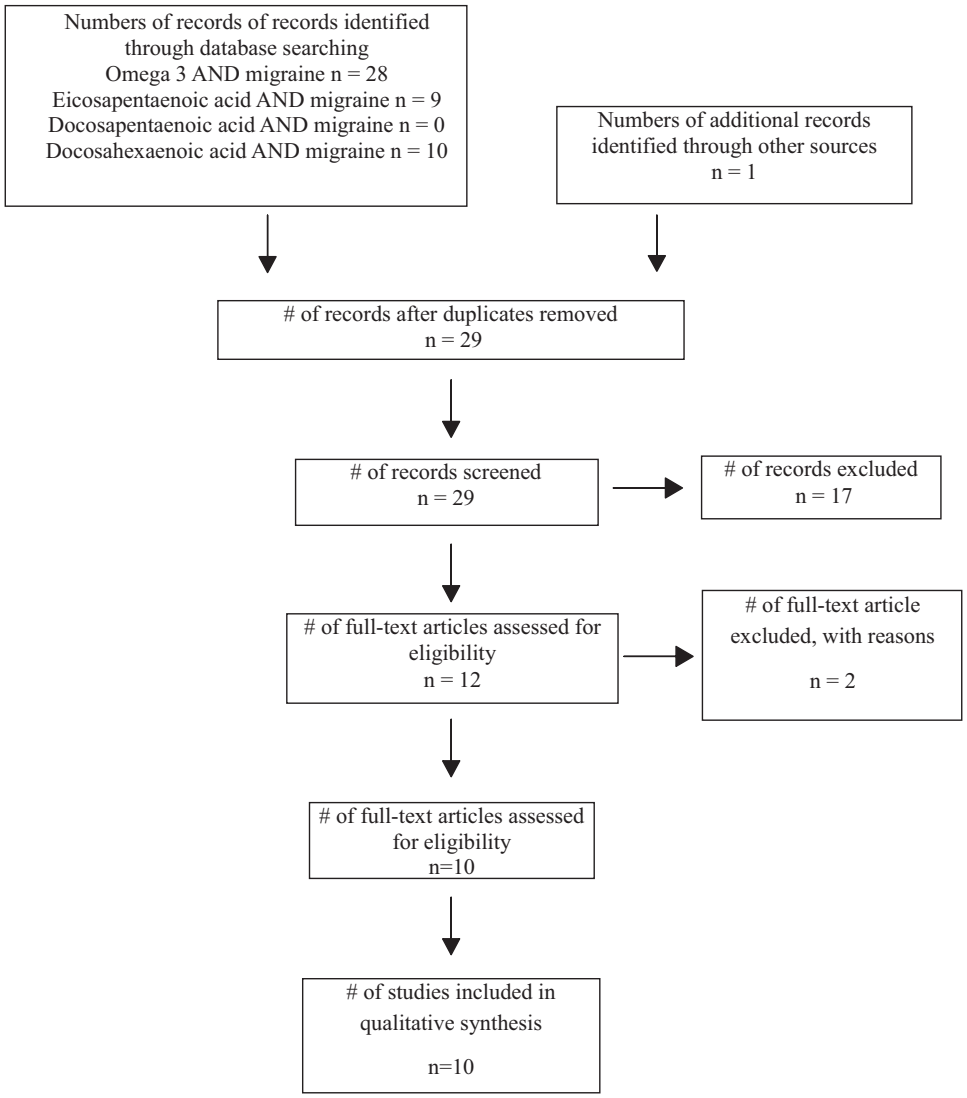

Figure 1. PRISMA flow chart diagram showing the process of literature search and studies selection. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

Table 1

Clinical studies investigating effects of omega-3 FAs in migraine patients.

Type of migraine	Study design	Population (no. of patients, sex, age)	Type of intervention and duration of the trial	Dose of intervention	Outcome	Reference
International Headache Society (HIS) revised criteria for migraine in children.	Randomized double blind placebo controlled trial.	25 patients 11 males 14 females Aged 10.36 ± 2.88 years.	Omega-3 (fish oil)/ sodium valproate. Duration of the intervention was 2 months.	Group I: sodium valproate syrup or tablet 20 mg per kg of body weight (maximum 200 mg twice daily) in 2 divided doses daily in combination with a placebo capsule. Group II: sodium valproate tablet or syrup 20 mg per kg of body weight (maximum 200 mg twice daily) in 2 divided doses daily in combination with an omega-3 capsule containing 1 g of fish oil (180 mg eicosapentaenoic acid [EPA] and 120 mg docosahexaenoic acid [DHA]).	Sodium valproate was effective in reducing the frequency and severity of attacks in children, omega-3 did not produce beneficial effects	Fayyazi et al (2016).
Primary headache type meeting our CDH criteria of headaches, according to International Headache Society (IHS) criteria.	Randomized, parallel-group clinical trial (single blind).	66 patients 9 males 57 females Aged 41.5 ± 12.25 years.	High omega-3 plus low omega-6/low omega-6 Duration of the intervention was 3 months.	Group 1: 1482 mg dietary omega-3 EPA + DHA and 114 mg omega-6. Group II: 114 mg omega-6.	Targeted dietary manipulation of omega-3 and omega-6 fatty acids reduced pain and improved quality of life in migraine with chronic headaches.	Ramsden et al (2013).
Migraine headache was defined according to International Headache Society (IHS) criteria.	Randomized, single-blind clinical trial;	67 patients 15 males 52 females Group I: N = 38 Group II: N = 29 Aged 35.3 ± 9.6 years.	Omega-3 (fish oil)/ sodium valproate Duration of the intervention was 12-weeks.	Group I: 400 mg/d of sodium valproate Group II: sodium valproate 400 mg daily plus fish oil supplementation (180 mg).	Sodium valproate plus fish oil supplementation significantly reduces migraine headache more than sodium valproate alone but only at the beginning of the treatment.	Tajmirriahi et al (2012).
Migraine headache was defined according to International Headache Society (IHS) criteria.	Randomized double-blind cross-over trial.	23 patients 7 males 16 females Aged 15 ± 1 years.	Fish oil/placebo (olive oil) Duration of the intervention was 2 months.	Group I: 2 capsules per day of a marine n-3 ethyl ester concentrate for the firsts 2 months (1-g n-3 ethyl ester concentrate soft gel capsule consisted of EPA 378 mg, DHA 249 mg, and tocopherol 2 mg). Group II: 2 capsules of placebo per day for the first 2 months (1-g placebo capsule contained olive oil ethyl ester concentrate including oleic acid 691 mg, palmitic acid 106 mg, linoleic acid 62 mg, and tocopherol 2 mg).	Patients experienced a similar reduction in frequency, duration, and severity of headaches during treatment with fish oil or with olive oil.	Harel et al (2002).
Migraine headache was defined according to International Headache Society (IHS) criteria.	Randomized double blind placebo controlled trial.	196 patients 100 males 96 females Aged 39.25 ± 11.1 years.	Omega-3/placebo (olive oil) Duration of the intervention was 4 months	After 4 weeks of a single-blind placebo run-in period, patients were randomized and treated in double-blind condition by placebo or omega-3 polyunsaturated fatty acids 6 g a day for 16 weeks, followed by a 4-weeks placebo run-out period.	Omega-3 treatment fails to reduce the number of attacks significantly compared with placebo.	Pradalier et al (2001).

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; CDH = chronic daily headache.

Table 2

Clinical studies investigating effects of omega-3 FAs in association with other drugs in migraine patients.

Type of migraine	Study design	Population (no. of patients, sex, age)	Type of intervention and duration of the trial	Dose of intervention	Outcome	Reference
Episodic migraines according to International Headache Society (IHS) criteria.	Randomized double blind placebo controlled trial.	74 patients; 12 males 64 females; Aged 20–50 years.	Omega-3 fatty acids/ nano-curcumin/ placebo. All patients were treated with 3 cyclic antidepressants (Amitriptyline or Nortriptyline, dose of 25–50 mg/d) and β-blocker (Propranolol, at a dose of 20–40 mg/ d). Duration of intervention was 2 months.	Group I: 1800 mg omega-3 fatty acids (2 capsules/d), and 80 mg nano-curcumin (1 capsule/ d). Group II: 1800 mg omega-3 fatty acids (2 capsules/d) and a nano-curcumin placebo (containing paraffin oil, 1 capsule/day). Group III: omega-3 fatty acids placebo (2 capsules/d containing paraffin oil) and 80 mg nano-curcumin (1 capsule/ day). Group IV: omega-3 fatty acids placebo (2 capsules/d containing paraffin oil) and a nano-curcumin placebo (containing paraffin oil, 1 capsule/d).	The combination of omega-3 and nano-curcumin significantly reduced the frequency, severity, and duration of headaches.	Abdolahi et al (2019).
Episodic migraine According to International Headache Society (IHS) criteria.	Randomized double blind placebo controlled trial.	80 patients; 16 males 64 females; Aged 20–50 years.	Omega-3 fatty acids/ nano-curcumin/ placebo. Duration of intervention was 2 months.	Group I: combination of omega-3 fatty acids (2500 mg) plus nano-curcumin (80 mg); Group II: omega-3 (2500 mg); Group III: nanocurcumin (80 mg); Group IV: omega-3 and nano-curcumin placebo included oral paraffin oil.	The combination of omega-3 and nano-curcumin can significantly reduce the expression and serum levels of IL-6, which is proinflammatory and play an important role in migraine pathogenesis.	Abdolahi et al (2018).
Episodic migraine recognized according to International Headache Society (IHS).	Randomized double blind placebo controlled trial.	72 patients, Aged 20–50 years.	Omega-3/nano-curcumin/Placebo. Duration of intervention was 2 months.	Group I: omega-3 two capsules per day containing EPA (600 mg and DHA: 300 mg) and curcumin placebo; Group II: nano-curcumin one capsules per day (80 mg) and omega-3 placebo; Group III: omega-3 supplements and curcumin; Group IV: omega-3 and curcumin placebo.	The ICAM-1 serum concentration in subject treated with omega-3 and nano-curcumin association, and omega-3 alone, showed a significant reduction at the end of the study compared with the beginning. In addition, a significant reduction in attack frequency was observed in patients treated with omega-3 and nano-curcumin association.	Soveyd et al (2018).
Chronic migraine according to the diagnostic criteria of International Classification of Headache Disorders, Third Edition -beta version- (ICHD-3β)	Prospective controlled, double-blind, and with comparison groups study.	51 patients 15 males 36 females Aged 35.9 ± 8.7	Omega-3 fatty acids/ placebo. All patients received three cyclic antidepressants (amitriptyline at a dose of 10 mg/d). Duration of the intervention was 2 months.	Group I: eicosapentaenoic acid (EPA) 400 mg and of docosahexaenoic acid (DHA) 350 mg, twice a day; Group II: placebo.	Dietary supplementation with polyunsaturated omega-3 fatty acids, associated with migraine prophylactic treatment, may reduce the frequency and intensity of headache attacks in migraine patients.	Soares et al (2017).
Episodic migraine recognized according to International Headache Society (IHS).	Randomized double blind placebo controlled clinical trial.	80 patients (80% female and 20% male); Aged 20–5 years.	ω-3 fatty acids/nano-curcumin supplementation/ placebo. All patients received 3 cyclic antidepressants (amitriptyline or nortriptyline) with β-blocker (propranolol). Duration of the intervention was 2 months.	Group I: omega-3 fatty acids and nano-curcumin supplementation Group II: omega-3 fatty acid supplementation and nano-curcumin placebo. Group III: nano-curcumin supplementation and omega-3 fatty acid placebo Group IV: omega-3 fatty acid placebo and nano-curcumin placebo.	The combination of omega-3 fatty acids and nano-curcumin synergistically is able to induce an anti-neuroinflammatory response, as well as headache frequency more than each of omega-3 fatty acids or no curcumin alone.	Abdolahi et al (2017).

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

Table 3

Quality assessment of clinical trials according to Jadad score.

Authors	Was the trial described as randomized?	Was the randomization procedure described and appropriate?	Was the trial described as double-blind?	Was the method of double blinding described and appropriate?	Was the number of withdrawals/dropouts in each group mentioned?	Jadad Score
Abdolahi et al (2019).	Yes	Yes	Yes	Yes	Yes	5
Abdolahi et al (2018).	Yes	Yes	Yes	Yes	Yes	5
Soveyd et al (2018).	Yes	Yes	Yes	Yes	Yes	5
Soares et al (2017).	Yes	No	Yes	Yes	Yes	3
Abdolahi et al (2017)	Yes	Yes	Yes	Yes	Yes	5
Fayyazi et al (2016).	Yes	Yes	Yes	Yes	Yes	5
Ramsden et al (2013).	Yes	Yes	No	NC	Yes	3
Tajmirriahi et al (2011).	Yes	No	No	NC	Yes	1
Harel et al (2002).	Yes	No	Yes	No	No	1
Pradalier et al (2001).	Yes	No	Yes	No	Yes	1

The JADAD scoring system was used for the assessment of randomized controlled trials with the following 5 items: Was the study described as randomized? (Yes = 1 point, No = 0 point); Was the randomization scheme described and appropriate? (Yes = 1 point, No = –1 point); Was the study described as double-blind? (Yes = 1 point, No = 0 point); Was the method of double blinding appropriate? (Yes = 1 point, No = -1 point. If the answer of Item 3 was No, Item 4 is not calculable); Was there a description of dropouts and withdrawal? (Yes = 1 point; No = 0 point).

Ten clinical studies were included in the review. Five studies conducted on the effects of omega-3 FAs alone (Table 1) and 5 clinical trials, carried out to study the antimigraine effects of omega-3 FAs in combination with other substances (Table 2), were included in this review. Type of migraine, study design, population, type and duration of intervention, dose of intervention, and outcomes of the trials, were reported.

Quality assessment of randomized controlled trials was reported according to the JADAD scale (Table 3). All the studies were described as randomized trials, however, only in 60% of them, the randomization procedure was described and appropriate. A double blinding procedure was adopted in 8 of the 10 studies commented. In 4 of the studies adopting double-blinding, this procedure was not appropriately described. According to the JADAD scale evaluation only 70% (6 clinical trials) of the studies were well designed and conducted following high methodological quality standard and the remaining 30% (4 studies) were poor from the methodological point of view.

4. Discussion

Current therapeutic measures for migraine included pharmacological therapies, moreover, other therapeutic strategies are represented by dietary supplements, and herbal ingredients, dietary patterns, acupuncture, relaxation techniques, biofeedback, and psychotherapy.[63,64]

Therapeutic strategies for the treatment of migraine largely include non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, and triptans.[34]

In an early study, Pradalier et al[65] did not find any difference in mean intensity, mean duration of the attacks, and rescue medication use, between the group treated with omega-3 FAs 6 g/d supplementation for 16 weeks in comparison with placebo.

Similar results were also observed in a cross-over study carried out on adolescent patients suffering from frequent migraines for at least 1 year treated for 2 months with fish oil and 2 months of olive oil (used as placebo). Results showed no difference in frequency, duration, and severity of headaches during treatment with fish oil and olive oil. Authors of the study suggested that, despite the absence of a significant difference between treatments, the marked improvement from baseline experienced by the patients should not be dismissed as simply a placebo effect.[15] However, in this study omega-3 FAs were not compared with a real placebo, and this can be considered a limiting factor to the possibility of evaluating antimigraine effects.

In patients suffering from chronic migraine who supplemented the diet by incrementing omega-3 FAs intake, a reduction of the number of headaches per month has been observed. The authors affirm that this beneficial effect of omega-3 FAs could be due to the decrease in the production of prostaglandins and leukotrienes or to a change in the synthesis and release of serotonin by platelets.[66]

Valproate antimigraine mechanism is based on the increase of brain gamma-aminobutyric acid (GABA) levels and the inhibition of inflammatory cytokine's mRNA expression (TNF-α, IL-1β, IL-6, and IL-17), and, the inhibition of macrophages and B, T cells aggregation leading to the suppression of neuro-inflammatory states.[67] Conventional medications for migraine in children include drugs such as sodium valproate, topiramate, propranolol, amitriptyline, naproxen, and flunarizine.[68] The treatment of migraine in teenagers consists chiefly of prophylactic medications and behavioral therapy.[69,70] However, often, unreliable results have been obtained, raising the necessity for the development of new therapeutic strategies to prevent and to treat migraine attacks in adolescents.

Effects of dietary supplementation with fish oil were investigated in migraine prevention in a 12-week, randomized, single-blind clinical trial conducted on 67 patients (52 women, 15 men) with migraine headache allocated to 2 groups. In the first group, 38 patients received 400 mg/d sodium valproate. In the second group, 29 patients received sodium valproate 400 mg daily plus fish oil supplementation (180 mg). A significant decrease in duration, monthly frequency, and severity of headache after month 1, 2, and 3 in comparison with month 0 occurred in both groups. A reduction occurred in headache severity ($P = .046$) and frequency ($P = .044$) in the group with fish oil supplementation after month 1 in comparison with sodium valproate alone. However, there was no significant difference between the 2 treatment groups in the duration of headache attacks after the first month. Mean intensity, mean duration, and mean frequency of the attacks after the second and third months also did not show a significant difference between the 2 treatments.[1]

The effects of omega-3 FAs in combination with valproate were also investigated in the prevention of migraine attacks in children aged 5–15 years. Results of a group treated with sodium valproate and 1 g of omega-3 were compared with a control group treated only with sodium valproate and a placebo for 2 months (12 cases and 13 controls were enrolled). While sodium valproate was effective in reducing the frequency and severity of attacks in children, omega-3 FAs did not produce beneficial effects.[71]

Data from these studies show contradictory results about the use of omega-3 FAs in association with sodium valproate in migraine.

Clinical and biochemical effects of targeted alteration in dietary omega-3 and omega-6 FAs for the treatment of chronic headaches were evaluated in a 4-weeks randomized, single-blinded, parallel-group clinical trial. The analysis of the results indicated that the combination of increasing dietary omega-3 FAs with a concurrent reduction in omega-6 produced statistically significant and clinically relevant improvements in number headache hours per day, severity of headache per days, and headache-related quality of life compared with baseline and compared with the omega-6-lowering group intervention.[14]

In a recent pre-clinical study, it has been observed that the intake of omega-3 FAs (both of EPA and DHA) in association with curcumin, active principle extracted by the plant *Curcuma longa*, synergistically decrease COX-2 activity and iNOS gene expression as well as nitric oxide (NO) production in macrophage cells, thus increasing antioxidant effects of heme oxygenase-1.[72]

Positive effects have also been shown with the association of omega-3 FAs and curcumin which together seem to potentiate the NSAID's anti-inflammatory effects.[73] A further possible advantage is that potential synergetic effects of the combination of omega-3/curcumin could allow a reduction of the dosage of both substances.[72] These compounds, in addition to their anti-inflammatory and cardio-protective properties, both show neuroprotective capabilities, suggesting wider clinical employment. Moreover, the use of this combination can induce anti-neuroinflammatory adaptation through the downregulation of TNF-α gene expression and gene production. This could cause a major reduction of migraine attacks concerning omega-3 FAs or curcumin when administered alone.[61]

High levels of (IL)-6 and (CRP) can lead to disruption of the integrity of the blood–brain barrier and can contribute to generating and maintaining neurogenic inflammation, and, consequently, to the progression of the disease. A recent study confirms that both omega-3 FAs and nano-curcumin down-regulate IL-6 mRNA and, if used in combination, significantly decrease the serum concentration of both IL-6 and CRP, confirming the possible synergetic relation.[74]

Adhesion of leukocytes to the walls of the cerebral blood vessels constitutes an important stage in the inflammatory process. Curcumin and omega-3 FAs, affecting transcription factors, can regulate the gene expression and serum levels of the endothelial factor ICAM-1, playing an important role in leukocyte trafficking, immunological synapse formation, and numerous cellular immune responses.[75] In a recent study,[76] the authors aimed to evaluate the synergistic effects of omega-3 FAs and nano-curcumin on ICAM-1 gene expression and serum levels in migraine patients, suggesting that the supplementation with these 2 nutrients can lead to an improvement in the function of metabolic pathways, and can also be employed in the treatment or prevention of migraine complications. Other authors agree with this conclusion[30] affirming that omega-3 FAs and nano-curcumin associations can be useful to spare drug consumption in migraine patients or even be a safer substitute for drugs.

A clinical trial involving 74 episodic migraine patients who received omega-3 FAs, nano-curcumin, a combination of them, or a placebo, for a period of over 2 months, evaluated the expression of COX-2/iNOS (in peripheral mononuclear blood cells isolated from patients) and COX-2/iNOS serum levels, measured using real-time polymerase chain reaction and enzyme-linked immunosorbent assay, respectively. Results showed that omega-3 FAs and nano-curcumin could reinforce each other's effects in the downregulation of COX-2/iNOS mRNA, as well as to cause a reduction of their serum levels. These experiments also confirmed that the combination of omega-3/nano-curcumin significantly reduced the frequency, severity, and duration of headache attacks.[39]

5. Conclusions

The rationale for the usage of omega-3 FAs is based on a mechanism showing partial similarity to the COX-2 inhibitor drugs, with the advantage that both EPA and DHA administrations are associated with a lower profile of effects. On the other hand, omega-3 FAs reduce inflammatory and neurogenic pain by decreasing the pain receptor's expression and activity. Comprehensively, data from literature show that they possess neuroprotective properties that result in the prevention of inflammatory, neurologic, and vascular diseases.

Moreover, albeit the exact role of omega-3 FAs in inflammatory processes has not been completely clarified, it was suggested that a therapeutic role is achieved through the inhibition or reduction of the release of inflammatory cytokines (including TNF-α, IL-1β, IL-6) reduced expression of endothelial dysfunction markers (ICAM and VCAM). In this view, the inhibitory effects of omega-3 FAs on cyclooxygenase-2 enzymes and nitrous oxide could be seen as an effective contribution to healing and/or preventing disease progression of migraine.

The limits of this review must be underlined and reported, mainly related to the relative inhomogeneity of the trials, and this is due to the few studies reported in the literature, although from the analysis of the results, the outcomes seem to converge.

In conclusion, from the analysis of the studies included in this narrative review, it is evident that part of the studies are not characterized by good quality methodology and they do not show established evidence of the therapeutic role of Omega-3 FAs in migraine. Further clinical trials of good quality are necessary to implement the knowledge concerning the use of omega-3 fatty acids in the treatment of migraine.

Author contributions

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