

Cet article porte sur l'administration d'un supplément en acides gras polyinsaturés (Polyunsaturated fatty acid=PUFA), qui est une forme de thérapie complémentaire et alternative courante chez les personnes atteintes de SEP. En raison de leur popularité, les cliniciens doivent avoir une connaissance approfondie des compléments PUFA largement répandus et des données d'efficacité et d'innocuité recueillies à partir des études cliniques. Des études réalisées à petite échelle semblent mettre en

évidence certains effets bénéfiques. Un supplément de PUFA est généralement bien toléré, bien qu'il soit préférable d'éviter certains suppléments spécifiques et que divers tableaux cliniques requièrent de la prudence. Les données d'efficacité et d'innocuité passées en revue suggèrent qu'un supplément en PUFA représente une approche prometteuse. Des essais réalisés à grande échelle permettraient d'en confirmer les bénéfices.

Bei diesem Artikel geht es um die Supplementierung mit mehrfach ungesättigten Fettsäuren (PUFA), eine von MS-Patienten häufig verwendete Ergänzungs- und Alternativtherapie. Aufgrund ihrer weitverbreiteten Anwendung sollten Ärzte über PUFA, die als Nahrungsergänzungsmittel vielerorts erhältlich sind, Bescheid wissen und über die in klinischen Studien ermittelte Wirksamkeit und Sicherheit der Präparate im Bilde sein. Kleinere Studien haben einen Trend zu einigen

positiven Wirkungen gezeigt. Die Supplementierung mit mehrfach ungesättigten Fettsäuren ist generell gut verträglich, obgleich einige Ergänzungspräparate besser gemieden werden sollten und in bestimmten klinischen Situationen Vorsicht angeraten ist. Eine Untersuchung der Wirksamkeits- und Sicherheitsdaten deutet darauf hin, dass die Supplementierung mit PUFA ein viel versprechender Ansatz sein könnte. Zur Untermauerung der Ergebnisse sind groß angelegte Studien erforderlich.

Questo articolo si sofferma sulla supplementazione con acidi grassi polinsaturi (PUFA), una diffusa terapia alternativa e complementare fra i pazienti affetti da SM. Per via della popolarità degli integratori di PUFA, i medici curanti dovrebbero essere conoscenza dei diversi tipi attualmente in commercio e dei dati sulla loro efficacia e sicurezza emersi dagli studi clinici. Studi su piccola scala hanno evidenziato alcune tendenze verso effetti benefici. In

generale la supplementazione con PUFA è ben tollerata, sebbene sia opportuno evitare alcuni specifici integratori e malgrado la cautela necessaria in alcuni contesti clinici. La rassegna dei dati su efficacia e sicurezza suggerisce che la supplementazione con PUFA può rappresentare un approccio promettente. Sperimentazioni su larga scala sono necessarie a conferma di questi benefici.

Este artículo se centra en el aporte complementario de ácidos grasos polinsaturados (PUFA), que es una forma popular de terapia complementaria y alternativa entre las personas con EM. Debido a su popularidad, los médicos deben conocer bien estos complementos de PUFA, ampliamente disponibles, y conocer asimismo los datos de eficacia y seguridad procedentes de estudios clínicos. Estudios a pequeña escala han demostrado tendencias

favorables a ciertos efectos beneficiosos. El aporte complementario de ácidos grasos polinsaturados es generalmente bien tolerado, aunque ciertos complementos concretos es mejor evitarlos y ciertas situaciones clínicas requieren precaución. Un análisis de los datos de eficacia y seguridad sugiere que los complementos de PUFA pueden ser un enfoque prometedor. Se requieren estudios a gran escala para confirmar esas ventajas.

本論文は多価不飽和脂肪酸(PUFA)補足に焦点を合わせ、これはMS患者間で人気のある補完型および代替型の療法である。その人気ゆえに、臨床医は広く入手できるPUFAサプリメント、ならびに効果および安全性に関する臨床試験データについて知る必要がある。小規模試験から、ある程度の有益作用を現す傾向のあ

ることが証明されている。PUFA補足の忍容性は概ね良好であるが、一部の特定のサプリメントは避けた方が良く、ある種の臨床状況では注意を要する。有効性および安全性データのレビューから、PUFA補足は有望なアプローチであることが示唆される。大規模試験によってベネフィットを確認する必要がある。

# Polyunsaturated Fatty Acid Supplementation in MS

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## Summary

This article focuses on polyunsaturated fatty acid (PUFA) supplementation, which is a popular form of complementary and alternative therapy among people with MS. Owing to their popularity, clinicians should be knowledgeable about the PUFA supplements that are widely available, and the efficacy and safety data from clinical studies. Small-scale studies have demonstrated

trends towards some beneficial effects. PUFA supplementation is generally well tolerated, although some specific supplements are best avoided and some clinical situations warrant caution. A review of the efficacy and safety data suggests that PUFA supplementation may be a promising approach. Large-scale trials are required to confirm the benefits.

### KEY WORDS:

MULTIPLE SCLEROSIS; DIET; POLYUNSATURATED FATTY ACIDS; PUFA SUPPLEMENTATION; OMEGA-3; OMEGA-6

## Introduction

Complementary and alternative therapies, including dietary modifications and supplements, are widely used by people with MS.<sup>1,2</sup> Although several dietary supplements and approaches are used, this article will focus on one particularly common strategy: polyunsaturated fatty acid (PUFA) supplementation. It is important for clinicians to become familiar with this form of complementary medicine, owing to its popularity with the public. There are two related issues about which clinicians should become knowledgeable. First, the evidence relating to PUFAs, especially the results of the few relevant clinical trials that have been reported. Secondly, because many different PUFA supplements are available to people with MS, clinicians should also have a basic understanding of appropriate doses, contraindications, drug interactions and safety for the widely used PUFA supplements.

A wide range of preclinical evidence has suggested that PUFA supplementation, including use of omega-3 and omega-6 fatty acids, may play a therapeutic role in MS. This type of evidence, which is not based on clinical trials, is speculative. Limited studies have shown that omega-6 fatty acids suppress experimental

allergic encephalomyelitis (EAE).<sup>3</sup> Epidemiological evidence demonstrates an inverse association between mortality rates due to MS and the ratio of polyunsaturated fats to saturated fats consumed in the diet.<sup>4</sup> Finally, in people with MS, supplementation with fish oil results in a decrease in the production of the inflammatory cytokines interleukin (IL)-1 $\beta$ , tumour necrosis factor- $\alpha$ , IL-2 and interferon  $\gamma$ .<sup>5</sup>

## Omega-3 PUFAs

### Background

Examples of omega-3 fatty acids include alpha-linolenic acid (ALA), which is an essential fatty acid, and eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), which are produced in the body through a series of desaturations and elongations. Omega-3 fatty acids may be obtained from fish or dietary supplements. Fish and fish products that are rich sources of omega-3 fatty acids include salmon, Atlantic herring, Atlantic mackerel, bluefin tuna, sardine and cod liver. Supplements that contain EPA and DHA include fish oil, cod liver oil and concentrated preparations of EPA and DHA.<sup>6-8</sup>

### Clinical Trials Related to Omega-3 PUFA Supplementation

Uncontrolled studies of PUFAs in MS have been reported.<sup>9-14</sup> Clinical improvement was noted in most of these studies; more importantly, no worsening of MS or other serious side-effects were noted.

There have been five prospective randomized controlled clinical trials (RCCT) of PUFAs among people with relapsing–remitting (RR) MS.<sup>15-19</sup> Three of these studies involved linoleic acid (LA) supplementation<sup>15-17</sup> and two involved supplementation with EPA and DHA.<sup>18,19</sup>

Two RCCTs have tested EPA and DHA in the form of fish oil as an intervention in MS. The larger study, involving 312 patients, used 10 g fish oil supplementation daily as the intervention and olive oil as a placebo.<sup>18</sup> Although no statistically significant difference was observed, there was a trend favouring the treatment group, showing fewer people progressing one point on the Disability Status Scale (DSS), ( $P=0.07$ ): the DSS is an earlier version of the Expanded Disability Status Scale (EDSS), which is used to measure disability change in modern clinical trials. Other statistically non-significant trends favouring the treatment group were observed. This study has limitations: it is unclear whether sustained disability was measured in this study; an intent-to-treat analysis was not used.

Although the findings in the fish oil study were not statistically significant, it is interesting to note that supplementation with fish oil provided an absolute risk reduction of 10% and a relative risk reduction of 18% of progressing one point on the DSS. This is similar to the risk reductions reported for standard medical therapies.<sup>20</sup> The study, which involved 312 people, may have been underpowered to detect a 10% absolute risk reduction of disability progression at the usual level of statistical significance.<sup>20</sup> Larger studies are needed to determine if fish oil supplementation has any definite therapeutic effect in MS.

Another small randomized study, involving 31 patients, investigated fish oil and other dietary fat changes as a treatment among users of approved MS therapies.<sup>19</sup> Patients who had been using FDA-approved therapies for at least 2 months were assigned to receive either six fish oil capsules (1 g

capsules) along with instructions to maintain a very low fat diet (<15% of calories from fat) or six olive oil capsules (1 g capsules) along with instructions to maintain a low fat diet (<30% of calories from fat). The primary outcome measure was the Physical Component Scale (PCS) of the Short Form Health Survey Questionnaire (SF-36). The authors reported a trend on the PCS favouring the fish oil group that was not statistically significant at the end of the 12-month study. EDSS scores worsened in the olive oil group and improved in the fish oil group, which the authors described as a 'weak trend'.

### Safety Aspects of Omega-3 PUFAs

#### Dosages

There is no conclusive evidence to demonstrate whether omega-3 PUFA supplementation has a therapeutic benefit in MS. Consequently a standard dosage is not known. In MS clinical studies with fish oil, the combined daily intake of EPA and DHA was 0.9–2.85 g.<sup>9,18,19</sup> While omega-3 fatty acids can be obtained from the diet, an intake of this level of EPA and DHA entirely from the diet may be impractical as it requires up to one and a half servings of salmon or other fish per day. In addition to being impractical, such a diet raises concerns about contaminants, such as mercury. One study used 'about' 20 g cod liver oil daily.<sup>12</sup> For flaxseed oil, 1 tablespoon daily is sometimes suggested.<sup>8</sup> In studies of other conditions, the combined daily intake of EPA and DHA has been between 1 g and 5 g, and it has been determined that a total daily intake of 3 g or less of EPA and DHA is well tolerated.<sup>7,8</sup> At high doses, fish oils may cause loose stools and nausea; high doses of flaxseed oil in particular (>45 g daily), may have a laxative effect.<sup>7,8</sup>

#### Contraindications and interactions

There are few known contraindications for omega-3 fatty acids. Since these supplements may have a mild anti-coagulant effect, they should be used with caution by people who take anti-platelet or anti-coagulant medications, have bleeding disorders or are undergoing surgical procedures.<sup>7,8</sup> Fish oil may impair pulmonary function in those who are aspirin-sensitive.<sup>7</sup> Fish oil in high doses (>6 g combined daily intake of EPA and DHA) may reduce

the efficacy of insulin and oral hypoglycaemic medications and cause hyperglycaemia: such supplements should therefore be used with caution in patients with diabetes.<sup>7,8</sup>

### Safety

Fish oils are usually well tolerated. In the USA, the Food and Drug Administration has stated that it is generally safe to consume fish oil supplements when the combined daily intake of EPA and DHA is <3 g.<sup>6–8</sup> As a result, fish oils are classified as Generally Regarded as Safe. A 7-year study of 295 people did not find any serious adverse effects of modest doses of fish oil supplements.<sup>21</sup> Side-effects of fish oils include a fishy taste, belching, halitosis, nosebleeds and heartburn.<sup>7,8</sup> Relatively high levels of vitamin A may be found in halibut, shark and cod liver oils – on average, 20 g of cod liver oil contains 15 000 International Units (IU) of vitamin A<sup>7</sup> and doses of vitamin A >10 000 IU daily should be avoided, especially during pregnancy.<sup>7,8</sup> Omega-3 fatty acid supplementation may also cause vitamin E deficiency. Therefore vitamin E supplements (0.6–0.9 IU/g PUFA) may be indicated.<sup>22</sup>

## Omega-6 PUFAs

### Background

Examples of omega-6 fatty acids include LA, which is an essential fatty acid, and its metabolites, gamma-linolenic acid (GLA) and arachadonic acid.<sup>23</sup> There are multiple sources of omega-6 fatty acids. Most studies of omega-6 PUFA supplementation in MS have used sunflower seed oil, which contains relatively high concentrations (about 70%)<sup>24</sup> of LA. Other LA sources include soybean oil, corn oil, walnut oil, wheat germ oil, grapeseed oil, safflower seed oil and flaxseed oil. GLA may be found in relatively high concentrations in evening primrose oil (EPO), borage seed oil, blackcurrant seed oil and spirulina (blue-green algae).<sup>6,8,25</sup>

### Clinical Trials Related to Omega-6 PUFA Supplementation

Three prospective clinical studies of LA supplementation in people with MS have been undertaken; all were similar in design.<sup>15–17</sup> The duration of each trial was between 24 and

### Key Points

- Polyunsaturated fatty acid (PUFA) supplementation is a common form of complementary and alternative medicine used by people with MS
- Some clinical trials have demonstrated trends towards beneficial effects of PUFA supplementation on MS outcomes
- PUFA supplementation is generally well tolerated in the short term, although the effects of long-term use of some PUFA supplements are not known. Some risks are associated with drug interactions
- Large-scale trials demonstrating statistically significant effects are required to demonstrate a beneficial effect conclusively.

30 months and between 58 and 96 people were involved in each, most of whom had RRMS. The trials used similar doses of LA, ranging from 17 g to 23 g daily (primarily in the form of 60 ml sunflower oil) while oleic acid, primarily in the form of olive oil, was used as a placebo in all of the studies. Overall, no effect on disability progression or exacerbation frequency was observed in any of the studies,<sup>15–17</sup> although with only up to 96 patients enrolled, the studies were probably too underpowered to detect small changes.

Two of the three LA studies reported statistically significant reductions in exacerbation severity and duration.<sup>15,17</sup> No *P*-values were reported in one of these studies.<sup>15</sup> In the other, the *P*-values were reported as <0.025 for reduction in duration of exacerbations and <0.01 for reduction in severity of exacerbations.<sup>17</sup> The method used for recording exacerbation severity involved the assignment of points based on specific symptoms. The use of a grading system that was of limited value and poor reporting make it difficult to evaluate the data used to support conclusions that LA supplementation decreased MS exacerbation severity or duration.

On the basis of *post-hoc* hypotheses, the three prospective LA studies were later pooled and reanalysed.<sup>26</sup> The reanalysis concluded that 'patients with little or no disability at the start of the trial (DSS

2 or less) had a significantly smaller increase in disability than did those in the control group ( $P=0.05$ ). For this subset of patients, mean increase in disability for the LA group was 0.12 and for the control group, it was 0.81. However, not all data from the three clinical trials were included in the reanalysis. One of the three prospective trials<sup>17</sup> was conducted at two sites in Belfast and London, UK. The data collected at the London site were excluded from the reanalysis because they were unavailable. Although not noted in the reanalysis, the treatment group in the London arm fared worse than the placebo group. Thus, excluding these data increased the probability of finding a treatment benefit. In addition, it is not clear whether the disability scale used – the DSS, which was the predecessor to the EDSS – was sensitive enough to measure less than a 1-point (0.69 points) difference between two groups or that such a difference is clinically significant. Given these criticisms, and the use of *post-hoc* hypotheses, it may be best to view the reanalysis as having generated an interesting but untested hypothesis.

### Safety Aspects of Omega-6 PUFAs

#### Doses

A wide range of doses has been used in studies of omega-6 PUFA supplementation. LA intake may be increased by directly consuming LA-rich oils, such as sunflower seed oil, or by using these oils in food preparation. In the studies of RRMS, LA was administered in the form of sunflower seed oil at a dose of 17–23 g daily.<sup>15–17</sup> In MS clinical trials, EPO was given at doses that provided 0.34–0.36 g of GLA daily.<sup>16,27</sup> In other conditions, daily doses of EPO are typically 2–4 g, approximately 10% of which is GLA,<sup>7,8</sup> and daily GLA doses of up to 2.8 g appear to be generally well tolerated.<sup>8</sup> The GLA content of EPO preparations may be variable.<sup>28</sup> There is limited information regarding dosage for the other oils, especially for people with MS, a disease in which their use has not been investigated. For other conditions, dosages that are sometimes used are: flaxseed oil, 1 tablespoon daily; borage seed oil, 1 g once or twice daily; blackcurrant seed oil, 0.5–1.0 g daily; spirulina, 3–10 g daily.<sup>6–8</sup>

#### Contraindications and interactions

There are few known contraindications for omega-6 fatty acid supplements. GLA-containing supplements may prolong bleeding<sup>7</sup> and, as a result, should be used with caution by people receiving anti-coagulant or anti-platelet agents, those who have bleeding disorders or who are undergoing surgery. There is a possibility that EPO may decrease seizure threshold and provoke seizures when used in patients who have epilepsy or schizophrenia.<sup>7</sup> Seizure threshold may also be decreased when EPO is used in combination with phenothiazines or anaesthesia.<sup>7</sup> In theory, other GLA-containing supplements may have similar effects. Borage seed oil should be avoided in patients who have liver disease or take hepatotoxic medications as it may contain pyrrolizidine alkaloids (PAs),<sup>7</sup> which have possible multiple toxic effects, including hepatotoxicity. Furthermore, omega-6 fatty acid supplements should be used with caution by patients with hypertriglyceridaemia, as triglyceride levels may be increased.<sup>6–8</sup>

#### Safety

The long-term safety of supplementation with LA or GLA has not been studied. In the short term, omega-6 fatty acid supplements are generally well tolerated. There has been concern that LA supplementation may increase the risk of cancer, and although one large analysis of the animal and human studies in this area concluded that it was not likely that use of LA supplements increased the risks of breast, colorectal or prostate cancer in humans,<sup>29</sup> this issue has not been resolved entirely.<sup>30</sup> The safety of blackcurrant seed oil has not been well studied. Some spirulina products contain contaminants including heavy metals, microbes and microcystins.<sup>7</sup> The ingestion of microcystins may cause abdominal pain, nausea, vomiting, hepatotoxicity and death. Adverse effects have not been reported with non-contaminated spirulina, but the GLA content of spirulina products may be variable.<sup>7,8</sup> Supplementation with LA, GLA and other PUFAs may cause vitamin E deficiency. As a result, vitamin E supplementation may be necessary (0.6–0.9 IU/g of PUFA).<sup>22</sup> GLA and LA supplements may also cause nausea and soft stools.<sup>7,8</sup>

## Conclusions

The different types of PUFA supplementation available, with their corresponding efficacy and safety data, have been reviewed here. Small-scale trials suggest some beneficial effects. Generally most supplements are well tolerated in the short term, although clinicians need to be aware of potential drug interactions. However, large-scale controlled trials showing statistically significant benefits are required to determine if there are any definite therapeutic effects.

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## Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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