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ω-3 and major depression: a review

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Background: The World Health Organization estimates that major depression affects about 350 million people all over the world and reports this disorder as the major contributor to the global burden of diseases. Despite the well-defined symptomatology, major depression is a heterogeneous psychiatric disorder whose pathophysiology is not clearly established. Although several treatments are available, most depressed patients do not achieve the complete remission of symptoms. Factors linked to the persistence of the disorder have been investigated, particularly those related to the way of life. Moreover, it has been suggested that nutritional aspects may influence its development. Among them, a diet rich in ω-3 has been associated with a reduced risk of major depression, although its deficiency is associated with depressive disorders.
Methods: This review provides a general view about evidences of the use of ω-3 in major depression cases.
Results: Several studies have demonstrated beneficial effects of ω-3 in the prevention and treatment of major depression. However, not all the results have shown significant statistical benefits.
Conclusions: More studies are necessary to clarify detailed mechanisms of the antidepressant effects of ω-3 and may explain the source of contradictions in results published until the moment.

Aline H. Mello[1], Aline Gassenferth[1], Luana R. Souza[1], Jucélia J. Fortunato[2], Gislaine T. Rezin[1]

[1]Laboratory of Clinical and Experimental Pathophysiology, Post-Graduation Program in Health Sciences, Universidade do Sul de Santa Catarina, Tubarão, SC, Brazil; and [2]Laboratory of Neuroscience, Post-Graduation Program in Health Sciences, Universidade do Sul de Santa Catarina, Tubarão, SC, Brazil

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Dr. Gislaine Tezza Rezin, Universidade do Sul de Santa Catarina, Av. José Acácio Moreira, 787, Tubarão, 88704-900, SC, Brazil.
Tel: +55 48 3621-3363;
Fax: +55 48 3621 3365;
E-mail: gitezza@hotmail.com

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Summations

- Major depression has well-defined symptomatology, but its pathophysiology is not clearly established.
- The most depressed patients do not achieve the complete remission of symptoms, despite the effectiveness of available antidepressants.
- It is biologically plausible that ω-3 has antidepressant effects.

Considerations

- Deficiencies of ω-3 in major depression are not completely understood.
- Not all data are consistent in terms of significant benefits of ω-3 in major depression.
- ω-3, until the moment, can be used only as adjuvant treatment.

Introduction

Major depression is one of the leading causes of morbidity and mortality in adult population, whose frequency has increased in the last few decades (1). The World Health Organization estimates that major depression affects about 350 million people all over the world and reports this disorder as the major contributor to the global burden of diseases (2).

Despite the effectiveness of available antidepressants, most depressed patients do not achieve the complete remission of symptoms (3). It is continued in the investigation of factors evolved in the persistence of disorder symptoms, particularly those related to the way of life, and it has been suggested that nutritional aspects may have an influence on its development. Among them, a diet rich in ω-3 has been associated with a reduced risk of major depression (4), although

its deficiency is associated with depressive disorders (5). In this way, the poor diet quality can be a risk factor changeable of major depression, which legitimates greater attention to nutritional factors on mental health, considering that nutrition interventions are ordinarily low cost, safe, easy to administer and mostly well accepted by patients (6).

Considering the facts, with the increase in the necessity of new treatments, several clinical and pre-clinical studies have demonstrated beneficial effects of ω-3 in the treatment of major depression and other psychiatric disorders (7–11). Thus, ω-3 seems to be a good option as an additional agent in the list of treatments for humour disorders (12), enlarging the options in treating major depression (13). In this way, the objective of this revision is to provide a general view of the relationship between ω-3 polyunsaturated fatty acids and major depression, like the adequate composition of these fatty acids in diet that can prevent this disorder, and studies that evaluate the ω-3 for the treatment of major depression.

Major depression

According to the Diagnostic and Statistical Manual of Mental Disorders – DSM-IV-TR (14)– major depression is characterised by single or recurrent episodes of depressed mood and loss of interest or pleasure in almost all ordinary activities during at least 2 successive weeks. Individuals also present further symptoms that include variation in appetite or weight, sleep disturbances, variation in psychomotor activity, fatigue, decreased energy, feelings of worthlessness and guilt, recurrent thoughts of death or considering suicide, and plans or suicide attempts (14). Moreover, a major depressant episode causes pain, social or professional impairment, or even impairment in other important fields of individual life (15).

Despite well-defined symptomatology, major depression is a heterogeneous psychiatric disorder, although the pathophysiology is not clearly established (16). The first theory was based on deficiency of monoaminergic neurotransmitters, mainly noradrenaline, dopamine and serotonin (17). Another hypothesis is the pseudo-aminergetic deficiency owing to the deficiency of transduction of the signal from the monoaminergetic neurotransmitter until the postsynaptic neuron in the presence of normal quantities of neurotransmitters and receptors (17). A possible mechanism purposed as a place of failure in the transduction of the signal of monoaminergetic receptors is the target gene of brain-derived neurothrophic factor (BDNF) (17). BDNF is an apoptotic protein that stimulates the growth of serotonergic and noradrenergic signalling, as well as protects from neurotoxic damage (18). In this way, a study shows that the hippocampus capacity of inhibiting the hypothalamic–pituitary–adrenal (HPA) axis is reduced in at least one subgroup of depressed patients, who present a deficit in the function and a decrease in hippocampus volume, sustaining the hypothesis that major depression is characterised by low BDNF serum levels (18). Besides, it is known that at least half of the depressed patients have HPA axis hyperactivity and, consequently hypersecretion of cortisol (19–21). Other studies also suggest that major depression is involved in an injury of brain metabolism (22–24), where the energetic metabolism becomes diminished, especially in the level of mitochondrial dysfunction, leading to neuronal damages and cellular death (25). In this context, it is known that the oxidative phosphorylate system generates free radicals and, if provoked by them, the electron transport chain is vulnerable to damage (26). Oxidative damage induced by stress can be a cause or consequence of mitochondrial dysfunction (22,27).

Pharmacological treatments used in major depression include monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitor (28,29), atypical antidepressants (which also act potentiating the release of monoamins) (30), antidepressants which act in the glutamatergic via (31,32) and antidepressants which act in the melatoninergic via (33,34). However, despite available treatments, the flow of this disorder still demonstrates wide complexity. Mostly individuals suffering from major depression recover within a year; nevertheless, some of them do not present remission, even after 5 years or more (35).

ω-3

ω-3 is a polyunsaturated fatty-acid fundamental for the organism working and which cannot be synthetised by the body, namely, essential fatty acids (36). The main ω-3 fatty acids are the alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (37). As these fatty acids cannot be synthetised by the body, we need to obtain them from other diet sources (6,38) such as from vegetal origin, ALA, or from some species of fish, DHA and EPA (37).

ALA is found in linseed, soy, canola and nuts, and it can be metabolised in EPA and DHA by the elongase and desaturase enzyme action (38,39). However, human beings are relatively ineffective to perform this synthesis (≤6% of conversion) from ALA (40), because these enzymes are influenced by

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several aspects, such as smoking, alcohol, diabetes and aging (39), and therefore ALA cannot be converted by some people (41).

EPA and DHA ω-3 are produced by some species of fish and they are more relevant to the mental health and predominant in the brain (6,42). Fish provides variable quantities of DHA and EPA ω-3 (38). Those from marine origin, such as sardine and salmon, generally present higher quantities of DHA and EPA than fish from continental waters. It occurs because of the expressive quantities of these fatty acids in the phytoplankton, which provides their distribution along the marine food chain (39).

The central nervous system constitutes the system with major concentration of lipids in the body, after the adipose tissue (43). The lipids in the brain are formed by fatty acids, and they are part of the membrane structure, from 50% of polyunsaturated fatty acids that are in the grey substance, one of the three are from ω-3 family, and therefore they are from food source (44). The adequate composition of essential fatty acids in a diet exerts beneficial effects for brain functions, such as memory, learning, cognition and mood, and it can improve the brain performance substantially, and is considered very important for the maintenance of a good state of mental health (45,46).

ω-3 antidepressant mechanism

Lipids in the brain are rich in polyunsaturated fatty acids and they play a fundamental role in the physical properties of the neural membranes (47), and they influence several aspects in the function of the membrane, such as permeability and interaction between lipids and lipid protein (48). It is important to highlight that specific interaction between some lipids and proteins of the membrane can affect the function of receptors, enzymatic activities, signal transduction and neural membrane excitability (49). In this way, chronic deficiencies of fatty acids, particularly essential fatty acids cause changes in the lipid composition of neural membranes, visual and behaviour disturbances (50).

The composition of the biological membranes can be changed by nutritional, environmental and xenobiotic factors (48). Greatest changes in DHA concentration in the brain are obtained by deficient diets in ω-3 during the gestation (51), the early stages of prenatal development (52) and several generations submitted to deficient diets in ω-3 (53). Breastfeeding causes a significant DHA decrease in the mother's plasma (54) and this depletion can be related to the depression that affects some women in postpartum period (55).

Despite some evidence that shows that fatty-acid deficiencies can be related to reduced ingestion of ω-3 (56,57), these associations are not completely understood. For example, certain number of desaturation, enzymatic and elongation processes are necessary to metabolise longer chain fatty acids, and there is the possibility of some defect in enzymatic desaturation and elongation damage in the ideal serum or brain level of fatty acids in individuals vulnerable to affective disorders. Besides, the increase in the production of free radicals related to behaviour factors associated with the mood disorders, such as smoking, alcohol, poor sleep quality and lack of physical exercises, can reduce the availability of polyunsaturated fatty acids, despite adequate diet patterns (58).

Before this, although it is not possible to exclude the probability of major depression caused by changes in the ingestion or in ω-3 concentrations, it is likely that low concentration of ω-3, caused by abnormal metabolism or reduced ingestion, contributes to the susceptibility of major depression (59).

In this sense, it is biologically plausible that ω-3 has antidepressant effects. Several mechanisms of action explain how the two ω-3 fatty acids found in fish oil (EPA and DHA) can have antidepressant effects in human beings (59,60). These proposed mechanisms involve cellular membranes (61,62), anti-inflammatory response and neurotransmitters (60).

The evidence presented in a review conducted by Kidd (61) suggests that the fundamental base of the use of DHA and EPA in the human health is their presence in the cellular membranes. Changes in the fatty-acid composition from the neural membranes can be obtained by supplementary diets, which include marine fish oil (rich in ω-3) (48). Suominen-Taipale et al. (62) also show studies that suggest that a role to be played by ω-3 in the major depression would be through changes in the structure and function of the neuronal membrane. Increasing the unsaturation enables higher fluidity and more versatile cooperation between the membrane lipids and the proteins immersed inside this medium. This principle suggests that adequate levels of DHA and EPA in the membrane systems is crucial for survival, growing, renovation and several functions of human cells (61).

A second mechanism is supported by the fact that major depression is accompanied by an inflammatory answer of the immune system, with an increase in eicosanoids and inflammatory cytokines (63,64). Polyunsaturated fatty acids exercise important effects on inflammatory pathways: the arachidonic acid (essential fatty acid from ω-6 family) is the main precursor of eicosanoid pro-inflammatory series (65), whereas ω-3 derivate from fish oil, reduce these eicosanoids' production, acting as anti-inflammatory (66).

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ω-3 also can modulate the neurotransmitter metabolism and synaptic functions (48). ω-3 plays an important role in the synthesis, degradation, liberation and reuptake of neurotransmitters (6,45). DHA-high concentrations increase the fluidity of the membrane and improve the serotonin-receiver sensitivity (46,67). Delion et al. (68) observe reduced dopamine concentration and 5-HT2 receptor's low density, as well as the reduction of dopaminergic D2 receptors in DHA-deficient rats. Besides, in rats subjected to traumatic brain lesion, DHA-dietary supplementation increases the recovery and the production of BDNF (69).

ω-3 and major depression

It was proposed that the increase in major depression prevalence for the last 50 years could be related to changes in feeding behaviour, particularly involving the reduction of food rich in ω-3 consumption, (44) and, consequently, some studies suggest that higher ω-3 ingestion can decrease the risk of depressive disorders (70,71). Then, whether ω-3 plays an important role in depressive disorders, it will be expected in countries where people consume higher quantities of these fatty acids (mainly by fish ingestion). There will be lower major depression prevalence. This hypothesis is confirmed by some population studies that link the high consumption of fish to lower incidence of mental disorders, and this lower rate is a direct result of ω-3 ingestion (70,71).

In the same direction, there are several lines of evidence that indicate an association between ω-3 and major depression: in six case–control studies, the analysis of blood lipids have revealed low-concentration of ω-3 in major depression cases, when they were compared with the non-depressed controls (56,65,72–75), and in two cohort studies, women in postpartum depression have had low concentration of ω-3 in relation to non-depressed women (76,77).

The results of randomised and blind studies about major depression and ω-3 supplementation have shown contradictory results: some studies found an apparent antidepressant effect, with significant statistical difference among groups who have received ω-3 and those who received placebo, what showed the benefits of ω-3 as adjuvant treatment in major depression (7–9,78–81), whereas other studies have presented negative results and evident differences among the groups that were not observed (82–84).

Two blind and randomised studies have shown that addition of ω-3 in antidepressant standard treatment results in response rates to the treatment from 53% to 60% in patients with recurrent or persistent depression, whereas the placebo has produced response rates from 10% to 29% (8,9). Peet and Horrobin (9) have tested the ω-3 antidepressant effect in 70 patients with persistent depression in treatment using antidepressant (tricyclic, ISRS, among others). The patients were distributed randomly in a double-blind base with placebo or ω-3 doses of 1, 2 or 4 g/day during 12 weeks, with unchanged background medication. The dose of 1 g/day has shown better significant results when compared with placebo, with strong benefit effects on evaluation items of depression, anxiety, sleepiness, fatigue, libido and suicide ideas. Nemets et al. (8) have evaluated the addition of ω-3 (2 g/day EPA) of antidepressant therapy in use by 20 major depressed patients, and highly significant benefits in this addition were observed, when compared with placebo after the 3rd week of treatment.

Controlled trials with placebo conducted by Su et al. (78) have evaluated ω-3 supplementation (880 mg EPA + 440 mg DHA) in 28 major depression patients without changes in the medicine used. In this study, the patients of ω-3 group have had a significant decreased score in Hamilton Rating Scale for Depression (HRSD), when compared with the placebo group.

Nemets et al. (79) have conducted a randomised and double-blind study with children between 6 and 12 years old that evaluates the effects of ω-3 on childhood depression, and it has shown significant effects of ω-3 on depressant symptoms, suggesting that ω-3 fatty acids can also have therapeutic benefits in childhood depression.

Another study that has demonstrated antidepressant potential of ω-3 was carried out by Mischoulon et al. (80) and they have examined antidepressant efficacy of DHA in a double-blind study. Thirty-five depressed adult outpatients were randomised in one of the three doses (A = 1 g/day, B = 2 g/day and C = 4 g/day) during 12 weeks. The groups, A and B, have had significant decrease in HRSD, showing that DHA can be effective in lower doses such as 1 g/day.

Jazayeri et al. (81) have compared EPA and fluoxetine therapeutic effects and a combination of both in 60 major depression patients. They were randomly allocated to receive 1000 mg EPA or 20 mg fluoxetine, or a combination of both daily during 8 weeks. In this study, EPA and fluoxetine have shown equal therapeutic effects in the treatment of major depression, and the combination of both was superior of any one alone. The latest study conducted by Gertsik et al. (7) has explored the efficacy of the combination therapy between citalopram and ω-3, comparing the citalopram associated with placebo in the initial treatment of 42 individuals with major depression, and it was

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verified that the combined therapy was more effective than monotherapy in the decrease in depression symptoms during the 8 weeks of active treatment. These studies have shown the combination between ω-3 and a selective inhibitor of serotonin reuptake in the treatment of patients with major depression.

However, not all data are consistent in terms of ω-3 significant benefits in major depression. Marangell et al. (82) have evaluated 36 depressed patients distributed randomly to receive 2 g/day of DHA or placebo during 6 weeks. Response rates are 27.8% in the DHA group and 23.5% in the placebo group. The difference in answer rates between the groups has not achieved significant statistical differences. Besides, a randomised trial conducted by Silvers et al. (83) using ω-3 as adjuvant treatment in 77 patients also has not shown any difference when compared with the placebo. However, the mood was significantly improved in both groups in the 2 early weeks of study ($p < 0.001$), and this improvement was maintained. Rogers et al. (84) have conducted a randomised double-blind and controlled study to evaluate the effects of DHA + EPA (1.5 g/day) supplementation upon the mood and the cognitive function in 190 mild to moderately depressed individuals, who were not using antidepressant medication. It did not find any benefit or prejudicial effects from ω-3 on the mood in mild to moderate depression.

Contradictory results were also observed in articles in which ω-3 was considered ωfor the treatment of major depression in women during pregnancy and postpartum, known as perinatal depression. Llorente et al. (85) have evaluated 138 healthy women who received DHA (200 mg/day) or placebo during 4 months, beginning at postpartum and they have not found any difference depression rates between the groups after the supplementation period. It was observed that ω-3 supplementation was only initiated postpartum, and perhaps it later resulted in the prevention of postpartum depression. Marangell et al. (86) have reported that supplementation with fish oil (EPA and DHA combination – 2.96 g/day), beginning between 34 and 36 weeks of pregnancy did not avoid, as the monotherapy, the occurrence of postpartum depression in women with previous history of postpartum depression in previous pregnancy. They have observed depressed episodes in four of the seven women evaluated.

Freeman et al. (87,88) published two studies in 2006 using the ω-3 as an intervention for perinatal depression. The first study (87) has used an EPA and DHA combination for the treatment of depression in 15 women during the pregnancy. The decrease rate, according to the Edinburgh Postnatal Depression Scale, was 40.9%. For women who have completed at least 8 weeks in the study, the decrease rate in the base line on that scale was 49.2%. In the second study (88), ω-3 efficiency has been evaluated for postpartum depression with randomised subjects for daily doses of EPA and DHA combination in 0.5 g/day ($n = 6$), 1.4 g/day ($n = 3$), or 2.8 g/day ($n = 7$). In that study, significant differences between the groups of dosage were not observed; however, all the individuals have shown significant improvement. ω-3 supplementation has presented well tolerance in both studies. In this way, these results support other studies on ω-3 as treatment for perinatal depression.

In a review, Deligiannidis and Freeman (13) have also shown that some studies on ω-3 suggest this attractive alternative for women with major depression during pregnancy and in the postpartum period, owing to the low risks and the benefits for mental health. In a cross-sectional study, Hibbeln (89) has reported that the per capita consumption of sea food was associated inversely with depressant symptoms in the postpartum period of participants in the study. Besides, in a cohort study, Golding et al. (90) have reported that higher ω-3 consumption levels during pregnancy were associated with the lower incidence of depressant symptoms during pregnancy, and in all the postpartum years.

Recent studies have also shown that ω-3 can be a good alternative for depressant symptoms treatment in the elderly (91,92). A controlled trial with placebo carried out by Rondanelli et al. (91), in which 46 elderly women received ω-3 or placebo 2.5 g/day during 8 weeks, ω-3 supplementation showed effective improvement in depressant symptoms and in health quality. Another controlled trial with placebo conducted by Tajalizadekhoob et al. (92) has evaluated 1 g/day oil fish supplementation containing EPA and DHA or placebo in 66 elderly patients during 6 months; four participants of the fish oil group and seven of the placebo group were using antidepressant drugs (tricyclic or ISRS). In this study, the treatment with ω-3 also was clinically more effective in the treatment of mild to moderate depression when compared with placebo.

Besides, a recent body of evidence has showed relative fatty-acid deficiency in the peripheral membrane in people with affective disorders, such as unipolar and bipolar depression. Studies conducted by Conklin et al. (58) have investigated whether there was any variation in fatty acids from the postmortem brain tissue (anterior cingulate cortex) according to the presence of major depression at the moment of death, and it was observed that, compared with the control group, the depressed group revealed low

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significant concentration of several saturated and polyunsaturated fatty acids, including ω-3 and ω-6. This discovery is consistent with the proposal that fatty-acid concentrations in the brain tissue can be an important factor of influence in psychiatric symptomatology. McNamara et al. (93) also have performed postmortem analysis of fatty acids in the brain tissue and have demonstrated, in the same way, a decrease in ω-3 in the orbitofrontal cortex in major depressed patients.

In conclusion, several studies have demonstrated beneficial effects of ω-3 in major depression prevention and treatment, but not all the results have shown significant statistical benefits. Thus, more studies are necessary to clarify the detailed mechanisms of ω-3 antidepressant effects, and may explain the source of contradictions in results published until the moment, which may provide a new therapeutic strategy for patients who do not respond to existing treatments.

Authors' Contributions

Aline H. Mello and Gislaine T. Rezin: (2) drafting the article or critical review by important intellectual content. Aline Gassenferth and Luana R. Souza: (1) substantial contributions for data acquisition. Gislaine T. Rezin and Jucélia J. Fortunato: (3) approval of the final version for publication.

Conflicts of Interest

None of the authors or funding sources has conflicts of interest.

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