



Photo: Adobe Stock/nenetus



## Omega-3 fatty acids as an alternative and complementary therapy option in depression

Philipp Gebhardt, Dr. med. Frank Ingwersen

**Depression is a mental disorder characterized by symptoms such as depressed mood, increased pondering and drive reduction. A corresponding symptomatology can also be caused by inflammatory processes and the thereby effective cytokines (peptide hormones). Because of their anti-inflammatory effects, omega-3 fatty acids are being studied as an alternative and complementary therapy option in depression. Studies in clinical settings could show significant antidepressant effects.**

Depression often goes along with additional physical ailments that affect the entire life of depressive people so that they do not or only rarely succeed in coping with everyday tasks. Due to self-doubt, difficulty in concentrating and loss of interest, the affected are often impaired in their self-esteem and well-being. The consequence is a social retreat, which is associated with a high level of suffering. Even in healthy people, e.g. in the context of the experience of the loss of a beloved person, complaints occur that do not differ in their appearance from a depression and usually pass by on their own. An illness is

present when the symptoms last disproportionately long or in severity and duration in an inappropriate relationship to the symptom-triggering factors. The prevalence of depression in Germany is assumed to be around 8.1 %; around 10.2 % for women and around 6.1 % for men (Fig. 1). [1]

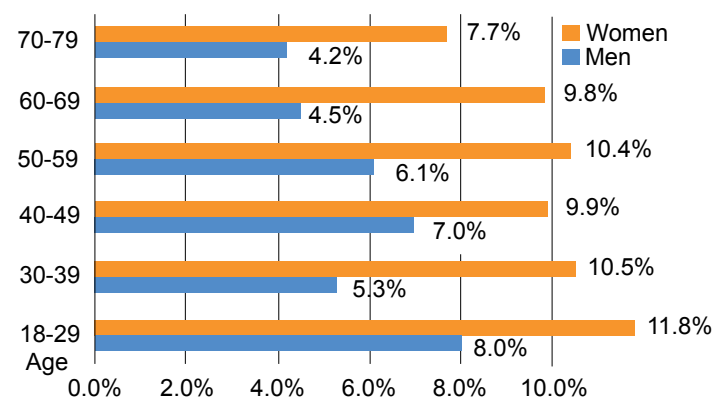


Fig. 1: Prevalence of depression in Germany in different age groups (Data from DEGS1, Robert Koch-Institut (2013), [1])

Although the causes of depressive illnesses are complex, it is assumed that the neurotransmitters serotonin, dopamine and norepinephrine are critically involved in the pathogenesis. Pharmacotherapies that affect the metabolism of the neurotransmitters can influence appropriate symptoms in a positive way. Because about one third of the patients do not respond adequately or insufficiently to these medications, it cannot be conclusively clarified to what extent the transmitter systems are causally involved in the aetiology. [2] According to the current state of knowledge, inflammatory processes and the involved cytokines also play a significant role in the development of depression. In the case of depressive people elevated levels of certain inflammatory markers can be measured and proinflammatory cytokines have been shown to be able to cause the underlying symptoms. [3]

### Omega-3 Fatty acids

The emergence of an inflammatory metabolic state is attributed in a significant proportion to a high dietary intake of omega-6 fatty acids. According to scientific research, around 10,000 years ago, before the start of agriculture, approximately equal amounts of omega-6 and omega-3 fatty acids were present in human diet. With the industrialization of livestock, the availability of omega-3 fatty acids has been further limited, since today's feed of farm animals is mostly based

on cereals and provides a significantly higher proportion of omega-6 fatty acids than the natural, green-based food. A high omega-6-to-omega-3 ratio thus promotes inflammatory processes and is associated with the development of chronic degenerative diseases (Fig. 2). [4]

Both omega-6 and omega-3 fatty acids are unsaturated fatty acids, which differ in that the last double bond in the carbon chain is found in the sixth-to-last ("ω-6") and third-to-last ("ω-3") carbon-carbon bond, respectively. Dietary fatty acids are either metabolized for energy production, incorporated into cell membranes, or used to synthesize various tissue hormones. Omega-6 fatty acids are converted by certain enzymes via arachidonic acid into predominantly pro-inflammatory signalling molecules (series II prostaglandins). The enzymes that synthesize arachidonic acid from omega-6 fatty acids are also involved in the synthesis of the essential fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from the omega-3 fatty acid α-linolenic acid. A higher proportion of α-linolenic acid in the diet is advantageous because the responsible enzyme system subsequently produces less arachidonic acid and increasing amounts of EPA and DHA.

EPA and DHA are directly contained in fish oils ("marine omega-3 fatty acids"), but can also be produced from certain algae. Since the conversion rates for EPA and DHA from α-linolenic acid are estimated to be low, an additional supply is recommended. The marine omega-3 fatty acids are being studied for their positive health effects in clinical settings. In a guideline published in September 2019, fish oil was recommended by the American Heart Association (AHA) for the treatment of hypertriglyceridemia. According to data from a total of 17 studies, it is estimated that elevated triglyceride levels (200-499 mg/dl) can be reduced by 20-30% by taking 4 g of EPA and DHA daily. For strongly elevated triglyceride levels (≥ 500 mg/dl) a reduction of more than 30% is possible. [5]

In the context of cardiovascular disease, the supplementation of omega-3 fatty acids is associated with a reduced risk of arrhythmias and thrombosis and can reduce atherosclerotic vascular changes in a verifiable manner. EPA and DHA have been shown to improve endothelial function, to reduce high blood pressure and to affect inflammatory processes in a favourable way. Among other things, improvements in serotonin activity, modulation of dopamine function and a positive influence on cerebral blood flow could be highlighted in regard to mental disorders. [6]

### EPA and DHA in depression

Various studies could confirm that the omega-3 fatty acids EPA and DHA are significantly effective in depression (Fig. 3). The antidepressant effect seems to be dependent on which of the omega-3 fatty acids or in which ratio they are supplemented. Unsaturated fatty acids form a quantitatively relevant component of the brain. Accordingly, lipids constitute about 50-60% of the dry weight of the brain

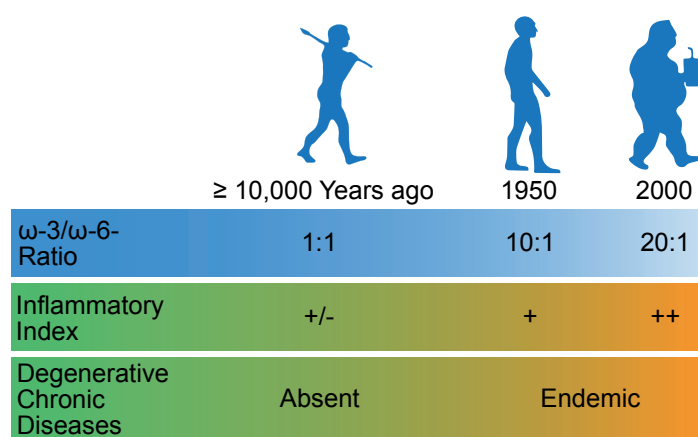


Fig. 2: It is thought that prior to the onset of agriculture, omega-6 and omega-3 fatty acids were contained in a balanced relationship in human diet. Modern diet usually provides considerably high quantities of omega-6 fatty acids and only little amounts of omega-3 fatty acids. A high omega-6-to-omega-3 ratio favours inflammatory processes and has been shown to be linked to the development of chronic degenerative diseases. [4]

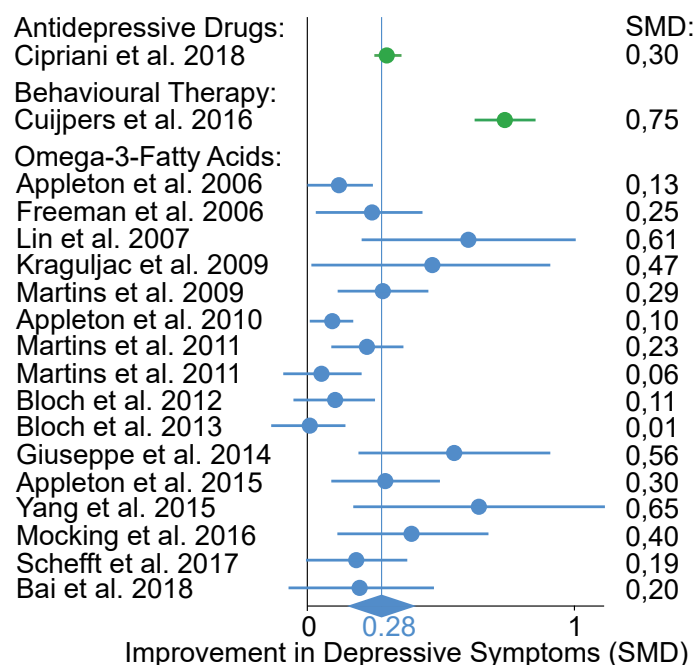


Fig. 3: Review of the efficacy of omega-3 fatty acids in depression from reviews, compared to pharmacotherapy and behavioural therapy, presented as Standard Mean Difference (SMD). [7]

tissue, with DHA accounting for 25 %. [8] Compared to DHA, EPA is only detectable in the brain in very low concentrations. Supplied EPA is therefore rapidly metabolized and affects the action of different signal molecules in the brain. [9] Compared to DHA, EPA causes a more pronounced inhibition of arachidonic acid-associated inflammatory processes. Increased EPA concentrations lead to a reduced synthesis of pro-inflammatory prostaglandins. A supplementation with omega-3 fatty acids containing a high proportion of EPA shows a clearer antidepressant effect in clinical trials. A proportion of  $\geq 60\%$  EPA thus seems to favour a therapeutic efficacy. When looking at the results of studies using either pure EPA or supplements with a corresponding omega-3 fatty acid ratio, a more pronounced effect is visible

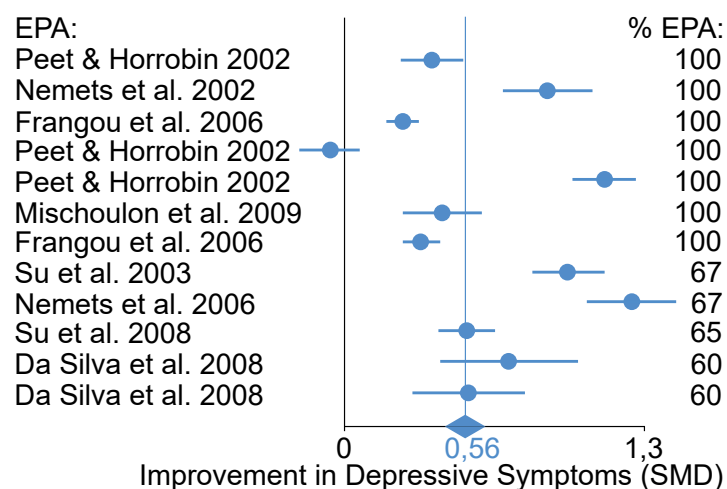


Fig. 4: Assessment of the efficacy of omega-3 fatty acids with increased EPA levels in depression, presented as Standard Mean Difference (SMD). [10]

(Fig. 4). [9, 10, 11] Effective doses appear to be in the range of 500 mg to 4000 mg, with an optimum of action assumed to be in the range of 2000 mg EPA [10].

### EPA as a complementary therapy option

It could also be shown that the omega-3 fatty acid EPA can improve the efficacy of antidepressant pharmacotherapies [12]. In appropriate investigations, the so-called Hamilton scale is usually used to estimate the severity of symptoms. This scale is a standardized questionnaire in which a higher score indicates a more pronounced expression of symptoms. In a randomized, double-blind

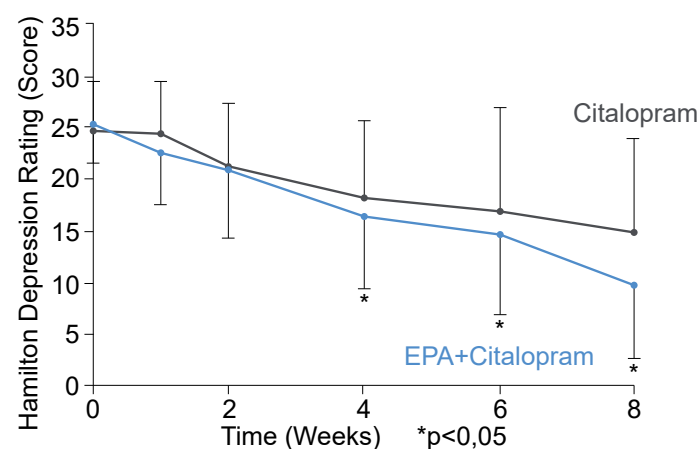


Fig. 5: Antidepressant effect of the selective serotonin reuptake inhibitor citalopram in comparison to the complementary application together with the omega-3 fatty acid EPA. [13]

study, 40 participants rated as “moderately severe depressed” on the Hamilton scale received either 20 mg of the selective serotonin reuptake inhibitor citalopram and a placebo or 20 mg of citalopram 20 mg and a supplement containing 540 mg of EPA and 100 mg DHA, daily. The complementary therapy resulted in a clearer improvement of symptoms, which reached a significant level after four weeks (Fig. 5). [13]

### Conclusion

Symptoms of depression can also be caused by deficiencies of certain micronutrients such as folate and vitamin B12 [14]. In the presence of appropriate symptoms,

a micronutrient deficiency should therefore be excluded as a causative factor. For this purpose, the homocysteine level in the serum can be determined (as an indicator of deficiency of folate, vitamin B6, and B12) and vitamin D. A clear antidepressant effect of the omega-3 fatty acid EPA, or a combination of EPA and DHA with an EPA content of  $\geq 60\%$  could be highlighted in several clinical studies. Supplementation of the omega-3 fatty acids therefore offers a side effect-free alternative to conventional pharmacotherapy. It has also been shown that EPA can improve the effect of antidepressant

medications. People with depression can also benefit from psychotherapy. In addition to gaining insight and learning coping strategies for problems, these therapies can help restore a positive self-image. Therefore, if appropriate symptoms occur, a physician or psychiatrist should be consulted, who can determine the above mentioned laboratory values and does not only treat with pharmaceutical drug substances. In addition, it may be useful to consult a psychotherapist. Ideally, the supplementation of micronutrients already leads to a significant improvement in symptoms.

## References

- [1] Busch, M., Maske, U., Ryl, L., et al. (2013). Prevalence of depressive symptoms and diagnosed depression among adults in Germany.
- [2] Hamon, M., & Blier, P. (2013). Monoamine neurocircuitry in depression and strategies for new treatments. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 45, 54-63.
- [3] Sublette, M. E., Ellis, S. P., Geant, A. L., & Mann, J. J. (2011). Meta-analysis: effects of eicosapentaenoic acid in clinical trials in depression. *The Journal of clinical psychiatry*, 72(12), 1577.
- [4] Singh, R. B., Takahashi, T., Nakaoka, T., Otsuka, K., Toda, E., Shin, H. H., ... & Pella, D. (2013). Nutrition in transition from Homo sapiens to Homo economicus. *HOMO*, 18, 21.
- [5] Skulas-Ray, A. C., Wilson, P. W., Harris, W. S., et al. (2019). Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. *Circulation*, 140(12), e673-e691.
- [6] Freeman, M. P., Hibbeln, J. R., Wisner, K. L., Davis, J. M., Mischoulon, D., Peet, M., ... & Stoll, A. L. (2006). Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *Journal of Clinical Psychiatry*, 67(12), 1954.
- [7] Nasir, M., & Bloch, M. H. (2019). Trim the fat: the role of omega-3 fatty acids in psychopharmacology. *Therapeutic advances in psychopharmacology*, 9, 2045125319869791.
- [8] Valenzuela, A., Sanhueza, B. J., & Nieto, S. (2006). Docosahexaenoic acid (DHA), essentiality and requirements: why and how to provide supplementation. *Grasas y aceites*, 57(2), 229-237.
- [9] Bazinet, R. P., Metherell, A. H., Chen, C. T., Shaikh, S. R., Nadjar, A., Joffe, C., & Layé, S. (2019). Brain eicosapentaenoic acid metabolism as a lead for novel therapeutics in major depression. *Brain, behavior, and immunity*.
- [10] Sublette, M. E., Ellis, S. P., Geant, A. L., & Mann, J. J. (2011). Meta-analysis: effects of eicosapentaenoic acid in clinical trials in depression. *The Journal of clinical psychiatry*, 72(12), 1577.
- [11] Martins, J. G. (2009). EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *Journal of the American College of Nutrition*, 28(5), 525-542.
- [12] Jazayeri, S., Tehrani-Doost, M., Keshavarz, S. A., et al. (2008). Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Australian & New Zealand Journal of Psychiatry*, 42(3), 192-198.
- [13] Gertsik, L., Poland, R. E., Bressee, C., & Rapaport, M. H. (2012). Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. *Journal of clinical psychopharmacology*, 32(1), 61.
- [14] Coppen, A., & Bolander-Gouaille, C. (2005). Treatment of depression: time to consider folic acid and vitamin B12. *Journal of Psychopharmacology*, 19(1), 59-65.

## For more information, please contact

Philipp Gebhardt  
65779 Kelkheim  
p.gebhardt@mitotherapie.de

Dr. med. Frank Ingwersen  
25885 Ahrenviöl  
www.institut-ahrnfolde.de  
www.dr-ingwersen-gmbh.de  
info@dr-ingwersen-gmbh.de



**ESI NUTRITION** SPECIALIZES  
IN THE **DEVELOPMENT,**  
**INDUSTRIALIZATION AND**  
**MANUFACTURING OF**  
**TAILOR MADE**  
**NUTRITIONAL PRODUCTS.**



 **OPTIMIZED  
TRACEABILITY**

 **GMP  
APPROACH**

 **PRODUCT  
SAFETY**

 **ENVIRONMENTAL  
PROTECTION**

[www.esi-nutrition.com](http://www.esi-nutrition.com)

