Psychother Psychosom 2020;89:48
DOI: 10.1159/000504100

Response to “International Society for Nutritional Psychiatry Research Practice Guidelines for Omega-3 Fatty Acids in the Treatment of Major Depressive Disorder” by Guu et al. (2019)

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The International Society for Nutritional Psychiatry Research (ISNPR) recently published clinical guidelines for the use of omega-3 fatty acids (n-3 PUFAs) in the treatment of major depressive disorder (MDD) in this journal [1]. We praise the authors for their effort to distill clear clinical indications from complex and heterogeneous research findings. Overall, these guidelines help bringing clarity on a highly debated field – the use of nutritional supplementation in psychiatry – in which patients and clinicians were until now left without any evidence-based guidance. Nevertheless, we would like to ask for caution on a specific recommendation. The expert panel states that “n-3 PUFAs could be recommended as a potential prophylactic treatment for high-risk populations (alongside standard medical care).” We believe that the limited evidence currently available does not support such recommendation.

Few longitudinal studies in initially non-depressed subjects provide conflicting findings: while n-3 PUFA dietary intake estimated from food-frequency questionnaires was associated with lower risk of subsequent development of MDD or clinically relevant symptoms [2], no association was found for measured n-3 PUFA blood concentrations [3]. Nevertheless, risk estimates from observational studies in nutritional epidemiology are biased by residual confounding and reverse causation [4]. Methodologically robust studies allowing to properly estimate causal effects also do not support a role of n-3 PUFAs on the risk or depression onset. The EU-funded MoodFOOD trial [5] examined the effectiveness of multi-nutrient supplementation (including n-3 PUFAs) to prevent depression over 1 year in 1,025 overweight individuals with elevated depressive symptoms. Supplementation (vs. placebo) did not prevent the 1-year onset of MDD nor had it a beneficial impact on the 1-year course of symptoms. More recently, a study [6] applied Mendelian randomization analyses – inferring causal rela-

tionship between modifiable risk factors and disease using genetic variants as natural experiment – on data from ~500,000 subjects. Findings provided no evidence of a causal role of n-3 PUFA on the risk of MDD onset. In their review of the literature, the authors of the guidelines mentioned only one prevention trial [7] on a highly specific sample of 152 subjects with chronic hepatitis C, showing an effect of n-3 PUFAs versus placebo in the prevention of major depressive episodes induced by interferon-alpha treatment.

All in all, we feel the clinical significance of preventive n-3 PUFA supplementation for MDD is not supported by adequate empirical evidence. In prevention efforts, premature translation of inadequate evidence may result in waste of resources and time, at the cost of research on more strongly grounded interventions; this risk is certainly present in this case. We agree with the ISNPR panel’s suggestion on the need of “well-designed randomized controlled trials with larger sample sizes and longer duration to confirm the (preventive) efficacy of n-3 PUFAs.” Until these studies become available, the recommendation on the use of n-3 PUFAs as prophylactic treatment should be reconsidered.

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