Review Article

Polyunsaturated fatty acids in emerging psychosis: a safer alternative?

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Abstract

Aim: A promising approach of indicated prevention in individuals at increased risk of psychosis was based on the finding of potential neuroprotective properties of omega-3 polyunsaturated fatty acids (PUFAs). Considering the rising interest in omega-3 PUFA supplementation as preventive treatment strategy in young people at risk of psychosis, the question of safety issues must be addressed.

Methods: For this systematic review, a literature search for studies on omega-3 PUFAs for emerging psychosis with a focus on the safety profile was undertaken. Because limited data are available, information regarding potential side effects of omega-3 PUFAs was additionally derived from currently available data in psychotic disorders at different stages of the illness. Furthermore, helpful evidence from somatic disorders and healthy controls was used.

Results: In terms of safety issues, evidence from the randomized controlled trial in ultra-high-risk individuals and a variety of studies in schizophrenia patients strongly suggests that omega-3 PUFAs are safe and well tolerated even when used in relatively high doses. Most commonly occurring but clinically rarely significant are mild gastrointestinal symptoms; similarly, the slight risk of prolonged bleeding time has not been shown to be clinically relevant. Differential effects on metabolic parameters, most of which appear beneficial, have been reported.

Conclusions: Taken together, one promising aspect of omega-3 PUFAs is that there seem to be no reports of relevant deleterious side effects in humans, even at high doses. The differential effects on lipid parameters and bleeding time are noteworthy and need further clarification.

Key words: adverse effect, polyunsaturated fatty acid (PUFA), psychotic disorder, safety, ultra-high risk (UHR).

INTRODUCTION

Early intervention in schizophrenia and other psychoses is suggested to being associated with improved outcome.[1] Psychotic disorders are usually characterized by a prodromal period that precedes the onset of full-blown psychotic symptoms. Over the last 15 years, criteria have been introduced in the hope to prospectively identify individuals at 'ultra-high risk' for developing a psychotic disorder.[2–4] This approach has been variably termed as ultra-high risk (UHR), at-risk mental state or clinical high risk (CHR).[5] This putatively prodromal psychotic phase is associated with an enhanced risk of developing the illness as compared to the general population (1%), ranging from 18% after 6 months to 36% after 3 years.[6] The majority (70) of the individuals developing a psychotic illness will transit towards a schizophrenia spectrum disorder.[7] The CHR state for psychosis is also characterized by significant cognitive impairments,[8] deficits in social functioning[9] and high prevalence of co-morbid disorders.[10] These alterations are associated with underlying neurobiological abnormalities in the structure,[11–13] function,[14–16] connectivity[17] and neurochemistry[18–20] of the brain, which are not

confounded by the effect of medications.[21] Interest in this area has exponentially grown to the extent that a new diagnostic research category is being discussed in the appendix of the forthcoming Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).[22]

This phase is a potential target for early intervention strategies. Initial early intervention strategies in UHR individuals were based on existing treatment concepts for manifest psychosis with the aim of delaying or preventing full-blown psychotic disorder,[23] such as low-dose antipsychotic medication with or without cognitive therapy.[24,25] Albeit the efficacy of these strategies on a symptomatic level, effects were not ongoing after the end of the intervention. As a matter of fact, meta-analytical data provide evidence that indicated prevention based on low-dose antipsychotics showed no significant benefit over non-pharmacological treatment which are nowadays recommended as first-line therapies.[23] Furthermore, the potential risk of side effects of antipsychotic medication and the dropping conversion rates to full-blown psychosis reported in UHR population treated in early intervention centres in the last years[26] underlines the necessity for more 'benign' intervention strategies with respect to efficacy and side effects. A recent meta-analysis[27] reported efficacy for cognitive behavioural therapy on reducing the risk of transition to psychosis during a period of 12 months (risk ratio 0.54) versus standard treatment. Most recently, a trial of indicated prevention in UHR population based on the concept of potential neuroprotective properties of omega-3 polyunsaturated fatty acids (PUFAs) has yielded promising results.[28] Treatment with omega-3 PUFAs is presumed to be safe because of the widespread belief that naturally occurring products are safe to consume. However, with increasing interest in omega-3 PUFAs in emerging psychosis, the question of safety issues needs to be addressed in more detail.

This systematic review aims at evaluating the existing data on this question.

METHODS

This systematic review is based on the literature on omega-3 PUFAs in emerging psychosis with a special focus on the safety profile. Because limited data are available on omega-3 PUFAs for emerging psychosis (i.e. currently only one published trial), information regarding the safety profile was additionally derived from data on the use of omega-3 PUFAs at different stages of psychotic illnesses (first-episode psychosis (FEP), schizophrenia). Beyond that, helpful evidence from somatic disorders and healthy controls was used where deemed necessary. It was presumed that conclusions on side effect profiles derived from studies in psychosis, somatic illness and the general population might, at least to some extent, be applicable to patients with emerging psychosis.

Relevant studies reporting on safety issues on omega-3 PUFAs in emerging psychosis were identified through a literature search in the PubMed electronic database. The following search terms were used: 'Psychosis' OR 'Psychotic disorder' AND 'Omega-3 fatty acids' OR 'Omega-3' OR 'Fatty acids' AND 'Safety'. The search cut-off date was the last day of March 2013. Criteria for inclusion in this review were: (i) publication of full text available; (ii) safety issues of omega-3 fatty acid treatment in emerging psychosis; and (iii) randomized controlled trials (RCTs). Keywords and application of inclusion criteria resulted in three papers (only one paper fitted the criteria concerning the safety profile of omega-3 PUFAs for emerging psychosis based on a RCT,[28] the two others being reviews). Additionally, a second search was performed using the terms 'Psychosis' OR 'Psychotic disorder' AND 'Omega-3 fatty acids' OR 'Omega 3' OR 'Fatty acids' AND 'Side effects' (15 articles, 7 of which being reviews, 1 case report, 7 intervention studies, 4 of these providing additional information regarding side effects of treatment with omega-3 fatty acids in manifest psychosis).[29–32] Furthermore, seven studies were identified by reviewing the references of relevant studies (three RCTs in manifest psychosis,[33–35] one in FEP[33] and three open-label trials in manifest psychosis).[36–38] Combined search resulted in 12 papers, see flow diagram (Fig. 1). The findings are presented as a narrative summary.

Physiological Role of PUFAs

PUFAs are the main components of cell membrane phospholipids and are involved in different important biological roles such as receptor binding; dopaminergic, serotonergic and glutamatergic neurotransmission;[39–41] signal transduction; and eicosanoid synthesis. PUFAs can be divided into omega-3 and omega-6 fatty acids. Humans are not able to implement double bounds between the ninth carbon atom making the parent molecules of the omega-3 and omega-6 fatty acid family alpha-linolenic acid (ALA, 18:3n-3) and linoleic acid (LA, 18:2n-6), respectively, *essential* fatty acids. Furthermore, the body-owned enzymatic conversion from LA and ALA to important long-chain PUFAs (LC-PUFAs), such as arachidonic acid

FIGURE 1. Flow diagram of study selection.
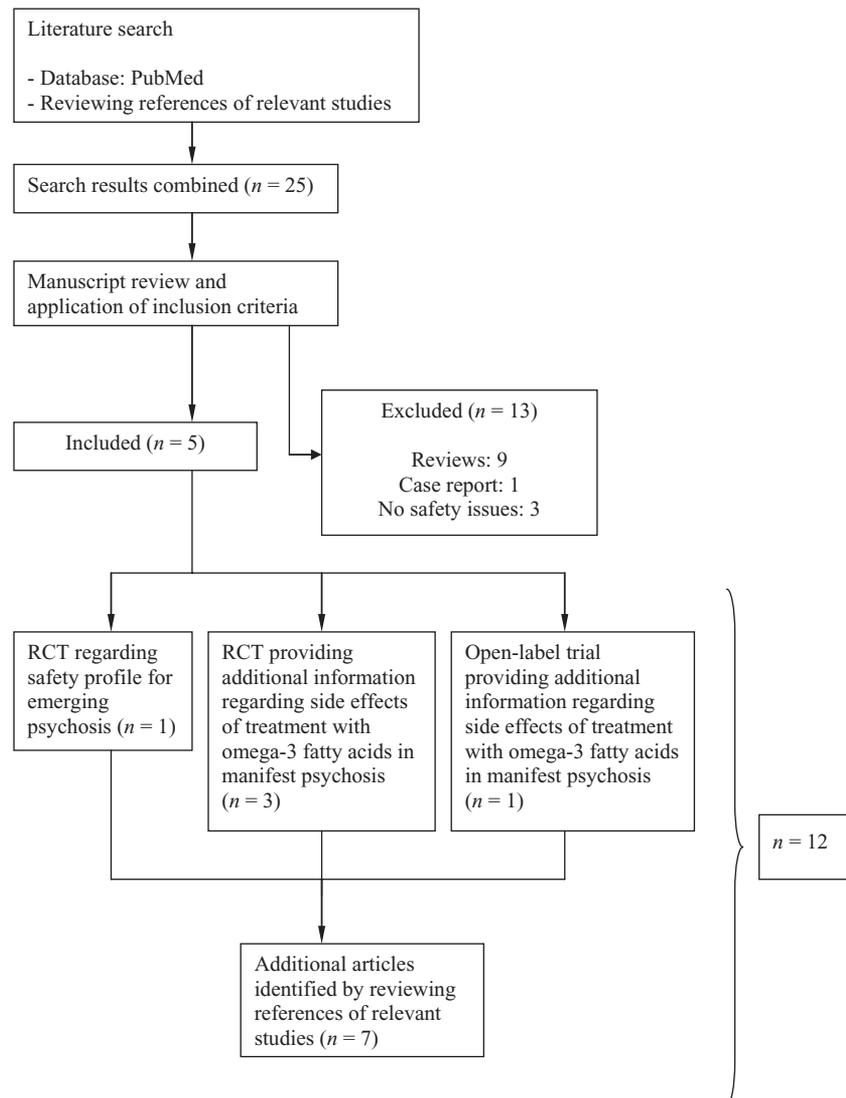
(20:4*n*-6), eicosapentaenoic acid (EPA, 20:5*n*-3) and docosahexaenoic acid (DHA, 22:5*n*-3), is probably insufficient.[42] Therefore, these fatty acids need to be consumed via dietary products (e.g. fish, meat, eggs). Notably, the ratio of omega-6 to omega-3 PUFAs in wild-caught fish and products from grass-fed, free-range animals is more in favour of omega-3 PUFAs as compared to grain-fed animals. Converging evidence from epidemiological, clinical and laboratory studies clearly indicates that metabolism of omega-3 and omega-6 PUFA is deregulated in psychosis.[41–43]

PUFAs in the treatment of psychotic disorders and emerging psychosis

Based on findings that in individuals with schizophrenia or related psychotic disorders certain omega-3 and omega-6 PUFA levels are reduced,[44] the idea that restoration of PUFA resources could be used as treatment option in psychotic disorders has been widely discussed. Although a growing number of studies have focused primarily on the efficacy of omega-3 PUFAs as add-on treatment in schizophrenia, FEP and, recently, in UHR, scant attention has yet been paid to their safety and tolerability. Eight trials, heterogeneous with respect to study design, illness stage, dose of LC-PUFA (range from 1 to 4 g per day in controlled studies and from 600 mg per day to 10 g per day in open studies) and the active ingredient (EPA, DHA, EPA/DHA, E-EPA), have shown inconsistent effects[31,33,35] (see Table 1). With respect to the primary outcome measure 'improvement of psychopathology', five of the eight available studies reported an improvement of psychotic

TABLE 1. Studies with omega-3 fatty acids in patients with emerging or manifest psychosis and/or schizophrenia spectrum disorders and adverse effects

Author, year	Study design	Population	Groups	Primary outcome	Secondary outcome	Adverse effects
Emerging psychosis						
Amminger et al. 2010[28]	3 months Parallel RCT DB Pb controlled	Patients with UHR for psychosis	Indicated prevention; 1,2 g per day EPA/DHA (n = 41) versus coconut oil pb (n = 40)	Transition to psychotic disorder: 2/41 (4,9%) in EPA/DHA and 11/40 (27,5%) pb	EPA/DHA group: PANSS ↓ and GAF ↑	No significant adverse effects between EPA/DHA versus pb Assessment: UKU
Manifest psychosis						
Peet et al. 2001[33]	3 months Parallel RCT DB Pb controlled	Patients with schizophrenia (first episode and chronic)	Mono; 2 g per day EPA (n = 15) versus corn oil pb (n = 15)	EPA group: required antipsychotic medication ↓	EPA group: PANSS total and positive ↓ than pb	No adverse effects attributable to EPA Assessment: patient report
Berger et al. 2007[30]	3 months Parallel RCT DB Pb controlled	Patients with acute FEP	Add-on; 2 g per day E-EPA (n = 35) versus liquid paraffin pb (n = 34)	NS differences at month 3 between groups (BPRS, SANS, CGI, GAF, SOFAS); EPA group: AP ↓ in first 6 weeks	EPA group: EPS ↓ in initial 9 weeks of constipation and sexual side effects ↓	No significant adverse effects between EPA versus pb Assessment: UKU
Peet et al. 2001[33]	3 months Parallel RCT DB Pb controlled	Patients with schizophrenia (chronic)	Add-on; 2 g per day EPA (n = 15) versus 2 g per day DHA-enriched oil (n = 16) versus corn oil pb (n = 14)	EPA group: PANSS total and positive ↓ than pb (EPA over DHA on positive PANSS)		No clinically relevant adverse effects attributable to EPA Mild adverse effects: nausea, irritable bowel, indigestion Assessment: patient report
Fenton et al. 2001[31]	4 months Parallel RCT DB Pb controlled	Patients with schizophrenia or schizoaffective disorder	Add-on; 3 g per day E-EPA (n = 43) versus mineral oil pb (n = 44)	NS differences at month 4 between groups (PANSS, MADRS, CGI)	NS effects for cognitive impairment, EPS or TD	Upper respiratory infection/diarrhoea occurred >5% in EPA Assessment: patient report
Emsley et al. 2002[35]	3 months Parallel RCT DB Pb controlled	Patients with chronic/severe schizophrenia	Add-on; 3 g per day E-EPA (n = 20) versus liquid paraffin pb (n = 20)	E-EPA group: PANSS total ↓ at month 3	E-EPA group: dyskinesia ↓ at month 3	No adverse effects attributable to EPA Assessment: no information
Peet & Horrobin 2002[34]	3 months RCT	Patients with schizophrenia	Add-on; 1 g per day E-EPA (n = 32) versus 2 g per day E-EPA (n = 32) versus 4 g per day E-EPA (n = 27) versus liquid paraffin pb (n = 31)	NS differences at all doses EPA versus pb; 2 g per day greatest change in PANSS total and global; clozapine-treated patients benefit most	E-EPA group (2 and 4 g per day): triglyceride levels ↓; no differences between groups in LUNSERS, AIMS, BAS and SAS	No significant adverse effects between EPA versus pb. Mild adverse effects: diarrhoea and nausea Assessment: LUNSERS, AIMS, SAS

Study	Design/Duration	Population	Intervention	Efficacy	Other results	Adverse effects/Assessment
Emsley et al. 2008[29]	12 weeks Parallel RCT DB Pb controlled + 40-week open-label phase	Patients with schizophrenia or schizoaffective disorder	Add-on; 2 g per day E-EPA (n = 39) versus liquid paraffin pb (n = 33) + add-on; open label: 2 g per day E-EPA (n = 47)	No information	No information	E-EPA(RCT): BMI ↑; bleeding time ↑ versus pb E-EPA (open label): BMI ↑; fasting blood glucose ↑; cholesterol ↓; HDL ↓ Mild adverse effects: diarrhoea, nausea, constipation, NS. versus pb Assessment: physical examination, laboratory tests, patient report
Arvindakshan et al. 2003[37]	4 months	Patients with schizophrenia	Add-on; 600 mg EPA/DHA + vitamins E/C (n = 33) versus NC (n = 45)	EPA/DHA group: BPRS, PANSS total and general ↓; QOL ↑		No adverse effects attributable to EPA/DHA Assessment: no information
Caniato et al. 2006[32]	4 weeks	Patients with schizophrenia or schizoaffective disorder	Add-on; 3 g per day EPA/DHA (n = 28)	No information	Triglyceride levels ↓; total cholesterol ↑; LDL ↑; VLDL ↓	Fishy burps/fishy breath (43%); diarrhoea (n = 2); flatulence (n = 1); nausea (n = 1) Assessment: feedback questionnaire
Mellor et al. 1995[36]	6 weeks	Patients with schizophrenia (chronic)	Add-on; 10 g per day MaxEPA (n = 20)	PANSS ↓	Dyskinesia ↓	No information
Sivrioglu et al. 2007[38]	4 months	Patients with schizophrenia	Add-on; 1 g per day omega-3 fatty acids + vitamins E and C (n = 17)	BPRS, SANS ↓	SAS and BARS ↓	No information

AA, arachidonic acid; AIMS, Abnormal Involuntary Movement Scale; AP, antipsychotics; BAS, Barnes Akathisia Scale; BPRS, Brief Psychiatric Rating Scale; CGI, clinical global impression; DB, double blind; DHA, docosahexaonic acid; E-EPA, ethyl-eicosapentaenoic acid; EPA, eicosapentaenoic acid; EPS, extrapyramidal side effects; FA, fatty acid; GAF, global assessment of functioning; LDL, low-density lipoprotein; LUNSERS, Liverpool University Neuroleptic Side Effects Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; Mono, monotherapy; NS, not significant; PANSS, Positive and Negative Syndrome Scale; Pb, placebo group; QOL, quality of life; RCT, randomized controlled trial; SANS, Scale for the Assessment of Negative Symptoms; SAS, Simpson-Angus Scale; SOFAS, Social and Occupational Functioning; UKU, Udvalg for Kliniske Undersogelser rating scale; VLDL, very low-density lipoprotein cholesterol.

symptoms with add-on treatment with EPA in patients with schizophrenia.[33,35–38] Three variable trials did not show improvements with LC-PUFAs; one trial assessed patients with schizoaffective disorder alongside those with schizophrenia[31] and one trial assessed patients with a FEP;[30] whether these differences with respect to the analysed population affected the results is not clear. In clearly manifest schizophrenia, PUFAs as supplementing agents alongside an antipsychotic therapy have been shown to have insufficient effects in a recent meta-analysis.[45] However, epidemiological data[46] and a recent RCT in emerging psychosis support the hypothesis that LC-PUFAs might have preventive effects in very early stages of psychotic disorders.[28] These findings are suggestive of possible neuroprotective properties of PUFAs.[30]

Indeed, results of the recent randomized, double-blind trial were promising:[28] Eighty-one individuals with UHR profile were randomly assigned to receive either 1.2 g per day of omega-3 PUFAs or placebo for 12 weeks. The total study period was 12 months. By the end of the study (at 12 months of follow up), 4.9% ($n = 2/41$) of patients in the omega-3 PUFA group and 27.5% ($n = 11/40$) in the placebo group had developed acute psychosis. This difference in the outcome parameter 'transition' was highly significant. In addition to the main effect reported, improvements in positive, negative and general symptomatology, as well as in psychosocial functioning levels were reported. As a matter of fact, the latter change was significantly correlated to the change in the omega-3 to omega-6 ratio between baseline and end of treatment after 12 weeks. The number needed to treat (NNT) for omega-3 PUFAs for indicated prevention in UHR was 4 and is comparable with the NNT reported in the two trials investigating antipsychotic agents in UHR individuals.[23,24]

Modulating effects of omega-3 FAs on glutathione and on the glutamine/glutamate cycle,[41] and antiapoptotic action of omega-3s[47] could explain the enduring clinical effects in UHR individuals, that is, treatment effects remained for months after the end of the 12-week intervention, although this has not been assessed in the study.

PUFAs and potential adverse effects

PUFAs and potential adverse effects in UHR

Only one study has investigated the effects of supplementation with omega-3 PUFAs as treatment in UHR individuals.[28] Thus, the only data regarding the safety of omega 3 PUFAs are derived from this trial.

Applying the Udvalg for Kliniske Undersogelser Scale (UKU) to detect adverse effects, frequency and intensity of possible side effects in the omega-3 FA condition were not different from placebo. Although not statistically different from the placebo group, the following adverse effects were reported in the omega-3 group: diarrhoea, nausea/vomiting, tension/inner unrest, depression, concentration difficulties, emotional indifference, tension headache, reduced duration of sleep, increased fatigability. All but 'increased fatigability' occurred – non-significantly – less frequently in the omega-3 group. Not listed are side effects that occurred with a prevalence of less than 5% in the omega-3 or in the placebo group.

PUFAs and potential adverse effects in schizophrenia

Additional data regarding adverse effects of omega-3 PUFA supplementation are available from add-on treatment trials in patients suffering a FEP or in chronic schizophrenia patients. Generally, the assessments of adverse effects in these trials varied between structured assessments (e.g. UKU) and spontaneous patient reports. In Fenton and colleagues' omega-3 PUFA supplementation, RCT patients with schizophrenia/schizoaffective disorder of the *verum* condition showed upper respiratory infection (8/43 patients, 19%) and diarrhoea (8/43 patients, 19%).[31] A lower dose of omega-3 PUFAs (600 mg EPA/DHA) in Arvindakshan and colleagues' open-label study was not associated with any gastrointestinal problems, but 5 of 33 patients did drop out due to the fishy odour of the capsules.[37] Taken together, the following common but clinically rarely significant side effects were reported here: mild nausea or diarrhoea, fishy eructation, loose stool.[33,34,45] Detailed information on adverse effects of omega-3 fatty acids from currently available supplementation trials is summarized in Table 1.

Specific adverse effects of PUFAs

Further data regarding safety issues are available from trials performed in patients with schizophrenia (see Table 1), other psychiatric and somatic illnesses, and the general population.

PUFAs and bleeding time

There is evidence that the intake of omega-3 PUFAs is associated with a prolonged bleeding time in healthy men[48] and in both healthy men and women.[48–50] A literature review by Knapp suggested that the prolongation of bleeding time is usually

modest, and there have been no reports of clinically significant bleeding.[51] A statement by the U.S. Food and Drug Administration (FDA)[52] confirmed that fish oils can significantly prolong bleeding time but a dose of up to 3 g per day EPA/DHA is considered safe.[53] According to a study by Emsley and colleagues,[29] in chronic schizophrenia patients a dose of 2 g per day EPA caused a significant increase in bleeding time, but remained in the high end of the normal range and was not associated with clinically relevant bleeding complications. Because patients with schizophrenia and other psychoses have been shown to be at increased risk for cardiovascular conditions and mortality,[54] a slightly prolonged bleeding time within normal range as well as other metabolic effects of PUFAs (outlined below) is discussed as being even beneficial.

PUFAs and metabolic parameters

There is sound evidence from studies in healthy populations and in individuals with lipid metabolism disorders that omega-3 LC-PUFAs are effective in lowering triglyceride (TG) levels.[55–57] A recent literature review of placebo-controlled RCTs regarding monotherapy with EPA and DHA or EPA versus DHA related a TG-reducing effect to both EPA and DHA (with an advantage of DHA), but reported divergent effects on low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs).[55] Compared to placebo, DHA increases LDL, whereas EPA non-significantly reduces LDL. In contrast, DHA, other than EPA, also seems to raise HDL.[55,58] Further research is needed to elucidate the mechanism of these differences.

Only one trial explicitly investigated metabolic effects of EPA in patients with chronic schizophrenia.[29] This study evaluated the effects of 2 g per day EPA versus placebo on weight gain, total cholesterol, HDL, LDL and TG levels on fasting blood glucose, and additionally on tardive dyskinesia (TD) over a period of 12 weeks with a 40-week open extension phase. The results point to a significant, but clinically probably only slightly relevant increase in body mass index in the EPA group (baseline 24.5 to end of treatment 25.2 kg m^{-2}; $P = 0.0001$). With respect to total cholesterol, HDL, LDL and TG levels, the findings depict a significant decrease in total cholesterol levels as well as in HDL levels, but there were changes in neither LDL nor in TG plasma levels.[48] Fasting blood glucose increased at trend level. Meta-analytical data of studies in individuals who were either healthy, and had diabetes, hypertension or dyslipidaemia, or cardiovascular disease show that omega-3 LC-PUFAs do not seem to have relevant effects on blood glucose.[59,60] Effects of omega-3 fatty acids on metabolic parameters were also investigated in patients with hyperlipidaemia under antipsychotic agents. In patients with an established diagnosis of schizophrenia and stable clozapine medication, augmentation of 2 and 4 g per day EPA significantly reduced TG levels, whereas augmentation of 1 g per day EPA and placebo group did not cause any effect on blood lipids.[34] Similar results (i.e. reduction of TG plasma levels) were revealed in an open-label study using 3 g per day EPA and DHA over a study period of 28 days in a population of clozapine-treated patients with schizophrenia or schizoaffective disorder.[32] However, in this latter study, total cholesterol level, and LDL and HDL levels significantly increased, and very low-density lipoprotein decreased. At the moment, no published data regarding PUFAs and metabolic parameters are available in patients with UHR for psychosis.

PUFAs and cardiovascular factors

Epidemiological studies suggest benefits of omega-3 PUFAs on cardiovascular health.[61] Omega-3 PUFAs may exhibit their cardioprotective effects, such as protection against atherosclerosis and arrhythmias, by affecting gene expression of factors involved in atherogenesis, inflammation and angiogenesis.[61] Indeed, the American Heart Association recommends 1 g per day EPA/DHA for secondary cardiovascular disease prevention.[57,62] No valid data are yet available in patients with schizophrenia. However, it is well known that patients with schizophrenia and other psychiatric disorders are at increased risk for cardiovascular disease as a consequence of a higher prevalence of the metabolic syndrome, due to possible disease-inherent factors, medication (antipsychotic-induced metabolic dysregulations and QTc-time prolongation) and lifestyle factors.[63] Therefore, positive omega-3 PUFA supplementation effects in patients with emerging psychosis might not only arise from protection against transition to acute psychosis, but there may also be a gain from the potential to prevent metabolic and cardiovascular detriments.[64]

PUFAs and cancer

Inconsistent findings have been reported for a slightly increased risk of prostate cancer with high level of ALA (18:3n-3) consumption;[65] however, meta-analytical data do not support this claim and rather point towards a weakly decreased risk ratio.[66]

Although omega-3 LC-PUFAs are generally associated with antioxidant effects, oxidation

by-products, that is, free radicals, may form during the enzymatic conversion pathway of PUFAs. Synergistic effects of LC-PUFAs and alpha-tocopherol have been shown to induce oxidative stability.[67] Thus, adequate levels of alpha-tocopherol seem necessary when supplementing with omega-3 LC-PUFAs.

Risk versus benefit of PUFAs in emerging psychosis

Taken together, one promising aspect of omega-3 PUFAs is that there seem to be no reports of relevant deleterious side effects in humans, even at high doses. However, the differential effects on lipid parameters described above are noteworthy and need further clarification. As mentioned, the slight risk of prolonged bleeding time is outweighed by the benefits. Aside from the benefit that treatment with omega-3 PUFAs may prevent or at least delay the onset of psychotic disorders in UHR groups, a notable benefit is that treatment with omega-3 PUFAs also significantly reduced positive, negative and general symptoms on the Positive and Negative Syndrome Scale and improved functioning.[28]

A side note to the postulated benefits of omega-3 PUFAs in antipsychotic-treated patients with schizophrenia or other psychotic disorders: there is some evidence that omega-3 fatty acids might have some positive effects on antipsychotic-induced extra-pyramidal side effects (EPS) and TD.[30,31,34–36,38,68,69] Indeed, EPA augmentation led to a decreased incidence of EPS in FEP patients treated with antipsychotics.[30] Additionally, Emsley and colleagues report significant decreases in motor side effects, mainly in dyskinesia scores, with omega-3 PUFA supplementation.[35] In addition, sexual dysfunction (orgastic dysfunction and a trend for ejaculatory dysfunction) – common and often very disturbing side effects of psychopharmacological medication – was found to be positively influenced by omega-3 PUFAs;[30] this might be especially important in a young and help-seeking population at increased risk for psychosis. Furthermore, four of the eight available add-on EPA supplementation trials have shown reduced doses of antipsychotic medication prescribed compared to the placebo groups in FEP[30] and in patients with schizophrenia,[33,35,70] and an improvement of the tolerability of atypical antipsychotic medication. No data are available in emerging psychosis.

When discussing safety issues in PUFAs, some common risk factors should not be ignored, for example, possible contaminations of the primary PUFA resources. PUFAs are usually extracted from fatty fish (e.g. salmon, herring and mackerel),

certain white fish, shellfish and other seafood of different origins.[71] Contaminations with substances such as methylmercury, polychlorinated biphenyls, dioxins and other environmental contaminants have been reported for these species.[72] The regulation of the quality of fish for human consumption is shared in the United States by two federal agencies, the FDA and the U.S. Environmental Protection Agency, and in Europe by the European Commission (Regulation 1881/2006). Consumption of a wide variety of species is recommended as the best approach to both minimizing mercury exposure and increasing omega-3 fatty acid intake. Currently, available information on methylmercury content of selected fish can be found on the FDA website (http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm115644.htm).

Indeed, a recent epidemiological study in women from the general population observed a slightly increased risk of experiencing psychotic-like symptoms under a very frequent or no fish and seafood intake, whereas a moderate consumption (three to four times a week) decreased this risk. These findings require further exploration; however, a possible effect of contaminants is discussed[46] Finally, on a more global scale, overfishing of fish stocks and biodiversity in our oceans has an impact on the ecosystem[73] and should be taken into account.

CONCLUSION

The current stage of knowledge based on the most recent trial of indicated prevention in UHR groups holds promise that treatment with omega-3 PUFAs may prevent or at least delay the onset of psychotic disorder. As replication studies are still underway, conclusions in terms of clinical effectiveness are still preliminary. In contrast, in terms of safety issues, evidence from the RCT in UHR individuals and a variety of studies in schizophrenia patients strongly suggests PUFAs are safe and well tolerated by young people at UHR of psychosis. Omega-3 PUFAs have been shown to be safe even when used in relatively high doses, and except for mild gastrointestinal symptoms they are presumed to be free of clinically relevant adverse events.[74] Nevertheless, clinicians should be aware of possible increases in bleeding time. Thus, regular monitoring of bleeding and metabolic parameters would seem prudent.[29] Some 'side' effects, such as regulatory function on TG, EPS and sexual function, might be beneficial. When balancing risks and benefits of omega-3 PUFA supplementation, it is important to note that in addition to the common positive effects on the cardiovascular

and other systems, omega-3 PUFAs might also unfold neuroprotective properties[75] that are of particular interest in the field of indicated prevention and psychosis research.

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