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Effect of omega-3 fatty acids for indicated prevention of young patients at risk for psychosis: When do they begin to be effective?

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ABSTRACT

The results of a recent double-blind, randomized, placebo-controlled trial performed in 81 young patients at ultra-high risk for psychosis indicated that a 12-week intervention of 1.2 g/day of ω-3 polyunsaturated fatty acids (PUFA) significantly reduced the risk of transition to psychosis and improved positive, negative and general symptoms as well as functioning. The aim of this post-hoc analysis was to determine at which time point ω-3 PUFAs start to significantly differ from placebo in improving psychopathology and functioning in young people at risk of developing psychosis. Analyses were performed using the mixed model repeated-measures analysis of variance. Compared to placebo, ω-3 PUFAs' significant effects on the amplitude of the reduction in General and Total PANSS scores are evident after the first four weeks of treatment; a reduction of positive symptoms and a lower mean PANSS positive score were apparent after eight weeks, whereas the significant drop in negative symptoms and the significant change and higher mean scores in global functioning occur later at 12 weeks. The delay of onset of ω -3 PUFAs seems comparable to that of antipsychotics and antidepressants.

1. Introduction

Indicated prevention in adolescents and young adults at ultra-high risk (UHR) of psychosis has been the focus of early intervention research in recent years. To reduce the risk of transition to a full-blown first episode of psychosis, trials have used low-dose antipsychotics (McGorry et al., 2002; McGlashan et al., 2006), cognitive therapy (Morrison et al., 2004, 2012), the combination of both (Yung et al., 2011), or intensive treatment with family intervention (Nordentoft et al., 2006). Although successful in reducing the risk of psychosis over the short term, trials using antipsychotic medication have not yielded significantly better longer-term results than non-pharmacological treatments, and introduce the risk of short- and long-term side effects (Preti and Cella, 2010). In light of recent findings on glutamate hypermetabolism as a possible firestarter in UHR patients, it is suggested that antipsychotics, which can increase glutamate levels, should be omitted in this patient group (Moghaddam, 2013). Furthermore, prospective longitudinal MRI data in patients with schizophrenia have recently provided evidence that antipsychotic treatment intensity is associated with long-term brain tissue loss (Andreasen et al., 2013). Thus, in the UHR population, with naturalistic transition rates of about 15–30% (Yung et al., 2003; Addington et al., 2007; Riecher-Rössler et al., 2007; Yung et al., 2007), more benign treatments might be more appropriate with respect to efficacy and side effects.

We have recently reported on the effects of long-chain omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) for indicated prevention of psychosis in adolescents and young adults at risk of developing psychosis. The results of this double-blind, randomized, placebo-controlled trial indicated that a 12-week intervention of 1.2 g/day of ω-3 PUFAs significantly reduced the risk of transition to psychosis at one year follow-up (Amminger et al., 2010). The number needed to treat (NNT) with ω-3 PUFAs in the study to prevent one individual from progressing to psychosis during a 12-month period was 4. The ω-3 PUFA group also showed greater improvement in positive, negative and general symptoms as well as in functioning. Interestingly, the protective effects were sustained for the entire 12-month observation period, although the duration of the intervention was only 12 weeks. This effect could be explained by the neuroprotective properties of

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ω-3 PUFAs (Gama et al., 2012). Indeed, ω-3 PUFAs show an anti-inflammatory action (El-Ansary et al., 2011) and induce antiapoptotic (Calon et al., 2004) as well as antioxidant factors (Kim et al., 2001; Calder, 2003; Calon et al., 2004; El-Ansary et al., 2011; Mossaheb et al., 2012).

Omega-3 PUFAs have the advantage of excellent tolerability, public acceptance, relatively low cost, and benefits for general health (Mozaffarian and Rimm, 2006.). The findings of our trial, while preliminary, might therefore reasonably suggest that psychiatrists recommend ω-3 PUFAs to UHR patients because there are known benefits and little risk associated with this supplementation. To further underpin the importance of lipid biology for the onset of psychosis, we have recently shown that decreased levels of fatty acids may serve as biomarkers predicting psychosis conversion (Amminger et al., 2011), and that lower levels of omega-3 PUFAs are specifically associated with negative symptoms in UHR patients (Amminger and McGorry, 2012). Together these findings raise the question at what time point during such an intervention ω-3 PUFAs begin to show beneficial effects on positive, negative and global symptoms as well as on functioning. Most of the previously published double-blind randomized controlled trials using ω-3 PUFA supplementation in patients with psychosis have used a timeframe of three months, however, the timepoint of onset of effects is not reported (Fenton et al., 2001; Peet et al., 2001; Emsley et al., 2002; Berger et al., 2007). The aim of this post-hoc analysis was to determine at which time point within the 12 weeks of the intervention ω-3 PUFAs start to significantly differ from placebo in improving psychopathology and functioning in young people at UHR of developing psychosis, i.e. at which time point were gains made.

2. Methods

2.1. Sample

Patients aged 13–25 years meeting at least one of three operationally defined criteria for increased risk for psychosis (i.e., attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or a genetic risk with decreased functioning) were included in the study if they did not fulfil any of the exclusion criteria. These included a previous history of a psychotic disorder or manic episode, a substance-induced psychotic disorder, acute suicidal or aggressive behaviour, a current substance dependence except for cannabis dependence, neurological disorder, relevant structural brain changes, IQ of less than 70, previous antipsychotic or mood-stabilizing treatment for longer than one week, previous supplementation with ω-3 PUFAs within 8 weeks of inclusion in the trial, abnormal laboratory values for transaminases, thyroid hormones, C-reactive protein, bleeding parameters or any other severe intercurrent illness that may have put the person at risk. For further details see Amminger et al. (2010).

2.2. Study design

The trial was a double-blind, placebo-controlled RCT with a 12-week intervention period of 1.2 g/d ω-3 PUFAs or placebo (Trial registration: clinical trials.gov Identifier: NCT00396643). During the intervention period participants received weekly assessments for 4 weeks and then at 8 and 12 weeks, as well as at the 6- and 12-month follow-up.

Eighty-one patients agreed to participate in the trial by giving informed written consent and were assigned to one of two intervention arms ($n = 41$ ω-3 PUFA, $n = 40$ placebo). The study was approved by the local ethics committee.

2.3. Data analysis

For secondary outcome measures, analyses were performed using the mixed model repeated-measures (MMRM) analysis of variance. The within-groups factor was measurement occasion, and medication group served as the between-groups factor. A Toeplitz covariance structure was used to model relations between observations on different occasions. A series of planned comparisons contrasted differences between the ω-3 and placebo groups in change from baseline to the 1-week, 2-week, 3-week, 4-week, 8-week, and 12-week time points. MMRM analysis of variance differs from traditional repeated-measures analysis of variance in that all available data are included in the model and the associations between the different times are also modelled (Gueorgieva and Krystal, 2004). Analyses were undertaken using the MIXED procedure in IBM® SPSS® Statistics Version 19.

In this trial, missing secondary outcome data occurred in two distinct ways. Observations could be missing data owing to patient withdrawal or missed assessments. These observations can reasonably be assumed to be missing at random, which allows for missingness associated with baseline covariates and past observed values, but not unobserved future values (Gueorgieva and Krystal, 2004) (p313). The second type of missingness relates to data that are absent following transition to psychosis. Treatment with antipsychotic medication was commenced in participants who made the transition to psychosis, and no further data were collected after transition. The outcome of interest—the values that participants would have had if active treatment for psychosis had not been initiated and the intervention and observation had continued—is thus effectively counterfactual. In these circumstances, missingness is not random and must be explicitly modelled. A conservative approach was taken to model post-transition outcomes. It was assumed that symptoms and functioning would have been maintained at the transition levels if antipsychotic medications had not been administered, but would not have further increased.

No adjustments were made for multiple comparisons because they can result in a higher type II rate, reduced power, and increased likelihood of missing important findings (Rothman, 1990). Thus, given the exploratory nature of this study, all p values were set at the $p < .05$ level.

3. Results

For the PANSS (Positive and Negative Syndrome Scale, Kay et al., 1987) measures, the omnibus interaction between medication group and occasion was significant for the Total ($F_{6,\ 158} = 2.37$, $P = 0.03$), General ($F_{6,\ 165.4} = 2.44$, $P = 0.03$), and Positive ($F_{6,\ 158.43} = 2.30$, $P = 0.04$) scores. The interaction between medication group and occasion was not significant for the PANSS Negative scores ($F_{6,148.2} = 1.66$, $P = 0.14$).

Planned comparisons indicated that the ω-3 group demonstrated a significantly greater drop in PANSS General and PANSS Total scores from baseline to 4 weeks (all $P < 0.05$), baseline to 8 weeks (all $P < 0.05$), and baseline to 12 weeks (all $P < 0.05$) as compared to the placebo group. The ω-3 group had a significantly greater reduction in PANSS Positive scores from baseline to 8 weeks ($P = 0.002$) and from baseline to 12 weeks ($P = 0.006$). For PANSS Negative, the ω-3 group had a greater reduction in scores as compared to placebo from baseline to 12 weeks ($P = 0.043$).

For PANSS Total and PANSS Positive, the ω-3 group had significantly lower mean scores than the placebo group at both 8 weeks (all $P < 0.05$) and 12 weeks (all $P < 0.05$). For the PANSS General, the ω-3 group had a significantly lower mean score at 12 weeks as compared to the control group ($P = 0.01$).

There was no significant omnibus interaction between medication group and occasion for the MADRS (Montgomery Asberg Depression Rating Scale, Montgomery and Asberg, 1979) ($F_{6,\ 151.9} = 1.81$, $P = 0.10$); however, planned comparisons indicated that the difference between scores at baseline and 1 week was greater for the placebo compared to the ω-3 group ($P = 0.038$).

The interaction between medication group and occasion was significant for the GAF (Global Assessment of Functioning, APA, 1994) ($F_{6,141.5} = 3.95$, $P = 0.001$), with the rate of change being significantly greater between baseline and 12 weeks for the ω-3 group ($P = 0.01$). Furthermore, at 12 weeks the ω-3 group had a significantly higher mean GAF score compared to the placebo ($P = 0$ .01).

See Fig. 1

4. Discussion

Analysis of the onset of therapeutic action during the 12-week intervention with ω-3 PUFAs in patients fulfilling UHR criteria for psychosis revealed a heterogeneous profile with respect to the different dimensions of psychopathology. Compared to placebo, ω -3 PUFAs' significant effects on the amplitude of the reduction in General and Total PANSS scores are evident after the first four weeks of treatment; a reduction of positive symptoms and a lower mean PANSS positive score is apparent after eight weeks, whereas the significant drop in negative symptoms and the significant change and higher mean scores in global functioning occur later at 12 weeks.

Interestingly, the temporal cascade of symptomatic improvement appears similar to that postulated for antipsychotic treatment in schizophrenia (Lehman, 1999). That is, positive symptoms decrease more rapidly and improvements of negative symptoms and of general functioning occur slightly later. Taking into consideration that global functioning is influenced by psychopathology, it is understandable that improvements on all psychopathological dimensions eventually may lead to better global functioning and not the other way around. However, it cannot be excluded that improvements may have occurred simultaneously in all domains but reached level of statistical significance according to the degree of symptom reduction at different time points. We believe this is a limitation in all pharmacological studies depending on external assessments, i.e. without biomarkers.

The long-existing idea of a delayed onset of action for antipsychotics has been questioned and well-founded studies have shown that early responses were seen after two weeks of antipsychotic medication (Agid et al., 2003; Leucht et al., 2005; Agid et al., 2006) and were predictive of responder status after four (Correll et al., 2003) six (O'Gorman et al., 2011), eight (Ascher-Svanum et al., 2008) and 12 Kinon et al. (2010), Stauffer et al., 2011) weeks in chronically ill patients with schizophrenia as well as in those with a first episode of psychosis (Stauffer et al., 2011). In the present trial, the ω-3 PUFA-group showed significant improvement of symptoms after four weeks, and of positive symptoms specifically after eight weeks; thus, the delay was slightly longer compared to early responses with antipsychotics. Similarly to antipsychotic effects, improvements

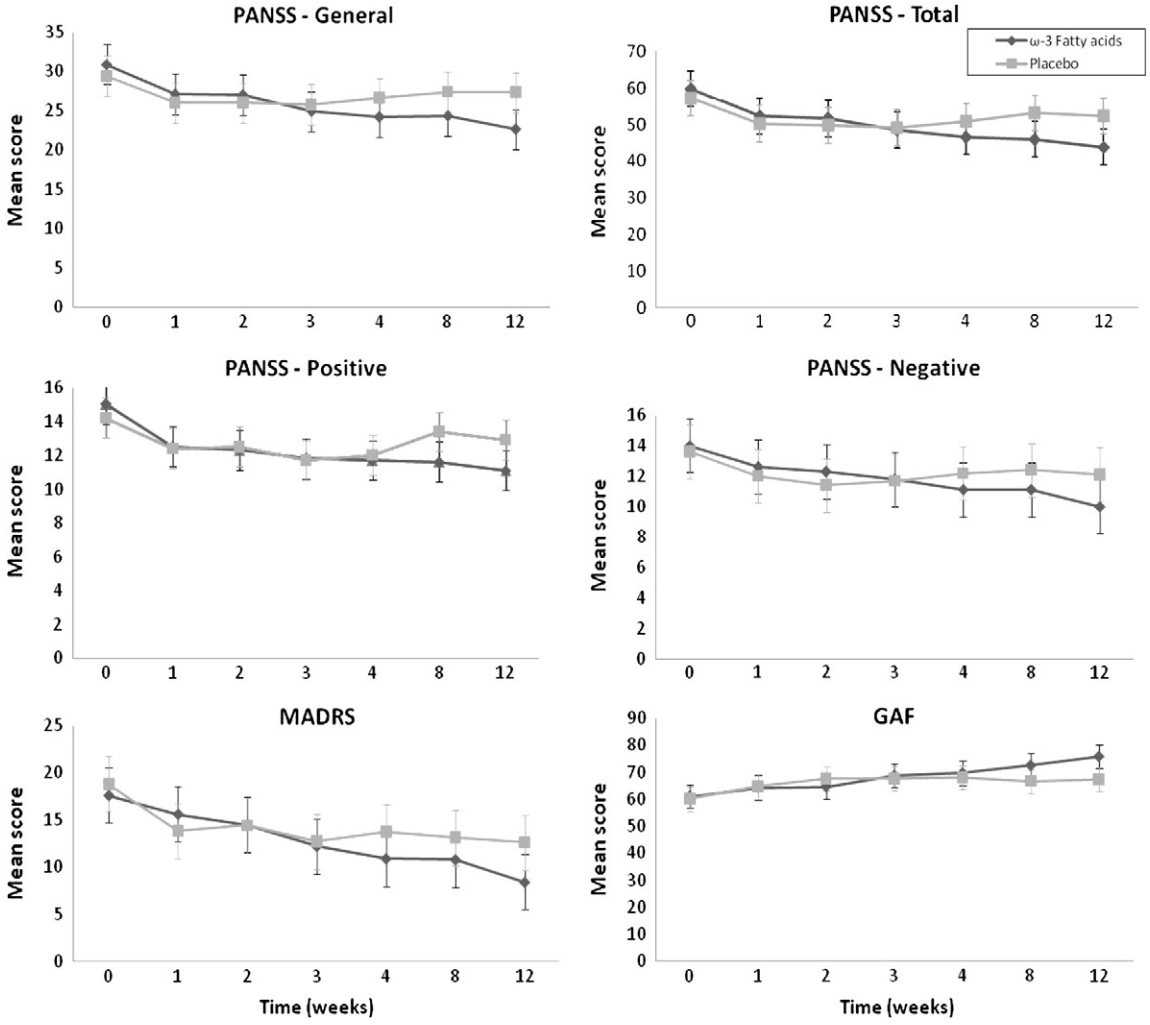

Fig. 1. Scores for symptom severity and functioning (secondary outcome measures). Scores for symptom severity and functioning (secondary outcome measures). Bars represent 95% confidence intervals. The minimum total score for the Positive and Negative Syndrome Scale (PANSS) is 30, and the minimum scores for the positive, negative, and general subscales are 7, 7 and 16, respectively. The Montgomery-Åsberg Depression Rating Scale (MADRS) measures the severity of 10 symptoms on a scale from 0 to 6. The Global Assessment of Functioning (GAF) measures social, occupational, and psychological functioning on a single numeric scale (0–100), with higher scores indicating better functioning.

on typical antidepressant drugs also usually occur within the first two weeks of treatment (Posternak and Zimmerman, 2005). Indeed, it has been shown that PUFAs exhibit effects on relevant neurotransmitters such as dopamine and serotonin (Piomelli et al., 1991; McNamara et al., 2008; Vines et al., 2012), thus possibly sharing similar mechanisms as some psychotropic drugs affecting the dopaminergic and serotonergic system, which might be one hypothesis explaining the comparable efficacy and time frame until onset of action of the more immediate symptomatic effects of ω-3 PUFAs observed here. Depression scores, however, were not significantly different between groups and both groups had reduced MADRS scores at the end of the trial period. On a further note: the beneficial effects on psychopathology, some of which were established as early as in the fourth week of treatment, were maintained throughout the entire 12-month follow-up period after an intervention period of only three months (Amminger et al., 2010). Since previous pharmacological studies have not yielded similar longer term effects after cessation of intervention (Preti and Cella, 2010), it is conceivable that other mechanisms of action, e.g. neuroprotective properties of ω-3 PUFAs, including membrane stabilization, reduction of excitotoxicity and of oxidative damage, come into effect on a longer run to establish the full extent of their effects. We have recently provided the first evidence to support this view by showing that activation of phospholipase A2 as one of the processes that compensate for membrane destabilization and damage is altered by omega-3 supplementation (Smesny et al., 2013).

5. Conclusion

In summary, ω-3 PUFAs lead to a seeming temporal cascade of responses with a delay comparable to that of antipsychotic and antidepressant drugs, resulting in longer lasting psychopathological and psychosocial improvements after a supplementation period of only 12 weeks. Because of their favourable risk-benefit profile, many clinicians have been considering ω-3 PUFA supplementation for UHR patients since the publication of the original trial (Amminger et al., 2010). With this in mind, the comparability of the time frame of action of the clinical effects of ω-3-fatty acids is noteworthy. This analysis reveals for the first time placebo-controlled data on these effects in clinical use in UHR patients. However no recommendations can currently be given as replication studies are needed, whereof two RCTs are currently underway.

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Contributors

Author NM contributed to: the literature searches, interpretation of results, and drafted the manuscript.

Authors GPA contributed to: design of the study, supervision, clinical part of the study, data analysis, interpretation of results and writing of the manuscript.

Author MRS, CMK and MS contributed to: clinical part of the study as well as writing of the manuscript.

Author SMC contributed to: data analysis, interpretation of results and writing of the manuscript.

Author PDM contributed to: design of the study, interpretation of results and writing of the manuscript.

All authors contributed to and have approved of the final version of the manuscript.

Conflict of interest

None of the contributing authors (Nilufar Mossaheb, Miriam R Schaefer, Monika Schloegelhofer, Claudia M Klier, Sue M Cotton, Patrick D McGorry, G. Paul Amminger) have any conflicts of interest to report.

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