Schizophrenia Research 158 (2014) 230–235

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

A randomized, controlled trial of omega-3 fatty acids plus an antioxidant for relapse prevention after antipsychotic discontinuation in first-episode schizophrenia

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ARTICLE INFO

Article history:
Received 3 March 2014
Received in revised form 9 May 2014
Accepted 1 June 2014
Available online 2 July 2014

Keywords:
Schizophrenia
Relapse-prevention
Omega-3
Antioxidant
Placebo

ABSTRACT

Background: While antipsychotics are effective in the maintenance treatment of schizophrenia they have safety and tolerability risks. We investigated whether a combination of omega-3 polyunsaturated fatty acids (ω−3 PUFAs) and a metabolic antioxidant, alpha-lipoic acid (α-LA), is effective in preventing relapse after antipsychotic discontinuation in subjects who were successfully treated for 2–3 years after a first-episode of schizophrenia, schizo-affective or schizophreniform disorder.
Methods: In this randomized, double-blind, placebo controlled study antipsychotic treatment was tapered and discontinued and participants received either ω−3 PUFAs (eicosapentaenoic acid 2 g/day and docosahexaenoic acid 1 g/day) + α-LA 300 mg/day or placebo. Subjects were followed up for two years, or until relapse.
Results: Recruitment was terminated prematurely due to the high relapse rates in both treatment groups as well as the severity of some of the relapse episodes. Of the 33 participants, 19/21(90%) randomized to ω−3 PUFAs + α-LA relapsed and one (5%) completed two years without relapse ($p = 0.6$); and 9/12 (75%) randomized to placebo relapsed and none completed two years without relapse. Mean times to relapse were 39.8 ± 25.4 and 38.3 ± 26.6 weeks for the ω−3 PUFAs + α-LA and placebo groups, respectively ($p = 0.9$). There were no significant differences between the groups in relapse symptom severity.
Conclusions: We found no evidence that ω−3 PUFAs + α-LA could be a suitable alternative to maintenance antipsychotic treatment in relapse prevention, in this small study. Antipsychotic discontinuation after a single episode of schizophrenia carries a very high risk of relapse, and treatment guidelines endorsing this practice should be revised.

1. Introduction

Relapse rates are very high when antipsychotic treatment is discontinued, even after a single episode of schizophrenia or related disorder. This has prompted calls for continuing antipsychotic treatment indefinitely (Zipursky et al., 2014). However long-term exposure to antipsychotic drugs carries other safety and tolerability risks and may be unacceptable to many patients. The availability of a safe and well tolerated alternative treatment that could effectively prevent relapse would therefore represent a major advance in the maintenance treatment of schizophrenia. The omega-3 polyunsaturated fatty acids (ω−3 PUFAs) represent one potential alternative. Supportive evidence is forthcoming from various sources. Schizophrenia has been proposed as a disorder of membrane phospholipid metabolism (Horrobin, 1998) and several studies have reported reductions of PUFAs in erythrocytes, cultured skin fibroblasts and brain tissue (for review see Emsley et al. (2003)). Seven randomized, controlled trials (RCTs) assessing the ω−3 PUFA eicosapentaenoic acid (EPA) versus placebo as supplemental treatment to antipsychotics in schizophrenia have been reported in the literature. Two of these studies reported a positive effect for EPA on the primary efficacy measure (Peet et al., 2001; Emsley et al., 2002) and all but one (Fenton et al., 2001) of the others reported at least some beneficial effect on secondary outcomes (Peet et al., 2001; Peet and Horrobin, 2002; Emsley et al., 2006; Berger et al., 2007). One study was conducted in 80 first-episode patients over 12 weeks.

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http://dx.doi.org/10.1016/j.schres.2014.06.004
0920-9964/

While no significant group differences were found for symptom change scores, a significant treatment by diagnosis interaction for time to response favoring EPA was found in a non-affective psychosis subset of participants. Also, EPA augmented participants required 20% less antipsychotic medication, suggesting that ω−3 PUFAs may facilitate antipsychotic treatment response, although the study did not demonstrate sustained benefits (Berger et al., 2007). A meta-analysis of these RCTs revealed no beneficial effect for EPA augmentation. However, no conclusions could be made for medium- to long-term effects, and in particular for relapse prevention in the early course of illness (Fusar-Poli and Berger, 2012). Importantly, a RCT in 81 ultra-high risk prodromal subjects provides preliminary evidence that an EPA-rich ω−3 PUFA preparation might prevent conversion into first episode psychosis (Amminger et al., 2010). It is therefore not unreasonable to hypothesize that ω−3 PUFA monotherapy may be effective in preventing illness recurrence after successful treatment of a first-psychotic episode. If effective, these agents would be preferable to antipsychotics insofar as they are natural products and they have been found to be safe and well tolerated with long-term use (Emsley et al., 2008). There is evidence to suggest that, perhaps via reduction of neuronal injury, antioxidants combined with ω−3 PUFAs would be better than giving the latter agents alone (Mahadik et al., 2006). We chose to use alpha-lipoic acid (α-LA) in combination with ω−3 PUFAs for our study as it has been described as unique in meeting the requirements for an ideal neuroprotective therapeutic antioxidant (Packer, 1996). Prior to the introduction of antipsychotic medications. Based on the findings of two small studies in the pre-antipsychotic era reporting that α-LA improved symptoms in schizophrenia and more recently animal studies showing that α-LA augmentation improves mitochondrial function, it has been proposed that α-LA supplementation should be re-assessed in the treatment of schizophrenia (Seybolt, 2010).

The main purpose of the study was to determine whether treatment with ω−3 PUFAs combined with a metabolic antioxidant is more effective than placebo in preventing relapse after antipsychotic discontinuation in patients successfully treated for a first-episode of schizophrenia or related illness. The primary outcome measure was the cumulative relapse rates. Secondary outcomes included time to relapse; changes (baseline to endpoint) in psychopathology, social and occupational functioning and quality of life and cognitive performance over time; and changes in bleeding time, fasting blood glucose and fasting lipogram.

2. Methods

This was a randomized, double-blind, placebo controlled study in subjects who had been successfully treated for between 2 and 3 years after a first episode of schizophrenia, schizoaffective or schizophreniform disorder and who elected to discontinue antipsychotic treatment under supervision. Approval to conduct the study was obtained from the Ethics Committee for Human Research of the University of Stellenbosch. The study was registered in the South African Clinical Trials Registry (DOH-27-0910-3386) and the Medicines Control Council of South Africa (regulatory authority) was notified of the study. It was conducted in accordance with Research Guidelines issued by the Medical Research Council of South Africa, and complied with ICH Guidelines for Good Clinical Practice (International Conference on Harmonization, 1996). Written, informed consent was obtained from all participants.

The risk of discontinuing antipsychotic medication in this study was carefully considered. There is no clarity as to how long antipsychotic medication should be continued after successful treatment of a first-episode of schizophrenia. Some guidelines do not specify treatment duration, while others recommend at least 12 months of treatment (Takeuchi et al., 2012). Therefore, a treatment period of 2 to 3 years seemed reasonable. Additional precautions that we took included: gradual tapering of antipsychotic treatment over 6 months; educating patients and caregivers about early signs of relapse; advising them to develop plans for action should these signs appear; providing an emergency mobile telephone number for 24 hour access to the study team; the appointment of a registered psychiatric nurse to contact all patients and caregivers telephonically on a weekly basis to enquire about possible signs of relapse; more frequent visits, depending on the need, for patients who showed signs of possible relapse; immediate reinstitution of antipsychotic medication in the event of relapse; and the establishment of an independent Data Safety Monitoring Board.

2.1. Subjects

All of the participants were drawn from completers of an earlier study that we conducted in which patients with a first psychotic episode were treated for two to three years with flexible doses of flupenthixol decanoate (Chiliza et al., in press). Eligible patients were invited to participate in this study, or to continue with treatment as usual, after the possible risks and benefits of participation were fully explained. Once randomized, antipsychotic treatment was tapered and discontinued over 6 months and participants received either ω−3 PUFAs + α-LA or placebo. Subjects were carefully followed up for two years, or until relapse.

Inclusion criteria were: completion of the initial study without relapse; currently in remission according to the Remission in Schizophrenia Working Group criteria (Andreasen et al., 2005); male or female; aged between 18 and 48 years; meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) diagnosis of schizophrenia, schizoaffective or schizophreniform disorder. Exclusion criteria were: other DSM-IV axis I diagnosis; current substance dependence; clinically significant general medical condition; and mental retardation.

2.2. Trial medication

Subjects were randomly assigned to receive either a combination of ω−3 PUFAs + α-LA or placebo. Each ω−3 PUFA capsule contained EPA 500 mg and docosahexaenoic acid (DHA) 250 mg, derived from fish-oil. The dose was 2 capsules twice daily to provide EPA 2 g/day and DHA1 g/day. Each α-LA capsule contained 150 mg α-LA (r- α-LA 75 mg and r-dihydro- α-LA 75 mg). The α-LA dose was one capsule twice daily. (Medication was provided by Solal technologies, PO Box 782484, Sandton, South Africa (www.solaltech.com). Participants randomized to the placebo group received 3 identical highly purified olive oil capsules twice daily. Trial supplies were packed by an independent contract clinical trials supplies company who prepared the placebo and active packs for the entire trial and assigned the computer-generated randomization numbers to the packs. The randomization code was broken after completion of the trial. No other antipsychotic medication was permitted throughout the study. Anxiolytic, hypnotic and antidepressant medication was permitted when indicated. Medication for general medical conditions that arose during the course of the trial was allowed, at the investigators' discretion. Other ω−3 PUFA supplements were not permitted. Participants were assessed by a registered dietician (EvN) and advised to adhere to a balanced diet for the duration of the study. During the trial drug accountability procedures included self-report, carer-report and pill counts.

2.3. Assessments

The pre-trial screening visit included the following assessments: informed consent; psychiatric history; medical history; physical examination; diagnosis; demography; vital signs; and laboratory tests. All of the patients were assessed by means of the following instruments: Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994); Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); Clinical Global Impression (CGI) (Guy, 1976); Scale of Prodromal Symptoms (SOPS) (Miller et al., 1999); Calgary Depression Scale for Schizophrenia