Protocol

Safety, Effectiveness, and Mechanism of Fish Oil as Adjunct Treatment for Major Depressive Disorder - a 12-month Randomized, Placebo Controlled Clinical Trial

Unique Protocol ID： MDD201610

Version number： 0001

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Second Xiangya Hospital of Central South University

Brief Summary

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Official Title	Safety, Effectiveness, and Mechanism of Fish Oil as Adjunct Treatment for Major Depressive Disorder - a 12-month Randomized, Placebo Controlled Clinical Trial
Version number/Date	0001/October 9, 2016
Sponsor	Second Xiangya Hospital of Central South University
Indication	Major Depressive Disorder
Aim	To investigare the role of n-3 polyunsaturated fatty acids in the treatment of depression.
Study Design	Randomized, double-blind, placebo-controlled Clinical Trial
Number of cases	Experimental Group:60, Placebo Group:60
Number of research centers	2
Estimated Primary Completion Date	October，2019
Study Arms	Placebo Comparator: Placebo (Soybean oil placebo capsules, 8 capsules daily for 24 weeks) Experimental: Fish oil (fish oil capsules, 8 capsules(containing EPA 1440mg, DHA 960mg) daily for 24 weeks)
Outcome Measures	Primary Outcome Measures: HAM-$D_{24,}$ HAMA, BDI, SAS Secondary Outcome Measures: CGI-S, CGI-I, SERS, RBANS, STROOP, BMD, MRI
statistical analysis	SPSS

Safety, Effectiveness, and Mechanism of Fish Oil as Adjunct Treatment for Major Depressive Disorder - a 12-month Randomized, Placebo ControlledClinical Trial

In this proposed study, we will evaluate the effects of fish oil add-on in treatment of major depressive disorder (MDD). Patients are randomly assigned to two groups (n=60): control group (placebo, soybean), fish oil group (fish oil capsules containing about EPA 1440mg, DHA 960mg). The experimental group will be compared to placebo group to evaluate if it may benefit clinical symptoms, cognitive symptoms and metabolic markers in depressive patients. We also plan to investigate the changes in markers of inflammation at the same time. The study will be carried out in the Second Xiangya Hospital of Central South University in China and recruit 120 depressive patients. Only outpatients will be recruited and the enrolled patients will be assessed (baseline). Eligible participants will be between the ages of 18-60. Subjects will be assessed at baseline, week 4, week 8, week 12, week 24 and week 48.

The specific aims are to compare fish oil versus placebo on: 1) clinical symptoms; 2) neurocognitive performance (NP); 3) metabolic markers; 4) makers of inflammation. We hypothesize that: 1) Fish oil add-on therapy is superior to placebo in the treatment of symptoms in patients with MDD, measured by the HAMD and CGI; 2) Fish oil add-on therapy is superior to placebo in the treatment of cognitive symptoms in patients with MDD, measured by the RBANS and STROOP; and 3) Fish oil add-on therapy is superior on alleviating the change of metabolic and inflammation markers induced by antidepressants compared to placebo.

1 Background and significance

Major Depressive Disorder (MDD) is characterized by markedly decreased mood, cognitive capacities and behavior, changes in sleep and appetite, and social functioning deficits. The treatment of depressive symptoms in MDD has made some progress since SSRIs were developed. However, the complete remission in MDD patients remains a major challenge with currently available antidepressent mono-therapies providing only modest benefit. And the pathogenesis of depression has not yet been defined.

Long-chain polyunsaturated fatty acids (LC-PUFAs) are essential fatty acids that primarily found in fish oil and play crucial roles in mechanisms of MDD. Omega-3 polyunsaturated fatty acids (Ω-3 PUFAs),

especially eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) are crucial for the body development. Although studies have shown that reduced N-3 PUFAs were correlated with MDD, and patients with an elevated rate of N-6 PUFAs /N-3 PUFAs or a low level of DHA may be at higher odds for suicide. Trials on whether N-3 PUFAs is effective in the treatment of MDD is still controversial, which might be affected by several factors, such as dose, duration etc.. Now there is no large-scale randomized controlled clinical trial in determining the effects of N-3 PUFAs add-on in treatment of MDD.

The modulate effect of Ω-3PUFAs on the pathology of depression are still unclear. Among many hypotheses, the neuroimmune theory continues to generate substantial interest. Several studies in both humans and animals have provided evidence for a link between the inflammatory process and the depressive disorders. Other possible assumption may be related to its effects on multiple neurotransmitter systems, such us glutamatergic system, dopaminergic system, noradrenergic system and serotonergic system. Moreover, fatty acids-alterations may also alter the feedback of the HPA-axis.

2 Study design

2.1 Overall Research Design

We will conduct a 48-week randomized, double-blind, placebo-controlled study to investigate the effects of adding fish oil to existing therapy for patients with MDD on: 1) reduce of clinical symptoms (measured by HAMD and CGI) 2) Cognitive improvement (measured by RANSE and STROOP); 3) Safety (UKU, BDI, SAS and clinical lab test) and 4) the biological indicator in blood serum, plasma and lymphocytes of patients between treatment groups and their correlation to clinical symptoms change.

The participators will take fish oil or placebo add-on to existing therapy for 24 weeks and the clinical symptoms, cognition, safety and blood samples will be assessed and collected before and after treatment (baseline, week 4, week 8, week 12, week 24 and week 48). The Evaluation scales used during the follow-up period are as follow:

HAMD (Hamilton depression scale);

HAMA (Hamilton anxiety scale);

CGI (Clinical global impression);

RBANS (Repeatable battery for the assessment of neuropsychological status);

STROOP (Stroop color-word test);

UKU (The UKU side effects rating scale);

CTQ (Childhood trauma questionnaire);

SSRS (Social support rating scale);

SAS (Self-rating anxiety scale);

BDI (Beck depression inventory);

ASEX (Arizona sexual experience scale);

HCL-32 (Hypomania Check List).

2.2 Subjects and Sites

We will work with Dr. Tang's team and select Mental Health Institute of Second Xiangya Hospital that has approved for carrying out CNS drug registration trial by China Food and Drug Administration and well experienced in doing the MDD trail in China. A total of 120 patients with MDD will be enrolled and randomly divided into 2 groups. Sixty subjects will be given fish oil and another 60 subjects given placebo (control group). We plan to enroll all 120 patients in 12 months and each patient will be on study medication (or placebo) for 24 weeks and then be followed up for after 24 weeks (the follow-up period will be last for 48 weeks). We plan to have this trial done in two year period.

Participants

Inclusion criteria:

①Able to provide informed consent;

②Men or women aged 18-50 years;

③ A primary psychiatric diagnosis of major depressive disorder (MDD), by Diagnostic and Statistical Manual-5th ed (DSM-5) using the MINI;

④HAMD total score≥21;

⑤ No significantly modification of their diet from the time they sign consent to the end of study participation.

Exclusion criteria:

①Suffering from other serious somatic diseases or comorbidities;

②Patients with serious nervous system disease;

③Patients in accordance with diagnostic standards of other mental illness;

④ Patients who need to take benzodiazepine every day, and who currently need to be treated by electroconvulsive therapy or have received electroconvulsive therapy in the past 6 months;

⑤Pregnant women or lactating women, women with pregnancy plans during the trial period (12 months), women with a high risk of pregnancy but without taking any contraceptive measures;

⑥Patients with apparent suicide attempt or suicidal behavior;

⑦ Any condition or medicines that may have an effect on biomarkers (within 1 week of the screening period or during whole trial period): long-term, regular use of NSAIDs, COX-2 inhibitors, immunosuppressant, steroids, interferon, chemotherapeutics, anticoagulants, malignancy, active autoimmune diseases, inflammatory bowel diseases, etc;

⑧Allergy history of PUFA;

⑨Intake of Fish oil more than 3g per day or eat fatty fish more than 3 times a week.

2.3 Intervention Medications

The experimental group will be given 4 fish oil capsules (1g/one capsule) twice daily after two meals at roughly the same time each day, and lasting for the first 6 months. Fish oil capsule will be provided by the Hunan Kangqi100 Biological Technology Co.Ltd.

The control group will be given 4 soybean oil capsules (placebo capsule,1g/one capsule) twice daily after two meals at roughly the same time each day, and lasting for the first 6 months too. Placebo capsule will also be provided by the Hunan Kangqi100 Biological Technology Co.Ltd. The placebo capsule's appearance and flavor are made the exactly the same as the fish oil capsules.

Study duration: 48 weeks.

2.4 Assessment

Following consent, patients met enrollment criteria to be in the study will be undergone assessments including:

① Demographic information, medical and psychiatric history and family history of mental illnesses at baseline；

②Labs: CBC, metabolic panel, liver panel and lipid panel (extra sample will be saved for biomarkers)；

③Clinical symptom will be assessed by HAMD;

④Cognitive assessment by RBANS and STROOP;

⑤Side effect rated on UKU and Lab tests.

Almost all clinical assessments will be done at baseline, week 4, week 8, week 12, week 24 and week 48, except some items being done at baseline only (See table 1 for details).

For the lab work, in addition to routine clinical safety lab, some extra blood sample will be collected and stored for future epigenetic and bio-inflammatory biomarkers assay.

Table 1: Schedule of Clinical, Neurocognitive Assessment and Lab testing for Evaluation of fish oil add-on therapy in MDD

	Baseline	W04	W08	W12	W24	W 48
Inform consent	*					
Inclusion/exclusion screen	*					
Demographic & medical, mental illness history	*					
Physical exam	*	*	*	*	*	*
Lab test and blood sample stored	*	*		*	*	*
Randomization	*					
Study medication dispense	*	*	*	*		
HAMD, HAMA, CGI, BDI, SAS, RBANS, STROOP, ASEX, Somatic Self-rating Scale	*	*	*	*	*	*
CTQ, SSRS	*					
UKU		*	*	*	*	*
BMD	*				*	*
MRI	*				*	*

3 Overall Approach to Statistical Analysis

Data will be examined for obvious outliers, distribution irregularities, and range errors and processed accordingly. Prior to analyses, the validity of assumptions (e.g., about distributions) will be confirmed. Transformations will be made or a nonparametric procedure may be utilized as needed. Means, standard deviations, ranges or interquartile ranges, and rates of primary outcomes will be reported. Baseline demographics and characteristics will be compared among study groups using F-tests or chi-square tests

or nonparametric equivalents as needed. Baseline variables with significant group differences will be treated as potential confounder variables and will be statistically adjusted for in analyses. Unless stated otherwise, two-sided testing and a 5% level of significance are planned for all statistical tests.

The primary outcome measures will be the clinical symptoms Changes in Hamilton Depression Scale HAMD 6 weeks at week 0, week 4, week 12, week 24 and week 48 among study groups. Secondary outcome measures the Changes in Clinical Global Impression (CGI), Hamilton Anxiety Scale (HAMA), Beck Depression Rating Scale (BDI) and Self-Rating Anxiety Scale (SAS) at week 0, week 4, week 12, week 24 and week 48. And time to relapse for the maintenance phase of the study among study groups.

For hypothesis: Subjects who are randomized to the fish oil will have reduced clinical symptoms and perform better in cognition and improve metabolic markers; inflammation markers than those who are randomized to placebos.

Analyses: After transformation (if necessary to insure the improvement is linear), the difference in the rate of HAMD improvement of fish oil group will be compared with that of the placebo group and the linear mixed effects models will be performed using subjects as the random effect (i.e. the drug-time interaction, with adjustment for baseline values). Secondary analyses will include using GLM to test if treatment arms show effect on CGI, HAMA, BDI, SAS, and other psychological variables. We will also evaluate possible cofounders as well as improvement of neurocognitive domains score and CGI.

4 Key investigator list

Principal Investigator (PI)

Jindong Chen. M.D.

Chief Clinical Professor

Mental Health Institute

Second Xiangya Hospital of Central South University

139 Renmin Middle Road, Changsha, Hunan, China

Tel: +86 13807319266

E-mail: chenjd269@163.com, or chenjindong@csu.edu.cn

Mimi Tang. M.D. (Co-PI)

Department of Pharmacy Xiangya Hospital, Central South University

87 Xiangya Road, Changsha, Hunan, China

Tel: +8615802607545

E-mail: tangmimi1989@163.com