Omega-3 fatty acids for the treatment of depressive disorders in children and adolescents: the protocol for a meta-analysis

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Background

Depression is one of the most common mental disorder, with more than 350 million depressed people worldwide [1]. The prevalence of pediatric depression is also high, with approximately 2.8% of children and 5.6% of adolescents with depression all over the world [2]. What's worse, a seventy percent chance of pediatric depression will relapse in 5 years, and 50% of young people will experience a recurrence at least once during their adult life [3]. Depression does great harm to young people's social ability, and it is a major risk factor for suicide in adolescents [1,4]. However, pediatric depression is always under-diagnosed, because they possibly have no those typical depressive manifestations, such as irritability, mood fluctuating, and school refusal [5,6]. There are maily two interventions: psychotherapy and pharmacotherapy. Psychotherapy is always the first-line therapy in pediatric depression, but pharmacotherapy especially antidepressants is also widely used. However, in 2004 the US Food and Drug Administration (FDA) alerted clinicians to the increased suicide risk in children and adolescents associated with antidepressants use [7].

Omega-3 fatty acids (O3FA), a kind of nutrients, is composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It was reported an effective treatment for adult depression because the deficiency in O3FA increased the risk of depression [8-10]. As O3FA cannot be synthesized efficiently by human body, so dietary intake is the main source . The mechanism of O3FA in treating depression may be associated with its anti-inflammatory effects and cell membrane stability [11]. Several meta-analyses and reviews showed that supplementation of O3FAs could relieve symptoms of depression for adult age groups [12,13], but no such evidence especially studied in depressed children and adolescents. Therefore, this meta-analysis is designed to pool present evidences on efficacy and safety of O3FA in the treatment of children

and adolescents with depressive disorders.

Method

Criteria for included studies

Types of studies

Only randomized controlled trials (RCTs) with a parallel design will be selected. Studies will be excluded : trials without random design or with just quasi-random design; data of outcomes couldn't be acquired; studies with duplicated data..

Types of participants

Children aged 6-12 and/or adolescents aged 13-18 with depressive disorders will be included.

Types of interventions

The intervention group could be O3FA treatment, or any component of it (EPA or DHA), but no combined treatments like psychotherapy or antidepressants. The comparison group should be placebo treatment.

Types of outcome measures

The efficacy outcome should be assessed by depression scales, such as The Children's Depression Rating Scale (CDRS), revised CDRS (CDRS-R), Beck Depression Inventory (BDI) and Children's Depression Inventory (CDI). We use the end-point score of depressive scale in each group as our primary efficacy outcome. The secondary efficacy outcome is the response rate to omega-3 treatment. The response rate is defined as $\geqslant$50% change from baseline on depression score or a score of $\leqslant$28 at the end-point of a trial on the CDRS-R [14]. We also investigate all-cause discontinuation as safety outcome.

Search strategy

Electronic databases: PubMed, Embase, Cochrane Library, Web of Science, PsycINFO citations and ClinicalTrials.gov, will be searched with these search terms: ('omega-3' or 'n-3' or 'polyunsaturated fatty acid*' or 'unsaturated fatty acid*' or 'PUFA' or 'eicosapentaenoic acid' or 'docosahexaenoic acid' or 'EPA' or 'DHA') and ('child*' or 'adolesc*' or 'pediatri*') and ('depress*'

or ‘dysthymi*’ or ‘affective disorder*’ or ‘mood disorder*’). Relevant articles will be hand-searched for eligible reports. No limitations will be applied in the search.

Selection of trials

Two author review the titles and abstracts of all the searched records, independently. Based on titles and abstracts , the two author choose those potential records for further evaluation. After reviewing the full texts, those eligible will be included in our meta-analysis according to the criteria.

Data extraction

The following data are collected: publication information (the first author, publication year, study country), study and patients characteristics (study design type, sample size, age group, diagnostic criteria, severity of depression, rating scales, daily dosage and duration of O3FA, ratio or dosage of EPA and DHA), outcome data (baseline data, post-treatment data, drop-out rate, adverse events). Data will be extracted by the two reviewers (ZL and ZXY) independently. When meeting missing data or information, one author will e-mail the authors for further acquisition. Disagreements are resolved by discussion.

Quality assessment

Quality of studies will be assessed by the Cochrane Collaboration’s risk-of-bias method [15]. According to the Cochrane’s recommendations, we will appraise risk of bias from six domains, including random sequence generation, allocation concealment, blinding of participants and personnel, binding of outcome assessment, incomplete outcome data, and selective reporting and other bias. Each domain is rated as ‘high bias’, ‘low bias’ or ‘unclear’. Quality of studies will be assessed by the two reviewers (ZL and ZXY) independently. Disagreements are resolved by discussion.

Statistical analysis

We will use RevMan 5.3 version software and Stata 13.0 to perform all the analyses in the meta-analysis. We choose standard mean differences (SMDs) with 95% confidence intervals (CIs) to estimate effect size of continuous variables and the odds ratios (ORs) with 95%CIs to estimate effect size of dichotomous variables. For continuous variables, difference of the end-point data with standard deviation (SD) between O3FA and placebo is the effect value [16]. A random-effects model will be used to calculate the effect sizes for expected heterogeneity. If SD is unavailable in a article and could not contact the authors, we will calculate it from reported P values, t values, CIs or standard errors (SEs) in the article [17]. The heterogeneity will be calculated by the test of inconsistency (I^2) [18]. To investigate the possible sources of heterogeneity, we will conduct subgroup analyses. The publication bias will be evaluated by Egger tests when there are more than ten trials [19]. A two-sided P value of less than 0.05 is considered statistically significant.

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References

1. Marcus M, Yasamy MT, Ommeren MV, Van Ommeren M, Chisholm D, Saxena S, et al. Depression: A Global Public Health Concern. World Health Organization, Department of Mental Health and Substance Abuse, Geneva;2012.

2. Costello JE, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? J Child Psychol Psychiatry. 2006;47:1263-71.

3. Lopresti AL. A review of nutrient treatments for paediatric depression. J Affect Disord. 2015;181:24-32.

4. Hopkins K, Crosland P, Elliott N, Bewley S; for the Clinical Guidelines Update Committee B. Diagnosis and management of depression in children and young people: summary of updated NICE guidance. BMJ. 2015; 350: h824.

5. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012; 379(9820):1056-67.

6. Olfson M, Blanco C, Wang S, Laje G, Correll CU. National trends in the mental health care of children, adolescents, and adults by office-based physicians. JAMA Psychiatry. 2014;71(1): 81-90.

7. US Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications. Accessed 2 May 2018.

8. Delion S, Chalon S, Guilloteau D, Besnard JC, Durand G. Alpha-linolenic acid dietary deficiency alters age related changes in dopaminergic and serotinergic neurotransmission in the rat frontal cortex. J Neurochem. 1996;66(4):1582-91.

9. Takeuchi T, Fukumoto Y, Harada E. Influence of a dietary n23 fatty acid deficiency on the cerebral catecholamine contents, EEG and learning ability in rat. Behav Brain Res. 2002;131(1-2):193-203.

10. Alpert JE, Mischoulon D, Rubenstein GEF, Bottonari K, Nierenberg AA, Fava M. Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression. Ann Clin Psychiatry. 2002;14(1):33-8.

11. Grosso G, Galvano F, Marventano S, Malaguarnera M, Bucolo C, Drago F, et al. Omega-3 fatty acids and depression: scientific evidence and biological mechanisms. Oxidative Med Cell Longev. 2014;2014:313570.

12. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, et al. Role of Omega-3 Fatty Acids in the Treatment of Depressive Disorders: A Comprehensive Meta-Analysis of Randomized Clinical Trials. Plos one. 2014;9(5):e96905.

13. Scheffta C, Kilarskib LL, Tom B, Köhler S. Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis. Eur Neuropsychopharmacol. 2017;27(11):1090-109.

14. Riedel M, Möller HJ, Obermeier M, Schennach-Wolff R, Bauer M, Adli M, et al. Response and remission criteria in major depression-a validation of current practice. J Psychiatr Res. 2010;44(15):1063-8.

15. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. Chichester, UK: John Wiley & Sons; 2011.

16. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin epidemiol. 2006;59(1):7-10.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

18. Egger M, Davey Smith G, Schneider M, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

19. Egger M, Davey Smith G, Schneider M, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.