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Youth Depression Alleviation: The Fish Oil Youth Depression Study (YoDA-F). A randomised, double blind, placebo-controlled treatment trial.

STUDY PROTOCOL

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Abstract

Aim: US authorities have recommended 'black-box' warnings for antidepressants due to the increased risk of suicidality for individuals up to age 25. There is thus a clinical and ethical imperative to provide effective treatment for youth depression with an acceptable risk-benefit balance. Long-chain omega-3 polyunsaturated fatty acids (PUFAs) play an important role in a range of physiological processes in living organisms. Supplementation with omega-3 PUFAs has been shown to have a range of beneficial effects on both physical and mental health, and results of previous trials suggest that omega-3 PUFAs may be a safe and effective treatment for depression. However, conclusions from these trials have been limited by their relatively small sample sizes.

Methods: This trial will test the effectiveness of a 12-week parallel group, double-blind, randomised, placebo controlled trial of 1.4 grams/day omega-3 PUFAs in help seeking 15 to 25 year olds (N=400) presenting with major depressive disorder (MDD). The primary hypothesis is that young people will show greater improvement after 12-weeks of treatment with omega-3 PUFAs plus cognitive behavioural case management (CBCM) compared to treatment with placebo plus CBCM.

Conclusion: Due to using a large sample, results from this study will provide the strongest evidence to date to inform the use of omega-3 PUFAs as first-line therapy in young people presenting with MDD. The study also heralds an important step towards indicated prevention of persistent depression, which may reduce the burden, stigmatisation, disability, and economic consequences of this disorder.

Trial registration: Australian New Zealand Clinical Trials Registry: ACTRN12613001352796

Keywords: Omega-3 fatty acids, major depressive disorder, adolescents, young adults, randomised control trial.

Background

Adolescence and young adulthood are the peak periods for the onset of depressive disorders (1), which often develop into recurrent depression in later adulthood (2). This may in part be a consequence of active biochemical processes that are neurotoxic and further catalyse vulnerability (3), with the result that depression affects a larger proportion of the total life course than any other chronic condition, either physical or mental (4). Youth depression is associated with significant developmental disruption, which has effects through adult life, including lack of educational qualifications, welfare dependency, unemployment, and fewer close friendships and intimate relationships (5-7). There is also emerging evidence that the prevalence of depression may be rising (8), potentially driven by alterations in environmental factors (9).

The safety and effectiveness of antidepressants in the treatment of youth depression

While many clinical researchers argue that SSRIs have an important role in treating MDD in young people (e.g., (10,11)), others claim the contrary (12). In 2004, a meta-analysis concluded that SSRIs doubled the risk of both suicidal ideation and behaviour in young people (4% versus 2%) (13,14). Consequently, a 'black box' warning was issued by the United States Food and Drug Administration (US FDA) for this class of medication for young people aged up to 24 years (15). This was followed by similar warnings by the Medicines and Healthcare Products Regulatory Agency in the UK (16), the European Medicines Agency (17), and the Therapeutic Goods Administration in Australia (18). In 2006, the US FDA expanded their warning to include young people up to the age of 25 on the basis of an extended examination of placebo-controlled trials that included almost 100,000 patients (14). It is not clear why young people started on antidepressant medication are more likely to develop increased suicidality, though one hypothesis is that SSRIs induce mixed symptoms (such as agitation) in depressed patients with latent bipolarity (19). Additional concerns have been raised about the efficacy of antidepressants in young people (e.g., (20)). The results of a recent Cochrane systematic review found the effectiveness of antidepressants in young people to be modest at best (21,22).

Omega-3 polyunsaturated fatty acids and MDD

The industrialisation and urbanisation of Western countries in the last 150 years has been associated with a marked change in diet, with long-chain omega-3 polyunsaturated fatty acids (PUFAs) from fish, wild game, and plants being replaced by saturated fats from domestic animals and omega-6 PUFAs from common vegetable oils (23). These changes

in dietary patterns have led to a large increase in the ratio of omega-6 to omega-3 PUFAs in the general diet from 1:1 to more than 15:1 (24). This has resulted in a high proportion of omega-6 PUFAs (i.e., arachidonic acid) rather than omega-3 PUFAs (i.e., eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA)), in the cell membranes of most tissues, leading to increases in inflammatory eicosanoids, which have numerous pathological consequences and are potent promoters of chronic diseases such as atherosclerosis, essential hypertension, obesity, diabetes, arthritis and other autoimmune diseases, and many cancers (24).

In relation to mental health, it has been suggested that the sharp rises in rates of depression and other neurological disorders in the 20th century are being fuelled by increased consumption of vegetable oils rich in omega-6 PUFAs (25,26). The lower incidence of depression in populations with high intake of marine or sea fish (rich in omega-3 PUFAs) provides support for a link between life-time intake of omega-3 PUFAs and proneness to depression and other psychiatric disorders (27-30), although there are some conflicting results (31,32). As omega-3 PUFAs are essential, it is possible that major nutritional deficits may interfere with normal brain development and nerve functioning (33), in particular during pregnancy and early childhood, implying that such a deficit may be of importance for the development of psychiatric disorders such as MDD, bipolar disorder and schizophrenia (34,35). However, there are many confounding factors that may be able to explain the association between low omega-3 PUFAs and depression. It is well known that individuals with mental disorders have an increased intake of saturated fats, lower intake of omega-3 PUFAs, increased cigarette consumption and alcohol use, less exercise and more obesity. Each of these is transduced into increased inflammation and oxidative stress, which are risk pathways for depression (36,37). However, it remains unclear if the reduced intake of omega-3 PUFAs has a direct negative impact on the course of the illness or represents an epiphenomenon (38).

Reduced membrane PUFAs in major psychiatric disorders

Omega-3 PUFAs may play a role in the pathogenesis of major affective disorders (23,39). Alterations in fatty acids in MDD include a low omega-3 PUFA intake, a decrease in omega-3 PUFAs and increased omega-6/omega-3 PUFA ratios in plasma, erythrocytes, adipose tissue and post mortem brain tissue (40,41). The nature of these fatty acid alterations still has to be elucidated (42). The patterns of fatty acid alterations in MDD patients are not specific for depression but are also found in other (psychiatric) conditions

accompanied by increased oxidative stress, e.g., bipolar disorder, schizophrenia, diabetes, Alzheimer's disease, and are also seen during normal aging (43). Lipid peroxidation data suggest that increased oxidative stress may be one of the mechanisms of reduced membrane omega-3 PUFAs in people with psychiatric disorders such as MDD and schizophrenia (44,45). In addition, the findings imply that supplementation of PUFAs and/or antioxidants could provide effective treatments for the early stages of depression and other psychiatric disorders.

Treatment studies using omega-3 PUFAs in MDD

Meta-analyses of studies of omega-3 PUFAs for the treatment of mood disorders demonstrate benefits in placebo-controlled trials of unipolar and bipolar depression (23,46,47), although heterogeneity of study designs and results has been noted as a methodological concern (48-50). Studies vary with respect to the type of omega-3 PUFAs used, doses, and durations of trials. Most randomised controlled trials (RCTs) have included small numbers of patients who had MDD persistent despite treatment with an antidepressant, with omega-3 PUFAs added as adjunctive treatment. Peet and Horrobin (51) demonstrated a benefit of EPA at a dosage of 1g/d in an RCT (N=70) of 1, 2, or 4 g/d versus placebo in patients with MDD. Nemets et al (52) also found EPA at a dosage of 2g/d to be more efficacious than placebo in decreasing symptoms of depression in MDD (N=20). Su et al (53) and Silvers et al (54) used combinations of EPA and DHA in patients with MDD with differing results. Su et al demonstrated a benefit of EPA and DHA over placebo (N=28), while Silvers et al did not find a difference between omega-3 and placebo groups (N=77). A recent trial by Grenyer et al (55) of omega-3 PUFAs adjunctive to antidepressants (N=83) did not show a benefit over placebo, although unlike most studies that used a combination of EPA and DHA, the DHA dose was higher than the EPA dose.

Most placebo-controlled studies of omega-3 PUFAs in MDD have been undertaken in addition to antidepressant medication. A few studies have assessed omega-3 fatty acids as a monotherapy. In one study, DHA (2g/d) for MDD in 36 adults was not significantly more efficacious than placebo (56). In another small monotherapy trial of EPA for MDD (N=57), investigators observed a trend toward efficacy (P=0.087) for EPA at a dosage of 1g/d compared to placebo, with response on the Hamilton Depression Rating Scale as the primary outcome (57). One trial in children (N=28) demonstrated a benefit of omega-3 PUFAs (EPA and DHA) monotherapy compared with placebo (58). In another recent

study, investigators assessed EPA at a dosage of 1g/d versus fluoxetine 20mg/d versus the combination of the two for MDD in 60 patients (59). EPA and fluoxetine had similar efficacy, with the combination superior to either alone.

In summary, positive studies of omega-3 PUFAs in mood disorders have generally shown efficacy for treatment with EPA alone or EPA and DHA in combination (with EPA present in greater doses than DHA). Side effects of the recommended doses of omega-3 PUFAs in MDD are relatively minor and include mild gastrointestinal discomfort, most commonly burping or unpleasant taste. Although increased bleeding is a theoretical risk, no actual cases of bleeding have been reported, even though there have been high-dose trials in which patients were medically compromised, postoperative, and/or using concomitant anticoagulants. Doses of 1 to 9 g/d of omega-3 PUFAs have been studied in mood disorders, with a majority of evidence supporting efficacy doses in the lower end of this range. A dose-finding study using 3 doses of DHA monotherapy demonstrated greater efficacy at 1 g/d compared to 2 g/d and 4 g/d (60), consistent with the findings of an RCT of ethyl-EPA as adjunctive treatment in MDD that showed greater benefit at lower doses (51). Adjunctive EPA or the combination of EPA and DHA, containing EPA $\geq$ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, appear most useful (47). However, the general health benefits of omega-3 PUFAs, epidemiologic evidence, modest efficacy data in MDD, and low risks make omega-3 PUFAs a reasonable treatment strategy for depression in particular in young people.

Study rationale

Omega-3 PUFAs have been shown to be very safe and are free of clinically relevant adverse effects. They have the advantage of excellent tolerability, public acceptance, relatively low costs, and benefits for general health. Epidemiological data linking fish intake with depression (28); observations of alterations in the fatty acid status of people with MDD (40); oxidative stress and inflammation in depression may further deplete omega-3 PUFA stores; and RCTs of omega-3 PUFAs in adults with MDD (for reviews see: (46,47)), suggest that omega-3 PUFAs may offer a viable treatment and prevention strategy for depression in young people with minimal associated risk.

To date, no study has investigated treatment with omega-3 PUFAs in adolescents and young adults up to the age of 25. Studies such as TADS (61) and ADAPT (62) enrolled

depressed patients from late childhood up to mid-adolescence; and by including patients in pre-pubertal, peri-pubertal and post-pubertal development periods such studies were likely to have increased the heterogeneity of the depression being investigated. The period from post-puberty to 25 years of age is continuous in a neurodevelopmental sense — studies show that important brain maturational processes start from puberty and continue up to the age of 25 (63) — and as the peak period for the onset of first episodes of depression (64), it is a key time for effective interventions. The importance of studies that include patients in this age range has been further emphasised by the FDA's extension of its 'black box' warning to patients up to the age of 25.

Hypotheses

We aim to answer an important clinical question: can major depressive disorder (MDD) in young people aged 15 to 25 be effectively treated with long-chain omega-3 PUFAs ('fish oil')? The primary hypothesis is that young people with MDD will show greater improvement after 12-weeks of treatment with omega-3 PUFAs plus CBCM compared to treatment with placebo plus CBCM. The primary outcome measure the clinician administered version of the Quick Inventory of Depression Symptomatology, Adolescent Version (QIDS-A17-C) (67). The secondary hypotheses predict that; at weeks 12 and 26, relative to placebo, treatment with omega-3 PUFAs will result in improved: (i) treatment response (defined as clinical global impression improvement score of $\leq$2 (68)); (ii) remission rate (defined by a score of $\leq$6 on the QIDS-A17-C); and (iii) MDD diagnosis rate (as assessed by structured clinical interview (69)). Finally, relative to placebo those treated with omega-3 PUFAs are expected to continue to report improved: (iv) change from baseline on QIDS-A17-C scores at 26-weeeks.

Methods/Design

Study objectives and design

The study will adopt a 12-week, double blind, parallel group, RCT design. A total of 400 (200 per arm) participants with MDD will be allocated to treatment with either omega-3 PUFAs plus cognitive behavioural case management (CBCM; see below) or to treatment with placebo plus CBCM. The total length of follow-up is 6 months. The study will be conducted in accordance with Good Clinical Practice guidelines (65). The protocol addresses the applicable SPIRIT guidelines that pertain to trial methodology (66). Ethical

approval for the trial, as described here, has been granted by the University of Sydney Human Research Ethics Committee (2012/2920).

Setting

The study will be conducted at participating *headspace* centres in Australia. *Headspace* centres provide an enhanced primary care services specialising in the treatment of emerging psychiatric disorders in young people (12-25 years) (70). Clinical services at *headspace* centres are delivered by a multidisciplinary group of clinicians e.g., nurses, occupational therapists, social workers, clinical psychologists and psychologists, GPs and psychiatrists.

Participants

All people presenting to participating *headspace* centres will be screened for eligibility. *Inclusion criteria* are: (i) being between age 15 and 25 at presentation; (ii) help seeking for psychological distress; (iii) moderate to severe depression, indicated by a score of ≥11 and ≤20 on the QIDS-A17-C (67) at first contact with the service, and again after approximately one week; (iv) a diagnosis of MDD at baseline (i.e., when the second QIDS-A17-C is completed) using a structured clinical interview (69); and (v) the ability to give informed consent (for individuals under 18, written informed consent of at least one parent or a guardian is required). *Exclusion criteria* are: (i) lifetime diagnosis or history of treatment for psychotic disorder or bipolar disorder or substance dependence; (ii) history of treatment with an antidepressant (more than four weeks during the last 12-months); (iii) acute suicidal behaviour or aggressive behaviour (indicated by a Comprehensive Assessment of At-risk Metal State (CAARMS) (71) score of 6 on the relevant items); (iv) depression secondary to a medical condition (e.g., low vitamin D level); (v) IQ < 70; (vi) pregnancy (indicated by blood test) or lactation; (vii) laboratory values more than 15% outside the normal range for bleeding parameters; (viii) current (or recent; within eight weeks of being included in the trial, for more than one week) use of omega-3 supplements or psychotropic medication; and (ix) known allergy of omega-3 supplements.

The trial will also use the following exit / transition criteria (i.e., indicating a participant develops more severe psychiatric symptoms that typically require psychotropic medication) and study withdrawal criteria (i.e., indicating a violation to protocol or safety concerns). Participants will *exit* the trial if they meet any of the following criteria: (i) develop very severe depression, as indicated by report a QIDS-A17-C score of >20 for a

period of four weeks; (ii) develop a first-episode psychotic disorder or manic episode; and/or (iii) are commenced on a regular psychotropic medication regime (i.e., antidepressant, antipsychotic, mood stabiliser). Participants who exit the trial (as per the above criteria) will be offered continuation of the trial medication up to 12 weeks while active treatments (e.g., antidepressant, antipsychotic or mood stabiliser) are commenced. To the extent possible, ongoing data will be collected per protocol. *Withdrawal criteria* (i.e., withdrawn from trial) will be applied if any participants experience: (i) a serious adverse event (e.g., severe gastrointestinal symptoms >1 week); (ii) acute suicidal behaviour (6 on CAARMS item 7.3); (iii) aggressive behavior (6 on CAARMS item 5.4); (iv) pregnancy; (v) commencement on omega-3 supplements other than the investigational product; and/or (vi) a break to the randomisation code (i.e., if circumstances require breaking of blinding before week 12).

Procedure

Randomisation and Treatment Allocation

This is a double blind randomised controlled trial. Allocation to treatment will be concealed and carried out by a statistician uninvolved with the conduct of the intervention or participant assessment. Permuted block randomisation with randomised block length of 2, 4 or 6 and treatment allocation will be managed within the trial management system. Randomisation will be stratified by site *(headspace* centre location), age ($< 18, \geq 18$), and sex (male, female). Participants will be randomised to one of two possible treatment groups. The participants, treating clinicians, and research personnel (including research assistants, investigators, study statistician, and project manager) will all remain blinded to treatment allocation until database lock.

The *headspace* access team will assist in identifying potential participants. Individuals will be assessed for eligibility at initial contact with *headspace* by a clinician as part of the routine clinical assessment. Once a participant is randomised, their treatment group allocation will be sent by the trial management system via an automatically generated email to the trial pharmacist. Access to online unblinding via the trial management system will be available and validated for emergency situations.

Side effects and safety

In all omega-3 PUFA trials, no treatment-related side effects or adverse biochemical or haematological effects have been observed (23,46,47). Omega-3s did not cause side effects other than mild gastrointestinal symptoms as a monotherapy, nor did it enhance the side effects of existing drugs. Patients usually find omega-3 PUFAs highly tolerable. In our previous psychosis prevention RCT, 94% of participants completed the 12-week intervention period (72).

In order to assure the safety of the study participants, risk (i.e., suicidal behaviour and aggressive behaviour) will be assessed weekly throughout the 12-week intervention period; this is a study withdrawal criterion (see: Withdrawal criteria, above). A research assistant will carry out the weekly safety assessments and immediately notify the treating team in instances of high risk to self or others (as per the approved protocol). Another safety measure implemented in this study are the Exit criteria; a person exits the trial by having a score of >20 on the QIDS-A17-C over 4 weeks, or by developing a first-episode of a psychotic disorder or mania (see: Exit criteria, above).

Interventions

Participants will receive either omega-3 PUFAs or placebo for 12-weeks. The experimental intervention will be provided in addition to 50-minute sessions of cognitive-behavioural case management (CBCM), which are offered as part of the study by a trial therapist, during the 12-week intervention period (approximately fortnightly). Depending on the participant's needs, additional sessions may be provided. After the 12-week intervention period (or if a participant meets exit or withdrawal criteria), treatment as usual will be provided by *headspace* clinicians. For the purposes of the study analyses, 'entry' will be considered to be the date the participant commences the study medication.

Cognitive-behavioural case management (CBCM): CBCM consists of cognitive-behavioural therapy (CBT) embedded within case management as per standard care at *headspace*. The treating clinicians will use a specifically developed manual that details the CBCM to be delivered in the trial, and which outlines the minimum standard of treatment to be delivered. The number of sessions delivered will be recorded for each client. In addition, fidelity will be monitored by therapists rating their own sessions on an established checklist of therapeutic interventions. Any additional interventions delivered

will also be documented. The case management component will consist of therapists addressing current issues relevant to the person and providing practical help.

Experimental intervention: The oral intervention comprises a daily dose of 4 gelatine capsules (participants will be instructed to take 2 in the morning and 2 at night; before meals) throughout the 12-week treatment period. Participants will receive bottles of capsules containing either: (i) 0.650 – 0.750 g concentrated marine fish oil (active treatment); or (ii) 0.650 – 0.750 g of paraffin oil (placebo).

Active treatment: The daily dose of concentrated marine fish oil will provide approximately 840 mg of eicosapentaenoic acid (EPA, 20:5n3), 560 mg of docosahexaenoic acid (DHA, 22:6n3), and 5 mg of vitamin E (which is added as an antioxidant to stabilise the PUFAs). Thus, patients who are randomised to receive fish oil will be taking a total of approximately 1.4g of omega-3 PUFAs per day. This daily dose omega-3 PUFAs is based on similar trials in major depression (23,46,47).

Placebo intervention: Paraffin oil was specifically chosen as placebo because it does not contain PUFAs and has no impact on omega-3 PUFA metabolism. To ensure blinding, placebo capsules will be carefully matched in appearance and flavour with the active treatment; they will also contain the same amount of vitamin E as the fish oil capsules, and approximately 1% fish oil to mimic taste.

Compliance assessment: Patient compliance will be assessed by monthly pill counts over the course of the study, as well as through self-report and the measurement of the PUFA content of red blood cells from blood samples collected at baseline and 12 weeks after study entry. The blood samples will be stored frozen for batched analysis. The results of the fatty acid analysis will not be revealed to the investigator until the end of the study.

Labelling, storage and accountability: The study medication will be labelled in compliance with local regulatory requirements and stored securely at an appropriate temperature. Accountability records will be maintained. Storage and accountability details, as well as information on how to obtain the study medication, will be specified in the YoDA-F Pharmacy Manual. Unblinding will only be permitted in the case of a medical necessity when the appropriate management of the patient necessitates knowledge of the treatment randomisation. All instances of unblinding will be documented.

Concomitant medication: The use of psychotropic medication or omega-3 PUFA supplementation other than the investigational product is not permitted at any time during the trial unless a participant is withdrawn from the study and these treatments are deemed necessary according to local clinical practice guidelines. All treatments administered will be captured in the 26-week course of the trial.

Outcome measures

Study assessments: Study assessments will be completed at baseline (i.e., prior to randomisation), and every 4 weeks for the 12 weeks of the trial. The primary endpoint is week 12. After week 12, participants receive *headspac*e standard care, and all treatment interventions will be documented until week 26. The final assessment will be completed at 26 weeks. The primary outcome measure is between group differences in change in depressive symptoms from baseline to 12 weeks, which will be assessed with the QIDS-A17-C (67). The QIDS-A17-C has been shown to be a reliable tool for assessing adolescent depression, making it one of the few depression scales that has been validated across adolescent and adult populations. In addition to the QIDS-A17-C, interviewer administered study assessments will include: (i) the Structured Clinical Interview for DSM- IV Axis I Disorders, patient version (69); (ii) the Montgomery-Asberg Depression Rating Scale (73); (iii) the Columbia Suicide Severity Rating Scale (C-SSRS; baseline and since last visit) (74); (iv) Comprehensive Assessment of at Risk Mental State (CAARMS) (71); (v) the Young Mania Rating Scale (75); (vi) the Social and Occupational Functioning Scale (76); and (vii) the Clinical Global Impressions Scale (68). Self-report study assessments will include: (i) the Kessler Psychological Distress Scale (89); (ii) the Overall Anxiety Severity and Impairment Scale (77); (iii) the Generalized Anxiety Disorder Assessment (78); (iv) the Alcohol, Smoking And Substance Involvement Screening Test (79); (v) the Dietary Questionnaire for Epidemiological Studies (Version 2) (80); and (vi) the Altman self-report mania screen (81). Ratings of therapeutic alliance (undertaken by participants and by their treating clinician) will also be made at Week-12 using the Working Alliance Inventory (82).

Safety assessments: Participants will be assessed weekly (until 2 weeks after the 12-week treatment phase) for the presence of suicidal ideation and harm-related behaviours. The weekly safety assessments will focus on suicidality and aggressiveness, subscales of the CAARMS. A record will be made of any adverse event that arises during the trial. An

adverse event will be defined as any unfavourable medical change that is accompanied by functional or clinical impairment, which may or may not be related to the study treatment. Any undesirable medical condition occurring from the time of signing consent (even if no study treatment or pharmaceutical product has been administered) will be considered to constitute an adverse event. Adverse events will be recorded using the Antidepressant Side-Effect Checklist (ASEC) (83).

Biochemical assessments: At baseline and week-12 biochemical assessments will be carried out in erythrocytes and serum, measuring oxidative stress markers (e.g., superoxide dismutase, glutathione, glutathione peroxidase, catalase), cytokines (e.g., interleukin-1, interleukin-6), phospholipase A2 (a key enzyme of phospholipid synthesis) and fasting erythrocyte membrane fatty acid/phospholipid composition (using mass spectrometry). The ratio of omega-6 to omega-3 will be used to index pre- vs. post-treatment PUFA composition as an objective measure of treatment adherence. Biochemical samples will be processed (centrifuged and aliquoted), and then frozen at -70 to -80°C until the time of analyses. Clinical blood analysis will be undertaken at baseline, and used to inform the inclusion criteria (e.g., bleeding parameters).

Statistical analysis

Primary analyses will be undertaken on an intention to treat basis, including all participants as randomised, regardless of treatment actually received. Effectiveness of omega-3 PUFAs will be established using a planned contrast of change from baseline to the week 12 endpoint in the active compared to placebo condition on the QIDS-A17-C within a mixed-model repeated measures (MMRM) analysis (84). Stratification variables will be evaluated and retained in analyses where they are significant or quasi significant. An unconstrained variance-covariance matrix will model within-individual dependencies. Transformation of scores, including categorization, may be undertaken in order to meet distributional assumptions and accommodate outliers. Contrasts comparing change on the QIDS-A17-C from baseline to other time points will be undertaken as secondary analyses. Should the number of participants meeting exit/transition criteria be non-negligible (defined as greater than 5% in either treatment arm), transition rates and time to transition will be considered as a secondary outcome and be subject to analysis using survival methods (88). Under these circumstances, analyses of continuous measures that treat exit as a competing outcome will be explored.

Models for binary outcomes analogous to the primary analysis approach will be used to compare the remission rates (MDD status) and other dichotomous outcomes between the two treatment arms at endpoint and other occasions of measurement. Relative and absolute risk reduction, number needed to treat (NNT) (85) and other relevant indices will be calculated for these outcomes. Analyses of scaled secondary variables will use comparable methods to the primary analysis. Subsidiary per protocol and related analyses will estimate the efficacy of omega-3 PUFAs in participants who have received an adequate dose of the supplement. Exploratory analyses will examine the effects of moderators and mediators of treatment (see (86)).

Safety data will be compared between treatment arms — in particular, the rates of harm and suicide-related adverse events — using Fisher's exact test. All tests will be conducted using a two-sided alpha level of 0.05 and 95% confidence intervals.

Power and sample size

The target sample size for the study is 400. Allowing for dropout or withdrawal of up to 20% participants, this sample will allow differences in change from baseline to endpoint of .31 standard deviations to be detected with 80% power. These calculations assume a correlation of 0.5 between baseline and endpoint measurements, alpha of 0.05, two-tailed test. This effect size is within the range observed for a wide variety of adjunctive treatments for depression and lies at the lower end of clinical utility. Confidence intervals for effect sizes will be approximately ±0.2 with the result that at the target sample size, the trial will be informative even if the outcome is not statistically significant. Although the study has not been powered for a binary primary outcome, power to detect differences in proportions at endpoint is quite high, with 80% power maintained for differences between groups of approximately 15%.

Discussion

The results of previous intervention trials suggest that omega-3 PUFAs may offer a safe and effective treatment for depression. However, conclusions from these trials are uncertain due to relatively small sample sizes. The use of antidepressants in young people is debatable (12,87). No antidepressants are currently approved for the treatment of major depressive disorder in this vulnerable population of young people < 18 years in Australia

(18), while US authorities have recommended that for individuals up to 25 years of age 'black-box' warnings about the increased risk of suicidality (14). There is a clinical and ethical imperative to provide effective treatment with an acceptable risk-benefit balance.

Omega-3 PUFAs are an ideal candidate for further evaluation for indicated prevention; there is consumer acceptance of a naturally occurring substance without significant side effects, omega-3 PUFAs have an evidence base in adult depression, and efficacy has been shown across a broad range of psychiatric disorders and conditions including depression, schizophrenia, bipolar disorder, borderline personality disorder, and substance use. Another important advantage of omega-3 PUFAs is that they are widely available and can be easily administered in large numbers of people in various settings. In contrast, psychotherapeutic treatments need specifically trained and skilled therapists providing the intervention which is an important limitation to their preventive use and research.

If found effective, this study could help establish omega-3 PUFAs as a novel, stigma-free first-line treatment in youth depression without causing clinically relevant side effects. Such a finding would be a significant development with major benefits for consumers and carers, and may prevent the progression to more serious stages of illness.

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Trial status

Participant recruitment is due to commence in April 2014.

Trial Sponsor

Orygen Youth Health Research Centre, Melbourne, AUSTRALIA

Study Monitoring

The trial will be monitored by an independent Data and Safety Monitoring Committee (DSMC). The DSMC Charter can be obtained from the senior author.

Author contributions

GPA, IBH, MB, CD, PM conceived of the study, and along with AM, AY, DH, SR, SH, AP participated in its design. GPA and SR drafted the manuscript with input from all authors. The final manuscript has been read and approved by all authors.

Competing interests

None

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