Short-term supplementation of acute long-chain omega-3 polyunsaturated fatty acids may alter depression status and decrease symptomology among young adults with depression: A preliminary randomized and placebo controlled trial

Annie T. Gintya,*, Sarah M. Conklinb

a Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
b Psychology, Neuroscience, and Global Health Studies, Allegheny College, Meadville, PA, USA

Abstract

The current study examined the psychological effects of acute and low-dose long-chain omega-3 polyunsaturated fatty acids (LCPUFAs) supplementation on young adults with depressive symptoms. Participants (N=23, M age (SD)=20.2 (1.25), 78% female), with a Beck Depression Inventory (BDI) score of greater than 10, were randomly assigned to a placebo (corn oil) or LCPUFAs group (1.4 g of eicosa-pentaenoic and docosahexaenoic acids) and were instructed to consume the assigned capsules daily for 21-days. BDI was completed prior to supplementation and at day 21. Group differences in depression status on day 21 were analyzed using chi-square tests. After 21-days of supplementation, there was a significant difference in depression status between groups. 67% of the LCPUFAs no longer met criteria for being depressed, while only 20% in the placebo group were no longer depressed. A mixed ANOVA revealed a significant group x time interaction for BDI scores. Post-hoc analyses revealed the LCPUFAs group had a significant reduction in BDI scores over time, while the placebo group’s scores did not significantly change. These findings suggest that LCPUFAs may alter depression and depressive symptomology in young adults in a relatively short amount of time.

1. Introduction

Depression affects 350 million people worldwide, making it one of the most common mental disorders (World Health Organization, 2012). American College Health Association (2012) recently found that 30% of undergraduate students have felt so depressed that it hindered their ability to function and 6% seriously considered suicide in the 12 months prior to the survey. Despite the prevalence, over 33% of cases in developed countries and 66% of cases among undergraduate students do not receive proper treatment (Demyttenaere et al., 2004; Active Minds, 2014). Therefore, it is crucial to assess and develop appropriate treatment interventions that are accessible to the general public.

Long-chain omega-3 polyunsaturated fatty acids (LCPUFAs) have shown promise in reducing depressive symptoms among those with major depressive disorder (Grosso et al., 2014a, 2014b; Lin and Su, 2007). However, some suggest that the complexity of combining LCPUFAs with antidepressant therapies makes it difficult to interpret these results (Appleton et al., 2007). Research examining the influence of LCPUFAs on depressed individuals not currently taking antidepressants is limited to a middle-age population and has produced mixed results (Rogers et al., 2008; Lucas et al., 2009). LCPUFAs have shown some benefit in reducing depression (Fontani et al., 2005) and fatigue (Antypa et al., 2009) in healthy undergraduate students. However, there has been scant research examining how LCPUFAs influence depressive symptoms in undergraduate students who currently meet criteria for depression.

The aim of the current study was to examine the psychological effects of acute and low-dose, equivalent of adding two fatty fish meals per week to their diet, LCPUFAs supplementation on undergraduate students with BDI scores indicative of depression who were not receiving any other treatment.

2. Methods

2.1. Participants

Twenty-three undergraduate students (age range 18–21 years; 78% female) with a score of 10 or above on the Beck Depression Inventory were randomly assigned to a placebo (corn oil) or LCPUFAs group (1.4 g of eicosa-pentaenoic and docosahexaenoic acids) and were instructed to consume the assigned capsules daily for 21-days. BDI was completed prior to supplementation and at day 21. Group differences in depression status on day 21 were analyzed using chi-square tests. After 21-days of supplementation, there was a significant difference in depression status between groups. 67% of the LCPUFAs no longer met criteria for being depressed, while only 20% in the placebo group were no longer depressed. A mixed ANOVA revealed a significant group x time interaction for BDI scores. Post-hoc analyses revealed the LCPUFAs group had a significant reduction in BDI scores over time, while the placebo group’s scores did not significantly change. These findings suggest that LCPUFAs may alter depression and depressive symptomology in young adults in a relatively short amount of time.
Inventory (BDI) were included in the present study. Participants were recruited through flyers placed across the college campus and announcements in Introductory Psychology courses during the summer and beginning of fall and spring semesters. Advertisements, which were also used as recruitment for a larger study, asked for healthy young adult volunteers. Participants were screened for exclusion criteria prior to enrollment in the study and those who had a BDI score of 10 or above were included in this study. Exclusion criteria included: taking any type of antidepressant or antianxiety medication, a change in medication over the past month (e.g., inhalers), diets that exceeded 2 fatty fish meals per week, current use of omega-3 fatty acid supplementation, or smoking more than 1 pack of cigarettes per week. None of the participants in the study had a previous history of receiving medication for a clinical diagnosis. The study was approved by the college Institutional Review board and all participants gave informed consent and understood they could withdraw from the study at any time.

2.2. Supplementation, design

Participants attended two laboratory visits (Visit 1 and Visit 2) during the summer or beginning of the academic semester. None of the visits took place during mid-term or final examinations. During Visit 1 participants completed questionnaires and were provided with either a 21-day supply of LCPUFAs or a matched placebo. Both the LCPUFAs and placebos were in identical foil blister packaging with different lot numbers printed on the foil. Participants were instructed to take the supplement every day until their follow-up visit (21 days later). Participants were randomly assigned using a number generator to one of two groups receiving either a 21-day supply of LCPUFAs (1000 mg EPA and 400 mg DHA) or a matched placebo (corn oil). The 1.4 g dose was selected on the basis that it could be obtained through minor diet changes in the future and the acute duration was selected based on the timing of therapeutic effects shown in a previous 8-week study of depressed adults (Su et al., 2003). LCPUFAs and placebos were provided by Nourish Life (Lake Forest, Illinois, USA) and were blinded with mint oil. The blind was broken by the manufacturer at the end of the study. The study was double-blinded neither participants nor experimenters knew which group participants were in until the last participant completed the study. After the last participant completed the study, sealed envelopes, were broken that revealed which groups the lot numbers were associated with.

2.3. Depression assessment

Participants completed the BDI at Visit 1 and during Visit 2, 21 days after supplementation. The BDI (Beck et al., 1996) is a 21-item self-report measure of depressive symptomatology (i.e., sadness, guilt, self-hate) during the past week. Participants respond to phrases that signal increasing symptom severity on a scale of 0–3. Scores can range from 0 to 63 with scores at or above 10 reflecting clinical significance (Deardorff and Funabiki, 1985). The BDI has acceptable internal consistency for both psychiatric (Cronbach’s alpha α = 0.86) and non-psychiatric (chronbach’s α = 0.86) individuals (Beck et al., 1988). The BDI demonstrates good test–retest reliability (0.96) among college students (Sprinkle et al., 2002). Recent research suggests it is important to examine the different components (e.g., cognitive, somatic) that contribute to depression (Stewart et al., 2012; Khambaty et al., 2014). With this in mind, the subscales (cognitive–affective and somatic–vegetative) were also calculated (Dozois et al., 1998). The cognitive–affective subscale consists of the following items: sadness, pessimism, past failures, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, indecisiveness, and worthlessness. The somatic–vegetative subscale consists of the following items: loss of pleasure, crying, agitation, loss of interest, loss of energy, changes in sleep, irritability, changes in appetite, concentration, tiredness–fatigue, and loss of interest in sex (Dozois et al., 1998).

2.4. Statistical analysis

Group differences in baseline BDI scores, age, and gender were explored using univariate ANOVAs and chi-square. Group differences in depression status at the final appointment were examined using chi-square test for independence. Analyses of group differences in depressive symptomatology across time were examined using a mixed-design ANOVA. Additional analyses using the last observation carried forward (LOCF) were used to accommodate missing follow-up BDI scores for two participants who did not complete Visit 2. A recent systematic review of analgesic clinical trials found LOCF to be the most common method used to impute missing data; 42% used this approach (Gewandter et al., 2014).

3. Results

Twenty-one of the 23 participants completed the study. Two participants did not return for the follow-up testing, one from the LCPUFA group and one from the placebo group. Therefore, the final analysis included 21 participants, LCPUFA (n = 12, %female = 62) and placebo (n = 9, %female = 100).

3.1. Demographics and baseline BDI

There were no differences between groups in baseline BDI scores (p = 0.54) or age (p = 0.56). There was a significant difference for gender, χ²(21) = 4.92, p = 0.03. Means and standard deviations are reported in Table 1.

3.2. Group changes in depression across time

Chi-square analyses indicated a significant difference in depression status between groups after supplementation, p = 0.04. 67% of the LCPUFA group no longer had a BDI score equal to or greater than 10, but only 20% of the placebo group met such criteria. There was a significant group x time interaction for total BDI score, F(1,19) = 4.72, p = 0.043, η² = 0.199. Post-hoc analyses revealed the LCPUFAs group had a significant reduction in depressive symptomatology over time, while the placebo group’s scores did not significantly change. There was a main effect for time, F(1,19) = 9.46, p = 0.006, η² = 0.33, but not for group (p = 0.34). There was a significant group x time interaction for the cognitive–affective subscale of the BDI, F(1,19) = 7.02, p = 0.016, η² = 0.270. Post-hoc analyses revealed the LCPUFAs group had a significant reduction in cognitive–affective symptomatology over time, while the placebo group’s scores did not significantly change. There was also a main effect for time, F(1,19) = 5.34, p = 0.032, η² = 0.219, but no main

Table 1

<table>
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<tr>
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<th>LCPUFAs (n=12)</th>
<th>Placebo (n=9)</th>
</tr>
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<tbody>
<tr>
<td>%female</td>
<td>62%</td>
<td>100%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.33 (1.15)</td>
<td>20.00 (1.14)</td>
</tr>
<tr>
<td>BDI total</td>
<td>15.58 (5.21)</td>
<td>15.89 (5.46)</td>
</tr>
<tr>
<td>BDI cognitive–affective subscale</td>
<td>7.00 (4.52)</td>
<td>9.00 (4.30)</td>
</tr>
<tr>
<td>BDI somatic–vegetative subscale</td>
<td>8.17 (2.29)</td>
<td>6.89 (2.93)</td>
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4. Discussion

The present double-blind, placebo controlled study examined the psychological effects of a short-term and low dose LCPUFAs supplementation (1.4 g, 1000 mg EPA and 400 mg DHA) on unmedicated and untreated undergraduate students with symptoms of depression. The results demonstrated that LCPUFAs, but not placebo, were successful in reducing depressive symptomology and depression below clinically indicated levels. The reduction in overall depressive symptoms was driven by a decrease in the cognitive–affective subscale of depression on the BDI-II.

Our results support two meta-analyses examining the effectiveness of LCPUFAs in reducing depression (Grosso et al., 2014a; Lin and Su, 2007). Previous research examining the influence of LCPUFAs on depressive levels in an unmedicated middle-aged sample with psychological distress (Lucas et al., 2009) and healthy undergraduate students (Fontani et al., 2005) also found similar results. However, our findings are at odds with a similar study examining the influence of LCPUFAs on an unmedicated, middle-aged population with depression (Rogers et al., 2008). This could be due to the difference in EPA (1000 mg in the current study, 630 mg in the other study); EPA has been shown to be more effective in reducing depressive symptomology than DHA (Lin and Su, 2007).

To our knowledge, this is the first study to demonstrate the effectiveness of a short-term, low-dose of LCPUFAs in reducing depressive symptomology in undergraduate students meeting clinical criteria for depression not currently receiving any other treatment. According to the American College Health Association’s National College Health Assessment (2011) over two-thirds of college students report feeling “very sad” and one-third feel so sad it inhibits their ability to function. However, a recent study found that only 36% of undergraduates who had clinically significant depression levels were actually receiving some form of treatment (Eisenberg et al., 2007). Each year, over 1000 undergraduate students commit suicide in the United States and most of these students were not seen by their college’s counseling center (Active Minds, 2014; Gallagher, 2006). Therefore, it is important to continue to conduct studies in this particular population to examine ways to reduce depressive symptomology. Results from studies such as this suggest that dietary changes may be a relatively easy and inexpensive option for students who are currently struggling with depression.

A decrease in HPA axis activity and inflammation levels or a change in neurotransmitter system activity could explain the reduction in depression symptoms in the LCPUFAs group. A deficiency of LCPUFA has been associated with hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis (Nieminen et al., 2006) and a recent animal study demonstrated that HPA hyperactivity caused by LCPUFA deficiency led to atrophy in the prefrontal cortex and negative mood (Larrieu et al., in press). Atrophy of the prefrontal cortex has been associated with depression (e.g., Drevets et al., 1997). A recent study, demonstrated that a 3-week supplementation of LCPUFAs resulted in decreased basal HPA axis activity and decreases in stress/anxiety ratings before and after a psychological challenge (Barbadoro et al., 2013). A positive relationship between dietary LCPUFAs intake and the volume of multiple prominent nodes of corticolimbic circuitry has been established (Conklin et al., 2007a). Therefore, it is plausible that the increase in LCPUFAs in this sample led to a decrease in HPA axis activity and/or structural change in brain areas associated with affective experience. However, it seems unlikely that 21-days of supplementation could alter gray matter volume. This is something that needs to be explored in future studies.

Another possible mechanism linking supplemental LCPUFA with mood improvement could be a reduction in inflammation as...
a result of the increase in LCPUFAs. High levels of omega-6 PUFA
compared to omega-3 PUFA are related to higher levels of de-
pression and inflammation (Conklin et al., 2007b; Kiecolt-Glaser et al., 2007). Two randomized controlled trials have shown
the LCPUFAs can reduce inflammation levels in healthy medical stu-
dents (Kiecolt-Glaser et al., 2011) and healthy middle-aged adults
(Kiecolt-Glaser et al., 2012). Both higher cognitive–affective
symptoms (Kupper et al., 2012; Shaffet et al., 2011) and somatic–
vegetative symptoms have been associated with increased levels
of inflammation (Dannehl et al., 2014). In this study we only saw
a significant decrease in cognitive–affective symptoms. Recent re-
views have discussed the importance of reducing inflammation as
a method of treatment for depression (Raison and Miller, 2013;

An additional mechanism that could explain the findings is
changes in serotoninergic and dopaminergic transmission (Grosso et al., 2014b). The unsaturated structure of LCPUFAs facilitates
alteration of membrane fluidity (Calder et al., 1994) and thereby
the function and regulation of monoaminergic systems, specifically
serotonergic and dopaminergic diffuse modulatory systems (Grosso et al., 2014b). Deficient levels of PUFA are associated with
deficits of serotonin and dopamine in the prefrontal cortex
(McNamara et al., 2009, 2010). Cognitive–affective components of
depression are associated with impaired prefrontal cortex activity
(Heinzel et al., 2009; Mayberg, 1997, 2003; Mayberg et al., 1999). A
recent study found that providing rats with LCPUFAs increased
dopamine levels in the frontal cortex by 40% (Chalon et al., 1998).
It could be possible that the decrease in depression, specifically the
decrease in cognitive–affective symptoms, could be driven by
alternations in neuromodulation, specifically serotoninergic and
dopaminergic transmission.

The study is not without limitations. First, the sample size is
small. However it is similar to other studies examining the asso-
ciation between LCPUFAs supplementation and mood (e.g., Su et
al., 2003; Zanarini and Frankenberg, 2003; Nemets et al., 2002). Second,
the gender composition was different between groups. The
placebo group consisted only of females and future studies
should use stratified randomization. However, Fig. 1 demonstrates
that the reduction in depressive symptomology across time was
similar for both males and females in the LCPUFAs group. Third,
blood samples were not obtained to verify compliance. Although
blood sampling would have been useful, practical considerations
prevented this from occurring. Fourth, participants were not asked
if they knew what group they were in. However, a recent study
using the same concentration and same mint blind in a similar age
group, but completely independent sample, found that partici-
pants were unable to correctly guess if they were in the LCPUFAs
or placebo group (Ginty and Conklin, 2012). Finally, the study
could have benefited from additional measurements of depression
or a confirmed clinical diagnosis of depression. One of the aims
was to examine the effects of LCPUFAs on depressive symptoms in
participants not currently receiving any treatment for depression.
Having participants with a confirmed clinical diagnosis by a clin-
ician would have made it difficult to enroll participants not re-
cieving treatment. Additionally, the BDII is a widely used, and well
respected measure and is recommended by the National Institute
of Health and Clinical Excellence for use in the primary care set-
ting to identify depression and responsiveness to treatment
(Smarr and Keefee, 2011).

In conclusion, this study is the first to demonstrate the positive
psychological effects of short-term low doses of LCPUFA supple-
mentation on undergraduate students with depression. The nature
of the dose, equivalent to two fatty fish meals per week, is
something that could easily be modified in the diet of under-
graduate students. A larger study is needed to examine these ef-
fects and other potential dietary strategies.

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References

activeminds.org/issues-a-resources/the-issue/)

American College Health Association. 2012. American College Health Association-
National College Health Assessment II: Reference Group Executive Summary
Fall 2011. American College Health Association, Hanover, MD.

(fish-oil) and depression-related cognition in healthy volunteers. J. Psycho-
pharmacol. 23, 831–840.

Appleton, K.M., Peters, T.J., Hayward, R.C., Heatherley, S.V., McNaughton, S.A., Ro-
polyunsaturated fatty acid intake from fish: non-linear or confounded asso-

Barbadoro, P., Annino, I., Fonzo, E., Romanelli, R.M., D’Erisco, M.M., Prosperi, E.,
Minelli, A., 2013. Fish oil supplementation reduces cortisol basal levels and
perceived stress: a randomized, placebo-controlled trial in abstinent alcoholics.

II. Psychological Corporation, San Antonio, TX.

pression inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8,
77–100.

of fatty acids by concanavalin A-stimulated lymphocytes and the effect on fatty

monoaminergic neurotransmission and behavior in rats. J. Nutr. 128,
2512–2519.

Conklin, S.M., Gianaros, P.J., Brown, S.M., Yao, J.K., Hariri, A.R., Manuck, S.B., Mul-
doon, M.F., 2007. Long-chain omega-3 fatty acid intake is associated posi-
Lett. 421, 209–212.

High omega-6 and low omega-4 fatty acids are associated with depressive
symptoms and neuroticism. Psychosom. Med. 69, 932–934.

Dannehl, K., Rief, W., Schwarz, M.J., Hennings, A., Riemer, S., Selberding, V., Stapf,
T., Lenzner, F., 2014. The predictive value of somatic and cognitive depressive
symptoms for cytokine changes in patients with major depression. Neu-

college students. Cognit. Ther. Res. 9, 227–263.

Dymenmaker, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Koves, V., Lepine, J.P.,
Angermeyer, M.C., Bernert, S., de Girolamo, G., Morosini, P., Poldori, G., et al.,
2004. Prevalence, severity, and unmet need for treatment of mental disorders
in the World Health Organisation world mental health surveys. JAMA 291,
2581–2590.


Drevets, W.C., Price, J.L., Simpson, J.P., Todd, R.D., Reich, T., Vannier, M., Raichle, M.E.,
386, 824–827.

Eisenberg, D., Gollust, S.E., Goldstein, E., Heffer, J.L., 2007. Prevalence and cor-
relates of depression, anxiety, and suicidality among university students. Am. J.
Orthopsychiatr. 77, 534–542.

and physiological effects of Omega-3 polyunsaturated fatty acid supple-

shington, D.C. International Association of Counseling Services.

Gewurtz, L.S., McDermott, M.P., McKeown, A., Smith, S.M., Williams, M.R., Hun-
and methods used to accommodate them in recent analgesic clinical trials:
ACTTION systematic review and recommendations. Pain 155, 1871
–1877.

Ginty, A.T., Conklin, S.M., 2012. Preliminary evidence that acute long-chain omega-
3 supplementation reduces cardiovascular reactivity to mental stress: a ran-

Grosso, C., Pujak, A., Marventano, S., Castellano, S., Galvanö, F., Bucolo, M., Drago, F.,
Carci, F., 2014a. Role of omega-3 fatty acids in the treatment of depressive
disorders: a comprehensive meta-analysis of randomized clinical trials. PLOS
one 9, 1–18.

Grosso, C., Galvanö, F., Marventano, S., Malaguarnera, M., Bucolo, C., Drago, F.,
...


