

## **Author's response to reviews**

**Title:** Effects of an open-label pilot study with high-dose EPA/DHA concentrates on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder.

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**Author's response to reviews:** see over

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Dr. Nehme Gebrayel  
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Dear Dr. Gebrayel and Reviewers:

Thank you for your time, energy and expertise in the review of our manuscript "Effects of an open-label pilot study with high-dose EPA/DHA concentrated on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder"; your suggestions and comments have strengthened the manuscript. Below you will find specific replies (in blue) to each of your comments and a reference to where in the paper each comment was addressed. In response to the general comments and major compulsory revisions, we have put greater emphasis on the arachidonic (AA) to eicosapentaenoic acid (EPA) ratio as it is this ratio that sets our manuscript apart from other studies that utilize varying amounts and types of essential fatty acids for the treatment of ADHD or related disorders. Clinically, practitioners are often seeking alternative means to manage ADHD primarily because of medication side effect concerns from parents. This small pilot study suggests that behavior may improve secondary to EPA/DHA supplementation and introduces a new marker to monitor EPA/DHA intake, both of which warrant a large randomized double blind placebo controlled trial.

Thank you again for your assistance in the peer review process; your time is much appreciated.

Sincerely,

Barry Sears, PhD

## Reply to reviewer report from Bonnie Kaplan

### Major Compulsory Revisions

1. It seems to me that what is unique about their approach is that they chose a target AA:EPA ratio and worked toward it. This method is different from the ones used by Stevens, Richardson & Puri, and others. As it currently stands, however, the uniqueness of this approach (and its success!) is not adequately highlighted. For instance, how that target was chosen is somewhat buried and not well justified. I think the idea of selecting a target ratio based on epidemiological studies of depression should be presented in the abstract very specifically. Then, in the last paragraph of the Intro, around line 14 of page 4, the study should be presented NOT in terms of what dose of EPA and DHA was ingested beginning at baseline (which is almost secondary), but rather in terms of the target AA:EPA range. (It would be sufficient to provide the initial EPA and DHA doses in the Methods section.) In order to do this sensibly, they will have to take the review of the literature on which they based their target (the Japanese data etc) out of the Results section (which is way too late; lines 21ff page 6) and present this information in the Introduction. Also, they need to relate that information to ADHD if at all possible – maybe even cite ratios obtained by Stevens or others? The reader should not have to accept on faith that the AA:EPA ratio is \*the\* important one to target --- what about AA:DHA or some other ratio? I also want to point out that in the Discussion on page 11, line 8, they actually seem to contradict this strategy (though they probably don't intend to) by saying that the true reason for the dosage adjustment was to avoid (unspecified) adverse events! But that statement contradicts others, and they never state what adverse events were possible. **REPLY:** To address your comments the literature review and epidemiological information is now presented in the abstract (page 2 line 8) and in the background section with regards to the AA:EPA ratio in other studies, depression and the Japanese population (page 4 lines 6-22); this information supports why the AA:EPA ratio is the important marker to monitor. In the discussion we make a statement that suggests it is important to monitor the fatty acids and AA:EPA ratio rather than looking at dosages of fatty acids alone (page 12 lines 1-5). The study aims were reworded to address the importance of the AA:EPA ratio as the marker to adjust the EPA/DHA concentrate dosage to (page 5 lines 5-8). The statement that may have contradicted our strategy for the dosage adjustments was addressed (page 12 lines 20-21).
2. Now having said all that, I have to express a concern about the absence of data to support the approach. Figure 1 needs considerable improvement (see below), and one very critical point needs to be clarified with it: did the ratios actually change in the 5 children who were instructed to change their dose at week 4? Maybe I am confused, but this information is not clear to me. **REPLY:** To clarify the changes that occurred in the AA:EPA ratio when the EPA/DHA concentrate dosages were adjusted, we added an additional figure (figure 1) that shows the AA:EPA changes from week 4 to 8 only in those with dosage adjustments. The new figure is referenced in the text (page 8 lines 8-12).
3. The basis of the behavioral data needs to be strengthened/clarified. I have not personally used the ADHD SC-4. On page 5 lines 22ff when it is introduced, we are told it covers inattention, hyperactivity, oppositional/defiant behavior, and conduct disorder (it is not accurate as currently written to say that medication side effects are a category of behavior). Curious that impulsivity is not mentioned. More importantly, since the psychiatrist who saw the child only every 4 weeks is the one completing the questions, the writers should tell us what the score is based on --- parent report? Teacher

information? Child comments? Solely observation during the appointment (unlikely)? It is unusual in this type of scenario not to have some parent-based information, so this should be clarified. **REPLY:** In regards to medication side effects, this was clarified (page 6 line 25). How the psychiatrist used the ADHD SC-4 to assess and record behavior was included (page 6 line 22-24). The medication side effects were reported in the results section (page 9 lines 18-21). During the study parent's also completed the Connors Parents Rating Scale (CPRS), this was originally not included because of redundancy and that we wanted to focus on the psychiatrist's assessment as other studies have not done so in the past. We have now included this data (table 3) methods (page 7 lines 7-10) and results (page 9 -10 lines 25-2).

4. We are told on page 4 line 14 that the primary goal of this study was to determine tolerability. Given this emphasis, the tolerability data are weak in several ways: a) on page 8 line 4 we are told 1 child had mild GI distress (which I thought was usually code for nausea), but on page 9 line 12 we learn it was loose stools – I simply suggest they be consistent in their descriptors, and more importantly b) if they were monitoring medication side effects on the ADHD SC-4 (page 5, line 24), why are these not reported? If there were none, fine.....but a total absence of the usual stimulant-induced side effects would be a little surprising. (Keep in mind that adverse events are by definition \*anything\* that occurs during the trial, even a headcold, even if not attributable to the intervention.) To be honest, if tolerability really had been their primary goal, I think they should have gotten some type of self-report from the children --- happy face scales of “yukkiness” or something like that! Were there fishy burps? Might the 2 noncompliant children have had higher yukkiness scores than the others? Tolerability is \*not\* the same as adverse events, and the writing confuses these two concepts. **REPLY:** Tolerability was a poor word choice on our part, for clarification we have switched to protocol adherence or adherence since what we wanted to know from this pilot is if the children would indeed actually take high doses of the liquid EPA/DHA concentrates. We have switched the wording in a number of places (page 5 line 4; page 6 line 11; page 7 line 7; page 9 line 1; page 12 line 20-21; page 13 lines 12-13). The GI distress was reworded to loose stools (page 9 line 13). Medication adverse effects were reported from the ADHD SC-4 and weekly phone calls (page 9 lines 17-21).
5. Interesting that 2/3 of the sample was male, 2/3 was the combined type, and 2/3 were on meds. But Table 1 unfortunately does not permit the reader to see whether there was a relationship between gender and subtype (for example). I suggest adding it to the table, or mentioning in the text. Also in relation to subtype, it would be good to know in the Results section whether there were any relationships (though I realize the sample is tiny). Were the 2 noncompliant children from one subtype? Maybe this info could be incorporated into the figure. **REPLY:** A statement regarding the gender in relation to ADHD subtype was added (page 5 line 16-17). The 2 noncompliant children were not of the same gender or subtype, this was also added to the text (page 9 line 11).
6. The fact that you obtained significant decreases in ODD and CD should be highlighted, as there really is not much in the way of effective interventions for these disorders right now. In fact, this aspect of your results is pretty exciting. **REPLY:** To address this comment we specifically stated in the text the behavioral categories that significantly improved for the ADHD SC-4 and the CPRS, which also had improvements in oppositional behavior and cognitive problems/inattention (page 9-10 lines 24-2).
7. As mentioned, I think your figure should be improved, as it is important. Given the paragraph on the top of page 7, I turned to the figure and wanted to see the pattern of data for the 4 children whose dosage did not change compared to the 5 who decreased their dose. Can that information be incorporated? Dotted vs. dashed lines or something of that sort. **REPLY:** Based on your comments, the children who did not have dosage

adjustments were given dotted lines, those with dosage adjustments were given solid lines (figure 2). As we could not see the discreet changes that occurred in those who did have the dosage change, figure 1 was added to show those changes more specifically.

8. Readers need more information on the issue of compliance: • Parents are remarkably 'absent' from this report (not completing any data forms etc), but did you get any reports from parents of the one apparently-noncompliant child regarding resistance to taking the supplement? You mention it for the second child labeled noncompliant, but not the first. **REPLY:** The first child's parent reported noncompliance for the second half of the study and this mirrors the fatty acid data (page 9 line 5-6). • I know that there are many nutrients (e.g., zinc) for which serum assays are \*not\* sensitive indicators of intake because of the tight biological regulation. I am not as familiar with EFAs. Is it legitimate to label a child noncompliant based solely on serum levels? In other words, have serum levels been shown to be that sensitive to daily intake? I think you need to support this. And are there any other reasons the ratio could return to baseline? Perhaps dietary modifications? **REPLY:** Fatty acid changes in the serum reflect dietary intake, a comment is added and referenced in the text (page 6 line 7-10). There is no support for other dietary modifications for the monitored fatty acids to return to baseline. • I would like to be reassured that you did not label these two children noncompliant because you didn't like their data (e.g., remaining at a 5 on the CGI). Again, child #2 was reported by the parent to be noncompliant --- but what about the first one you mention? **REPLY:** Please refer to comments above and in text (page 9 line 5-6). Some children were reported (by the parents) to have missed a day or two, however, the two labeled as non compliant had consistent reports from the parents that they were not following the protocol.
9. Did you actually evaluate your 9 participants for thirst or itchy skin? If not, you should say so. **REPLY:** The symptoms of EFA deficiency were not evaluated in this study, this was added to the text (page 10 line 20).
10. If the authors agree with me (and perhaps they don't; perhaps I have even misunderstood) that the major importance of their intervention was using an empirically-based target ratio of AA:EPA, then this approach should be emphasized in their Conclusions page 11, line 23ff. The way I see it, the results warrant future RCT studies of EFA supplementation based on individual AA:EPA ratios. That is the exciting contribution of this pilot study. **REPLY:** The conclusion statement was strengthened (page 13-14 line 22-2).

### Minor Essential Revisions

1. When an author is listed as Smith et al – the 'al' is an abbreviation for alia and requires a period to indicate that it is an abbreviation. Unless this journal uses a different style? **REPLY:** This was corrected, thank you.
2. page 3 line 12: move the acronym so that it appears before the word 'deficiency' **REPLY:** This was corrected.
3. Just to reinforce point #1 in the previous section above: when I arrived at line 15 on page 3, I felt completely lost and wrote in the margin: "what is an appropriate ratio??" --- the reader needs this info in the Intro **REPLY:** the goal ratio information was moved to the intro, discussed and was supported (page 4 line 6-22).
4. page 4 line 12, insert a comma after the word 'ratio' **REPLY:** This was corrected (page 5 line 2).
5. page 5, line 14: I suggest a colon after the word 'points' **REPLY:** This was corrected (page 6 line 13).
6. page 6 line 2: I believe you have provided the wrong reference for the CGI. **REPLY:** The

- reference was indeed incorrect and the correct reference was cited.
7. page 6, line 4: When I read that the psychiatrist was blind to dosage adjustments, had to go back and reread some of your methods. I don't think you mean to overstate this. The reality is that your psychiatrist \*did\* know the timing of the potential dosage adjustments; he just didn't know whether one occurred and if so, by how much. Perhaps this could be clarified. [REPLY: This statement was clarified \(page 7 line 6\).](#)
  8. page 9, line 22: Change to "compared to placebo, suggesting that not enough..."  
[REPLY: The change was made to ... "in the PUFA group compared to olive oil placebo" and the Stevens et al. study was referenced in greater detail \(page 11 line 18-24\).](#)
  9. Throughout the manuscript, it is confusing that there are changes in the number of significant figures reported. So, for instance, in table 2 the mean AA:EPA ratio is reported as 5.95 + 7.35, but in the text page 10 line 12 the numbers become 6.0 + 7.4. I suppose only a reviewer looks this carefully, but the reality is that there are rules for reporting significant figures, and customs for rounding, and the paper would be cleaner if these were adhered to consistently. [REPLY: The number references in the text were changed to match those in the tables.](#)

### Discretionary Revisions

1. Why did you add nutrition counseling to your intervention? I appreciate that you discussed the issue in the Discussion, and recognize it as a confound. I don't think anyone would seriously attribute your behavioral results to your counseling, but I certainly wish you hadn't done it! Since you did, you really should have collected food records to determine whether food intake actually changed. [REPLY: In hindsight, yes, we should have collected dietary records.](#)
2. The correlation between CGI and AA:EPA ratio was very high. Can you compute correlations with the ADHD SC-4 scores? Would that be interesting? [REPLY: There were no significant correlations between the AA:EPA ratio and ADHD SC-4 scores or the CPRS \(page 10 line 9-10\).](#)
3. It would not be possible to publish this paper in some journals without further info as to how the children were evaluated so that the subtyping could be considered valid. I realize these children were seen in a clinical setting, but is there anything at all that could be said to strengthen this section, to indicate how the psychiatrist determined what subtype a child belonged to? Perhaps not, but I raise it for your consideration. [REPLY: The Psychiatrist used DSM IV criteria for diagnosis and sub typing \(page 5 line 14-16\).](#)
4. Would it be legitimate to list the AA:EPA ratio (last line in Table 1) also without the 2 noncompliant children? As a separate entry? [REPLY: The AA:EA ratio of compliers was added to table 2.](#)

## Reply to reviewer report from Julian Bailes

### No Major Compulsory Revisions

### Minor Essential Revisions

1. The use of the term significant should be limited to statements with statistical significance and p value <0.05. Page 7, line 18 **REPLY:** The statement regarding significance was deleted (page 9 line 3)
2. The first paragraph of the results section details the method used to adjust supplementation quantities based on AA:EPA ratio. This should be moved to the methods section. Also, it is unclear if the method of dosage changes was established prior to initiation of the study. **REPLY:** The statement regarding dosage adjustments made at week 4 was moved from the results section (page 6 lines 5-11) as this was determined at study initiation and part of the study protocol.
3. No data is presented regarding the number of participants with an AA:EPA ratio less than 1.5 at the 8 week point. **REPLY:** Two participants still had an AA:EPA ratio less than 1.5 at week 8, this statement was added to the text (page 8 line 10-12).
4. The selection of target AA:EPA ratio > 1.5 was selected to avoid adverse events, what are the most common specific adverse events that are correlated with an AA:EPA ratio less than 1.5? **REPLY:** A statement addressing this concern was added to the text (page 7-8 line 24-4).
5. Compliance with treatment is described as greater than 100% increase in EPA and DHA levels. However, Figure 1 would suggest that 3 of 9 participants were not compliant as demonstrated by AA/EPA ratio. Was criteria for determining compliance established prior to initiation of the study; if so this should be addressed in the methods section. **REPLY:** Criteria to determine adherence (AA;EPA ratio change and absolute changes in EPA levels) was established prior to study initiation and a statement was added in the text (page 6 line 10-11). The third participant whose AA:EPA ratio that does not decrease as dramatically as the others still had great than a 100% increase in EPA and decrease in AA:EPA ratio. Although he might not look as compliant as the other participants, he was compliant by the fatty acid changes.
6. Percentages of mean AA:EPA ratio (Page 7, line 9) decline and relative increase of the mean from 4 to 8 weeks (Page 7, line 12) are presented. The validity of the accuracy of these percentages are difficult to determine as the values have high SD (presumably due to inclusion of noncompliant participants). Further, the percent change in the median values may be more reprehensive of actual changes in the compliant participants. **REPLY:** Statement added (page 8 line 21-24) to attempt to address this concern.
7. Table 3 presents data suggesting continued improvement in 3 of 4 ADHD SC-4 scores from 4 to 8 weeks and improvement in CSI score from 4 to 8 weeks despite the majority of participants having a decrease in the supplementation dosages. **REPLY:** While the dosages were adjusted, AA:EPA ratios remained below 3 and continued to improve for the others in the study (except non compliers), therefore strengthening the importance of the monitoring the AA:EPA ratio and not just rely on dosage (similar statement made in text page 12 line 1-5).
8. Correlation between AA:EPA ratio and CGIS is presented. Was correlation analysis performed between AA:EPA ratio and the ADHD SC-4 scores? **REPLY:** There were no significant correlations between the ADHD SC-4 or CPRS and the AA:EPA ratio, statement added in text (page 10 line 9-10).

### No Discretionary Revisions