Reviewer's report

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.

Version: 1 Date: 7 March 2007

Reviewer: Bonnie Kaplan

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General
This is a generally excellent pilot study which warrants publication. It adds to scientific knowledge a bit, but more importantly it employs an interesting twist on the usual methodology in a way that may significantly move this field forward. As it stands now, the supplements used in published interventions vary widely as to their composition (EPA and DHA ratios) and accompanying nutrients (it always amuses me to see Gesch's BMJ article referred to as an EFA study, when 25 of his 27 ingredients were vitamins and minerals, not EFAs) and sometimes seem quite arbitrary. So this study employed a novel approach of targeting an allegedly-beneficial AA:EPA ratio. Nevertheless, there are some modifications I would suggest. Within each grouping below, the sequence is chronological rather than reflecting any particular priority.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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.

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.

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.

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.

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.

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.

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.

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.
   • 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?
   • 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?

9. Did you actually evaluate your 9 participants for thirst or itchy skin? If not, you should say so.

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.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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?
2. page 3 line 12: move the acronym so that it appears before the word ‘deficiency’
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
4. page 4 line 12, insert a comma after the word ‘ratio’
5. page 5, line 14: I suggest a colon after the word ‘points’
6. page 6 line 2: I believe you have provided the wrong reference for the CGI.
7. page 6, line 4: When I read that the psychiatrist was blind to dosage adjustments, I 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.
8. page 9, line 22: Change to “compared to placebo, suggesting that not enough…..”

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.
Discretionary Revisions (which the author can choose to ignore)
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.
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?
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.
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?

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.