Reviewer's report

Title: Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial

Version: 1 Date: 12 February 2004

Reviewer: William C Heird

Reviewer's report:

General

This manuscript reports data from a 6-week, double blind, placebo controlled trial of zinc plus methylphenidate vs. methylphenidate alone in the treatment of children with attention-deficit hyperactivity disorder (ADHD). The 44 children enrolled ranged in age from 5 to 11 years (mean ? SD, 7.88 ? 1.67) All met the DSM IV diagnostic criteria for ADHD. The principle outcome measure was the Teacher and Parent ADHD Rating Scales. Scores on both scales improved in both groups of children but were lower at 6 weeks in the group that received zinc sulfate plus methylphenidate vs methylphenidate alone. The authors conclude that zinc may be an efficacious adjunct to methylphenidate treatment in children with ADHD.

The study appears to have been well designed and executed although use of more objective outcome measures would have been preferable. Nonetheless, despite the subjectivity of the Teacher and Parent ADHD Rating Scales, they have been used for some time and appear to be reliable.

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

1. The manuscript is succinct but the statistical analysis section could be reduced somewhat and also made more "user friendly" to those of us who are not quite as sophisticated in statistical analysis. Also, a number of additional assessments apparently were done but the data are not reported. Omitting mention of these would reduce the manuscript even further.

2. The sentence beginning on line 13 of page 7 should be re-worded. I gather that what is meant is that a score above 20 on the Rating Scales was required for entry into the study.

3. The power calculation beginning on line 15 of page 8 is not clear.

4. As stated previously, the Statistical Analysis section should be simplified. This is also true for the presentation of the results; the actual F values, degrees of freedom, etc. really are not necessary.

5. The use of “Greenhouse-Geisser, F” in discussion of the Teacher ADHD Rating Scale (page 10) is confusing, particularly since the discussion of the Parent ADHD Rating Scale refers only to F. Were these, in fact, the same F?

6. Although nausea was more common in the zinc sulfate group, the difference in nausea between the two groups was not statistically significant; this should be stated or the p value provided in the text.

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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. Were the children taking methylphenidate or another stimulant medication prior to enrollment? It is implied that these were newly diagnosed patients but this should be further clarified.

2. In several places, including line 19 of the Abstract, it is stated that the “…two treatments were not homogeneous across time”. The meaning of this term is not clear to me. The problem may be the definition of “homogeneous”.

3. The first sentence of the Background section requires a reference.

4. The sentence ending on line 20 of the Background section as well as the one ending on line 21 also require references.

5. Was the assent of the child to participate in the study also obtained?

6. In the legends to Figures 1 and 2, “protocols” should be changed to “groups of children” and “between subjects comparison” should be changed to “between group comparisons”.

7. The units for age in Table 1 should be specified.

8. Although it is fairly obvious, Table 2 should indicate that the clinical complications or side effects are reported as number per group.

9. It is unfortunate that plasma zinc concentrations were not included. In this regard, something about the prevalence of zinc deficiency in Iran should be provided. I am aware that this is common in some areas of the Middle East but I don’t know specifically about Iran. Such an indication will provide some insight into whether the findings reported here are likely to be observed in other settings. Also, if such data exist, it would be interesting to see plasma zinc concentrations of patients with ADHD vs. patients without ADHD.

Discretionary Revisions (which the author can choose to ignore)

1. The statement on lines 15 and 16 of the Abstract should indicate why the patients were assessed by a child psychiatrist - presumably, as stated elsewhere, to assess side effects related to the medication.

2. The sentence beginning on line 5 of page 5 should indicate that the affect of zinc plus methylphenidate vs. methylphenidate alone was assessed.

3. The psychiatric evaluation, the structured diagnostic interview and medical history assessed at the beginning of the study are never mentioned again. Were these data actually used in some way? If so, this should be cited.

4. Again, line 15 of page 7 states that patients were assessed by a child psychiatrist but the findings of this assessment are never mentioned again but toward the end of the page, we learn that side effects were assessed using a checklist at the same times.

5. The use of “protocols” in the Results section should be replaced by “treatments”; alternatively, the specific treatment could be mentioned.

6. The Discussion section is quite short. Moreover, no information concerning the metallic taste is
mentioned prior to line 17, page 12. This, ideally, should be included in the Table of side effects. Again, it should be noted that the prevalence of nausea, although greater in the zinc group, did not differ significantly between groups.

7. Although the study population was somewhat small, it was large enough to detect the differences for which it was designed. Thus, I would not call this a limitation of the study.

8. Further investigations with both the same dose as well as different doses of zinc are required, not necessarily to replicate the findings reported here but to further assess the role of supplemental zinc in treating patients with ADHD.

9. Finally, if the study reported in this manuscript is the post-graduate thesis of Dr. Khademi, one wonders why he/she is not the first author.

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

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

None