Author's response to reviews

Title: Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey.

Authors:

Richard E Frye (Richard.E.Frye@uth.tmc.edu)
Swapna Sreenivasula (Swapna.Sreenivasula@uth.tmc.edu)
James B Adams (Jim.Adams@asu.edu)

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Author's response to reviews: see over
Dear Dr. Solera:

We greatly appreciate the opportunity to re-revise our manuscript entitled “Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey” and respond to the referees’ comments. In general, we have considered the excellent suggestions from the referees and have revised the manuscript accordingly.

However, we are a little confused with some of the current comments from referee 1 as this reviewer appears to be raising the same points that referee 2 previously raised in the last round of comments. Such points were addressed appropriately (at least in the opinion of referee 2) in the last version of the manuscript. We apologize if these changes were not clear to referee 1 and we have done our best to clarify these points again and revise the manuscript accordingly.

Below is a point-by-point response to the referees’ comments. We have attached a revised manuscript with the changes highlighted.

**Referee 2**

Discretionary Revisions

1. Questionable phrase, p. 5: “The survey was designed to skip irrelevant questions to keep the completion time to less than 30 minutes.” Just say the survey took under 30 minutes to complete.

   This has been changed as suggested.

2. Tables 6 and 7: Change the titles to say “usage” of these treatments. Otherwise, the percentage does not indicate what it is a percentage of.

   This has been changed as suggested.

3. Need to acknowledge the contribution of the second author by including this author’s bio.

   This information has been added as suggested.

**Referee 1**

Major Compulsory Revisions

1. I am still not exactly sure why a control group of individuals with ASD and no documented seizure activity was necessary since the authors state that purposes
of the study were (a) to determine whether there are specific AEDs that are more appropriate to use in children with ASD; (b) to determine whether there are any non-traditional treatments that appear to be specifically effective for treating seizures in children with ASD; and (c) to provide data that may help clinicians in selecting treatments which are more likely to reduce seizures with minimal side-effects, and to help increase their awareness of potential side-effects. Since the children making up the control group did not have documented seizures I am not sure they are an appropriate control group for these questions. It appears that it would be more appropriate to include children with ASD and documented seizure activity who were reported to not take use these treatments. Comparing treatments for seizure to a group without seizures is not a comparison with minimal differences.

The control group was added to obtain baseline data regarding treatment and characteristics of the children with autism spectrum disorder sampled by this survey as addressed on page 11 of the manuscript.

We do not at all understand why a control group of children with ASD and documented seizures who were not taking treatments would be important. One of the goals of the survey was to examine the perceived effectiveness of treatments. If children were not on treatments how would the respondents rate the perceived effectiveness of treatments?

2. I am still not sure who the respondents are for the survey. It is reported that it was parents but still no demographics of these individuals are provided which makes the generalization of the results hard to determine.

This was addressed in point #1 from Referee #2 in the previous version of the manuscript. The demographics of the respondents were not collected. We have addressed this in the previous version of the manuscript on the bottom of page 34.

3. Tables 1 and 2 provide percentages of practitioners who regular manages the child with ASD (Table 1), and who evaluated and managed ASD individuals for seizures (Table 2), were these categories mutually exclusive or could one practitioner cross multiple categories. For example, The authors state several times that there were “Doctoral affiliated with Defeat Autism Now!” were the third most common doctors. Did these doctors also represent other fields such as pediatrics and neurology, or where they exclusively DAN! Doctors without other affiliations. Without specifying the overlap, some categories may be over counted rather than true percentages.

The categories were mutually exclusive. Usually “Doctors affiliated with Defeat Autism Now!” are mostly pediatricians or family practice physicians.
4. On pages 8-9, the authors state that treatments came from a think tank at the AutismOne meeting in May 2009. A caveat should be made that this is a small group of individuals who have a specific theoretical bias for the cause of autism and do not necessarily represent the autism field as a whole. Since that bias is there, the treatments provided may not represent the entire range of options available to individuals with ASD in the general public.

As stated on page 9 we assembled a group of experts from a wide range of specialties (primarily pediatrics, neurology, family practice, and researchers) to represent a broad range of treatments for seizures. It is not true that there was one cause for ASD or seizures represented in the think tank. Basic mechanisms for seizures discussed in the Think Tank ranged from abnormalities in cortical architecture, neurotransmitter imbalances, genetic syndromes, immune dysregulation, mitochondrial dysfunction, environmental toxins, infection, etc. In addition, we did our best to provide a full range of both traditional and non-traditional treatments. Clearly all of the traditional treatments were included, as several of Think Tank participants were classically trained neurologists and epileptologists trained at some of the best institutions (e.g., Harvard, Johns Hopkins) with large epilepsy programs and regularly treat children with primary epilepsy without ASD. Personally, the first author regularly attends on a busy general neurology service where he manages children with severe epilepsy and teaches residents, student and fellows how to manage children with epilepsy.

5. Were the control group and seizure groups both recruited from the same sources? This was unclear from the manuscript. Again, what were the directions given that allowed respondents to make the correct choice of surveys to complete? What is a child was diagnosed with a seizure in the past but currently does not have them, the instructions were unclear as to which survey to complete.

This was addressed in point #1 from Referee #2 in the previous version of the manuscript. Page 11 outlines the recruitment of the subjects. The invitation letter is provided in Appendix B. A link to the actual survey is provided for the referee’s review.

6. Even though the data indicated that 77% of the children respondents reported on were male, were there any significant differences in treatments used, side-effects, etc. in females? Grouping them together does not provide enough data to answer the questions posed by the authors since males and females often have different reactions to medication.

The numbers of females is too small to compare males vs. females for treatments.

7. Although mentioned as a limitation, without any clinical follow-up, how could the authors be certain answers provided were accurate? Since children often began having seizures 4-5 years prior to the actual survey completion, how well can parents remember the specific diagnosis given, type of seizure indicated, and all
treatments provided? Also, were authors asking about just current treatments or were past treatments surveyed as well. It would be interesting to investigate current versus past treatments since children with ASD often undertake multiple treatments in a lifetime.

The questions were worded to ask parents about a treatment that was ever used, past or present. The reviewer may use the link to review the survey questions if he wishes to review the wording of the questions. An example of a question regarding a treatment is as follows "Has your child ever been prescribed valproic acid in any form (Depakene, Depakote) as a seizure treatment?" The fact that this information is being provided by the parents rather than the medical record is discussed in the limitations section of the discussion. This limitation was added as a result of the comments of referee 1 point 5 in the previous version of the manuscript.

8. The authors also indicate (pp. 9-10) that each treatment and its effects were queried individually. If multiple treatments were provided at same time, then it would be virtually impossible to determine effects of individual treatments and side-effects. By not looking at combination of treatments virtually all three stated purposes of the study are impossible to determine making this publication irrelevant for the stated purposes.

This was addressed in point #9 from Referee #2 in the previous version of the manuscript follows.

A caveat has been placed in the limitations section of the paper and an explanation has been placed in the methods section of the paper: “Although children were most likely provided multiple treatments at the same time, information regarding response to specific treatment was queried individually for each treatment. This assumes that each treatment is having an influence independent of the other treatments. This is necessary as asking about each combination of treatments would create a questionnaire that would be prohibitively long and complex. In addition, it is likely that the number of respondents with experience with specific treatment combinations would be prohibitively small for valid analysis. “

We have also added the following sentence to the above paragraph to further clarify this point: “From a practical point of view, most practitioners usually start and/or stop treatments independent each other so that the clinical effect (and adverse effect) can be determined for the specific treatment.”