Author's response to reviews

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

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

We greatly appreciate the opportunity to revise our manuscript entitled “Traditional and non-traditional seizures treatments for autism: an on-line survey” and respond to the referee’s comments. In general, it appears that in the interest of trying to make the manuscript compendious, we limited discussion of important details in the manuscript. We have considered the excellent suggestions from the referees and have revised the manuscript accordingly. Below is a point-by-point response to the referee’s comments. We have attached a revised manuscript with tracked changes. We have included a copy of the invitation letter with links to the seizure and control surveys in Appendix B. These links are active and the data entered through these links will not be saved or included with the study data.

Referee 2

Major Compulsory Revisions

1. The participants (the caretakers who responded) are not described. The reader needs to know the relationship of the respondent to the person with ASD. Please report the number/percentage who are mothers, fathers, other family members, hired caregivers, etc. In particular, the term “caretakers” brings to mind matrons in group homes, though I doubt that many of the individuals were living in out of home settings. Perhaps the term ‘caregiver’ is too much of an ambiguous term. The survey was directed at parents of children with autism rather than other family members or hired caregivers. We have clarified the recruitment strategy in the method section in order to make this less ambiguous and changed our reference of ‘caregiver’ to parent since this is who was directly asked to respond to the survey. We have clarified in the methods and the abstract. We have also provided a copy of the recruitment letter in Appendix B. Unfortunately, we did not collect demographic information on the responders. We have outlined this limitation in the limitations section is the discussion.

2. In the same way, the demographics of the target individuals with ASD need to be reported, including the age range, the ethnicity, etc. Table 1 eventually shows what appears to be the mean and s.d. of the age of the individuals with ASD (though this is not clearly labeled as such).

We apologize for this information being ambiguous. We have moved this information from the table to the text in order to make the demographics of the sample clearer. We
have now included some more important information regarding the type of practitioner that manages the child’s general medical and developmental disorders and their seizures specifically.

3. The authors need to make clear at multiple points that treatment efficacy is the perception of the caregivers and that this was not assessed by the researchers or reported by professionals. It is clear to me that this is what the paper is reporting, and they do say so, but it needs to be at every turn—“perception of change” rather than “improvements.”

We have made this adjustment and the new wording is now prominent in the wording of the abstract, introduction, methods, results and conclusions. We also discuss the limitation of parental perceptions in the limitations.

4. In the introduction, references are needed for a number of points. For example, p. 4, 1st paragraph, “Finally, individuals with ASD can be very sensitive to medication side effects [reference needed for this], so older AEDs which tend to have higher rates of side effects [reference needed for this] might be less appropriate for individuals with ASD.” Next paragraph—“There is reason to believe that some non-traditional treatments may help with the frequency and severity of seizures [reference needed].” Note, I am not questioning these points but rather ask that they be backed up with references to the literature. If no such references exist, then the points should be made in a more hypothetical way rather than as assertions of known truth.

The appropriate references have been added.

5. I am very much concerned about the methodology for the questionnaires. Apparently, there was a separate questionnaire for caretakers of individuals with and without seizures. WHY are they separate, and in what ways are they different? Does this mean that participants had to make the decision at the onset, at the point of clicking one or the other link, as to whether their family member was in the seizure group? I can picture this being a fuzzy question for the participant. (Hm, we thought maybe he had seizures when he was two, but it was never really confirmed. Or, he had seizures when he was younger but hasn’t had any since puberty. Or other scenarios of uncertainty.) What questions do the participants in the non-epilepsy sample answer (and not answer)?

We apologize for this not being clear. We have included a copy of the invitation in Appendix B and have now clearly described the differences in the survey in the methods section.

6. Page 9, the authors report that responders to the ARI advertisement used certain treatments more often than the responders to the non-ARI support group ads. How did you know? Did people report on the questionnaire where they saw the ad? What are samples of the “other” sources that advertised the study; were they mainline autism organizations or specialty subgroups of some kind? Were different questionnaires
used? Importantly, how many came from each source? This should have been reported in the Methods.

We apologize for this not being clear. Since the survey was web-based we were able to send different links to the survey to different groups. This enabled us to direct different groups to the exact same version of the survey but have the survey responses separated into different databases. This is now explained in greater detail in the methods section.

7. The 733 participants who reported on the individuals’ seizures had to report on the seizure type. Were they given a checklist? Did they volunteer the type? Could they affirm several types, or just one? How confident can we be that they knew all those labels? Do families really know if their child had each of those types of seizures—do their doctors tell them, and does it make sense to them? I do not mean to question the truth of the parents’ reporting or their ability to understand, but I wonder whether doctors routinely tell parents their child had “subclinical epileptiform discharge” and whether the parent remembers that term years later. Reporting to the readers on what the parents had to answer would help here.

We apologize for this not being clear. As now described in the methods section, we provided a checklist of the different seizure types along with a detailed explanation of each seizure type.

8a. I have similar questions about the treatments. Did the participants volunteer the names of medications used, or were these provided as a checklist? Did the “control” group have the same opportunity to report on the medications? These families may have been using these same medications for other symptoms. Similarly, were the non-traditional treatments provided as a checklist? Did both groups of respondents respond to this list? All of this should be made clear in the description of the measure and the procedure. Did you ask questions about “tried it” versus “using now?” Did you ask if they had discontinued a treatment?

We apologize for this not being clear. As now described in the methods section, we provided a sequence of questions that asked if the treatment was ever used. If the respondent answered ‘yes’ they were directed to a webpage where they could rate the effect of the treatment and list the adverse effects. If they answered ‘no’ the respondent was questioned about the next treatment. The treatments considered were determined previous to the survey by a group of experts from a wide variety of disciplines.

8b. Your reported list does not include some of the behavioral treatments that are most commonly used (e.g., speech therapy, sensory integration therapy, EIBI, etc.). Did you ask about these?

No we did not ask about these, although the reviewer has a good point that these would have been interesting to ask about.
9. Families are most often using multiple treatments at the same time. You need to assert this early and often! This makes it very hard to ascertain what a specific treatment is doing. There is not way to change this reality—we cannot ask families to do just one thing for 6 months—but it needs to be stated. In particular, I am guessing that many (most?) families were using both traditional and non-traditional treatments at the same time. If so, and if they perceive a change in their child’s symptoms, how can they say which treatment was responsible? There needs to be cautionary statements about this.

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.”

10. We need a more complete explanation of Ward’s technique for cluster analysis, as this procedure is not well known. Do the clusters relate to what people used the same treatment? Or to the relationship between the treatment and some outcome?

A better explanation of the wards technique for cluster analysis is provided as well as how the cluster analysis was conducted. A cluster analysis does not relate one variable to another as in a treatment-outcome relationship but rather finds similar relations between variables among different observations. In this case, the observations are the different treatments and the variables are the ratings. In essence, the cluster analysis finds treatments in which the ratings were similar. This is now explained in more detail in the methods section.

11. What post hoc test is used (e.g., Scheffe, etc.)?
Planned contrasts using the ‘estimate’ command in SAS for the ‘glimmix’ procedure was used for the contrasts. This essentially used both the fixed-effects and random-effects matrices to construct a matrix with an approximate t distribution. The unadjusted t-values and p-values are presented and the Bonferroni correction was used to calculate the appropriate alpha levels for each set of comparisons. To answer the reviewer’s question specifically, the Bonferroni correction not the Scheffe correction was used. We have now clarified this in the text.

12. I find the adjustment of p value to p < .01 to be insufficient. For accuracy, you should use Bonferroni corrections and then report p values in light of that correction. This could at least be used for the contrasts within one little set of analyses.
We have corrected all analysis with respect to the number of comparisons made with the Bonferroni correction. The mathematical calculation for the Bonferroni and the exact correction used is described in the legend of each table containing statistical
comparisons. In some cases 0.01 is sufficient where as 0.001 is more appropriate in others. Most of the interesting findings survived any change in the alpha rate.

13. The tables are not properly prepared. They cannot be published in this form. These tables and the text that refers to them have been revised.

14. Tables S7 and S8 are totally un-interpretable. I cannot even tell what they are trying to report. They are barely mentioned in the text, so there is no help there. These tables and the text that refers to them have been revised.

15. The figure (the one with 6 figures on it) is hard to understand. After studying it for a while, I figured it out, but . . . . It would help to not have them smushed onto one page and for each to have its own title. As there is no page limit, these should be prepared as individual figures with titles. We have modified the figures accordingly.

16. The authors say that a limitation of the study is the potential bias of the responders (p. 14) as individuals who use non-traditional therapies tend to be critical of traditional drug treatments. I would like for them to expand on the “potential bias” of the participants due to the study’s association with ARI. ARI (and the whole DAN movement) promote a version of ASD that is not universally accepted, to say the least. Something needs to be said about the source of the study.

This is discussed in the limitations of the study. We make comparisons between the responses that are derived from ARI and non-ARI sources throughout the study. For the most part, there are few differences. We discuss the implication for responders from the ARI source. We also specifically ask individuals about which practitioners manage their children. For the most part we demonstrate that the great majority of children are managed and diagnosed, at least in part, by a pediatrician or neurologist.

Minor Essential Revisions

1. The authors provide a key for some of their abbreviations, but there are still many abbreviations that are not “translated” for the reader. These should be explained either in the text or the key.

Although we did not find any abbreviations that were not defined we agree that there were a lot of non-standard abbreviations. We have eliminated the majority of the abbreviations to improve clarity in the manuscript

2. In the Discussion, p. 13, please mention that the KD can be dangerous. This is likely true of some of the other treatments as well. This may be more than minor.
This has been included in the discussion.

3. The references are inconsistently prepared. Some (many) lack dates. Some have unusual formatting. This must be cleaned up.

We have carefully reformatted the references.

Discretionary Revisions

1. Table 1 lists ages for “seizure onset—resolved,” “seizure resolved—resolved,” and “seizure onset—ongoing.” There is no explanation for this, and the issues of resolved and ongoing are not addressed in the paper or in analyses. Is this important to the study?

This has been moved out of the table and put into the text to improve clarity of this information.

2. Very little is reported about side effects. I would recommend either expanding this treatment considerably or leaving it for another paper. As is, it is un-interpretable.

We have expanded this section to make it more relevant.

Referee 1

Major Compulsory Revisions

1. The authors have done a good job summarizing what is currently known about seizures in individuals with autism spectrum disorders in the introduction. Even with this summary, I did not feel that the authors did a thorough job of bringing us to the purpose of their study. Without a specific research question stated it was hard to determine what exactly the research were hoping to gain from this survey, and how the results would specifically add to the field as a whole. After reading the introduction I was left asking myself why is this study needed.

We have reworded the introduction to clarify the purpose of the study.

2. My major concerns revolve around the survey itself. How was this survey developed and what was the stated purpose? Did the authors have any sort of literature that they were drawing from in order to generate the survey questions/topics? Were any experts in ASD and/or seizures used when developing the survey to insure internal and external validity? Were standard survey research protocols used in the development of the survey (viz., Bradburn, Sudman, & Wansink, 2004, for ways to state questions; Scheaffer, Mendenhall, & Ott, 2006, for survey development). More information on the survey development is needed for me to feel comfortable with their instrument.
We now outline the development steps of the questions per Keenan, Brian (1993). *Developing and Using Questionnaires*. United States General Accounting Office, Program Evaluation and Methodology Division: Washington, D.C.

3. Authors state that 2 surveys were developed, with one specifically created for ASD without seizures. What were the differences in these surveys and why was this one needed? More information on these and maybe an appendix with them included would be helpful.

We have provided a detailed explanation of the differences between the two surveys. Paragraph one of the methods section previously indicated that the second survey was a control survey. We have clarified why a control survey was needed. We have also provided copies of the surveys so they can be examined in detail by the reviewer.

4. With the control group, who exactly made up this group and how was it determined that the participants in the control group did not actually have seizures or other conditions which could bias results.

The invitation to complete the survey contained detail information to help the parent choose the correct survey to complete. We have included the wording of the invitation in Appendix B.

5. Was group membership determined specifically from the caretakers accessing the correct survey? Were individuals sampled to confirm ASD and seizure subtype? Were gold standard diagnostic measures used (e.g., ADOS and ADI-R)? What about documentation of seizure activity? If not, this should be addressed as a limitation to the research in the discussion.

This is a very good point and we have addressed this limitation in the discussion. We have also now included information regarding the type of practitioner who managed the patients which should be helpful in verifying that parents consulted with an adequately trained physician.

6. Was there any questions related to dosage of medications for seizure taken? Were participants of tradition and non-traditional seizure treatments monitored by a medical professional? Was this professional contacted to ensure reports were accurate?

We have also now included information regarding the type of practitioner who managed the patients which should be helpful in verifying that parents consulted with an adequately trained physician.

7. Without knowing the validity and reliability of the survey instrument the results are read with caution, which reduces the impact they can have in this field. Once the survey (the basis for the results) has been shown to be reliable and valid a resubmission review should concentrate on the analyses and result interpretation. Until that time, these results should be viewed as incomplete.
Hopefully, the revision of the methods section will help the reviewer assess the validity and reliability of the survey we developed.

**Minor Essential Revisions**

1. *The authors should do a though editing of the manuscript before submitting a revision. There are several places where words appears to be missing from sentences and some sentences do not convey complete thoughts.*

   We apologize for the incomplete sentences and any portion of the manuscript that in which the writing is poor. We have revised the manuscript accordingly.

2. *The authors may want to consider revising the title to include autism spectrum disorders rather than autism only since the research clearly uses individual across the entire spectrum and not just the subtype of Autistic Disorder.*

   We appreciate the suggestion and have changed the title accordingly.