Author's response to reviews

Title: Corticosteroid therapy in regressive autism: A retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior

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Author's response to reviews: see over
Reviewer’s Report and Authors’ Reply

Title: Corticosteroid therapy in regressive autism: A retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior
Version 4 Date: 7 March 2014
Reviewer: Deborah Fein

Reviewer’s Report and Authors’ Responses:

This paper continued to address a very important topic in the treatment of a group of quite severely affected children, and the main point, that an RCT is needed, is amply made. The manuscript is certainly much improved. Some needed detail and explanation is added, and conclusions are considerably softened. I am still quite troubled by the likelihood that some parents and physicians will leap to treatment. I consider the following points minor essential revisions.

Authors’ Response: The authors agree that there have been many inappropriate treatment modalities utilized in futile attempts to ameliorate autism. No doubt there will, unfortunately, be more. An unexpected side-effect of the publicity around these inappropriate, controversial, and failed treatments however should not be to suppress pilot data from reputable sources. Our approach is to push for a multicenter trial of steroids and perhaps other promising drugs for R-ASD. In order to obtain funding for such a trial, however, one must point to published positive pilot data. For this reason we feel strongly that it is important to present the data of our study and, as the Reviewer rightly requested, highlight the methodological deficiencies of the study as we now have outlined in more detail in the Discussion and Conclusion sections.

1. Specifically, I am troubled by the dissimilarity of the control group to the STAR group, and the language and behavior ratings, which are not validated measures and done with full knowledge of the treatment the child is under, but at least the claims are softened accordingly; if I were editing this paper, I would soften them a bit more, especially with regard to comparison of language and behavior in the two groups (see below).

Authors’ Response: The authors believe that these issues have been thoroughly and directly addressed, primarily in the ‘softening’ direction, and that further change would distort the actual cautions taken to obtain as objective assessments as was clinically feasible given the acknowledged shortcomings of this, nevertheless, methodologically carefully conducted study.

2. I would add some points to the limitations: The authors do say: Aside from the FMAER, language and behavior description transformed into quantitative data were obtained by by clinicians in collaboration with the parents. Neither of the language measures is standardized or published’. However, equally serious is the fact that the parents and clinicians who rated the child’s language were fully aware of the steroid treatment and quite possibly invested in the outcome. As I may have mentioned in my first review, I frequently see parents whose children are undergoing a treatment of some kind, who report great improvement, which fails to materialize upon formal testing. While the FMAER and EEG readings were done blindly (I believe), the language and DSM symptom- behavior ratings were definitely not, in the sense that the clinicians and parents knew about the child’s treatment.
Authors’ Response: The authors have thoroughly addressed these concerns in the revision. The authors agree that both the language tests and the behavior ratings based on the DSM-IV criteria are not published standardized tests yet were constructed independent of the raters and rating process applied to the records. The reviewer is correct that the clinician arrived at the ratings in collaboration with the parents, yet as pointed out, great diligence was practiced in exploring the validity of the parents’ statements in order to avoid ‘wishful’ reporting on the parents part. The manner of the conduct of clinical visits for the subjects undergoing treatment differed little from other visits in child neurology practice. For example, in managing ‘intractable epilepsy’, neurologists and the family agree upon a trial of a new drug and agree to try just one medication at a time. The medication is started and the neurologist meets with the child and family every so many weeks at which time the family, child, and other caregivers are polled for information about change in seizure frequency, severity, and type; they are also polled about adverse effects including changes in language, attention, cognition, memory and behavior. Blood tests may also be ordered. Child neurologists in our experience are quite skilled in avoiding the pitfalls of wishful parent reporting in gathering information from family members. This includes awareness of unreasonable family optimism (wanting a cure) and unreasonable family pessimism (unable to deal with adverse side effects despite a good response). In this context both family and physician ‘want’ improvement but it is the physician who has to carefully assess benefits and risks. Physicians are guided by the principle “First, do no Harm”. There is no real physician benefit to falsely claiming success or failure. Reality is always determined by outcome. Notably, physician impressions and clinic chart notes guide decisions – there are few relevant standardized tests employed in acute neurological practice. Children with autistic regression in this study were typically referred to rule-out LKS, which is typically accomplished by sleep EEG as outlined in the paper. The use of steroids was entirely a clinical decision as at the time of drug administration a clinical trial destined for publication was not a consideration. The manner by which behavior, language, and complications were followed during steroid administration in our study was augmented, as indicated in the manuscript, by physician-designed scoring as suitable, alternative tests were not available. These physician-designed tests were essential in order to assess benefits and complications in order to have an objective basis to make the decision on an approximately monthly schedule to continue or discontinue the steroids. Again, there would be no positive physician benefit – perhaps even harm to professional reputation - from falsely claiming a positive result. Indeed, the FMAER test was utilized, since it was performed completely without bias and reported completely independently. It was quantitatively scored only much later when it was decided to review the data base and to analyze the group results.

3. Furthermore, the paper asserts that ‘Neurologists using the CLSQ are sensitive to the language performance definitions in question and trained to reliability in score assignment’. Unless there are data to back up this claim of reliability, I would delete it.

Authors’ Response: We agree with the Reviewer and have deleted this sentence.

4. Along the same lines of my discomfort with the control group, especially with regard to changes in behavior and language (less so with the FMAER and EEG changes), the authors state: Moreover, significantly more STAR group subjects (17/20) than NSA group subjects showed improvement (6/24 ‘better’ receptive, and 10/24 ‘better’ expressive). These data suggest that steroid treatment may be associated with improvement in language and that more subjects who receive steroid treatment may
show such improvement than subjects in the non-treated group.’ I appreciate that all such statements are now qualified with ‘may show’ but I still think this is overstated, especially ‘...that more subjects who receive steroid treatment...nontreated group.’ The control group was quite different in many regards from the STAR group – they were mostly non-regressive, it is not clear that demographics were matched in any way – this is indeed a convenience sample. The only real basis for this comparative statement would be to take similar groups of children and treat one and not the other, based on something approaching random assignment and not clinical judgment and parent willingness. Even an open trial with better matched control and experimental groups might warrant the cautious claim, but the really unmatched groups do not seem to warrant it. In other words, I appreciate the qualifications but I don’t think they really go quite far enough.

Authors’ Response: We have fully explained the limits of the assessments and clearly pointed out the group inequalities.

5. I previously raised the question of additional treatments for either group. The ms. now states ‘Post hoc record review revealed that none of the STAR group children received any additional pharmacological, behavioral, or educational interventions during the steroid treatment period.’ This is extremely unlikely, at least I hope it is. These are 3-5 year old autistic children receiving treatment for an average of 9 months, to a maximum of 14 months. Surely, they were in behavioral or other educational interventions during this time, and not sitting at home? If these data are not available, that could just be stated as a limitation.

Authors’ Response: Steroids alter behavior, usually in a negative direction (see table) and render most children inappropriate for a behaviorally-based therapy. It was agreed with the parents that no new treatments be commenced during the steroid trial. This is not unique to steroids. Child neurologists generally conform to the “one new drug at a time” approach to facilitate attribution of change to a single pharmacological agent. It was not at all surprising to the authors that no secondary treatments were added during the steroid treatment phase.

6. Some smaller writing issues: I would add the average length of treatment to the abstract, so the reader has a better idea of the scope of the study.

Authors’ Response: This has been added as suggested.

7. More STAR group children showed significantly improved behavior scores after the steroid treatment period as compared to before the treatment.’ More than what? The untreated group?

Authors’ Response: This sentence has now been edited to include the untreated comparison group in the comparison made.

8. In my original review I noted with regard to the title of Table 6: ‘Effect of steroids on CLSQ difference scores for STAR group’, that this is really misstated – these data are not the effect of steroids – they are change in score over time, which the authors are attributing to the use of steroids. The authors replied: This is correct and the Table title and text have been modified. However, in the version of the Tables in the supplementary material that I had access to, the title does not appear to have been changed.
Authors’ Response: The Reviewer is correct. We apologize for this oversight. In error, the wrong copy of this Table was transferred. This has now been corrected.

9. *Table 11a: see text and Table XX – XX needs to be fixed*

Authors’ Response: This is now corrected; same error as noted for item 8.

We thank the reviewer for her continued great investment in the improvement of our paper and trust that we have exercised due diligence as warranted given this importance of the topic and the potential for misinterpretation of the study.