Author's response to reviews

Title: Valproic acid is associated with cognitive decline in HIV-infected individuals: a clinical observational study.

Authors:

Lucette A Cysique (lcysique@ucsd.edu)
Paul Maruff (pmaruff@cogstate.com)
Bruce J Brew (b.brew@unsw.edu.au)

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Cover letter for the revised version of MS: 1704500403112957
Valproic acid is associated with cognitive decline in HIV-infected individuals: a clinical observational study. Lucette A Cysique, Paul Maruff and Bruce J Brew

San Diego, November 18th 2006

Dear Dr Jo Appleford
Senior Assistant Editor
BMC-series journals

Thank you for considering our revised manuscript for a potential publication in BMC Neurology. We did not include additional changes to the original revised manuscript, but addressed the comments of reviewer 2 below.

Thank you for your consideration,

Lucette Cysique, Ph.D.

Reviewer: Giovanni G Schifitto

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

It is my understanding that the reliable index of change (RCI) is a composite score that uses a specific cutoff to define change. It appears to me that in this study the authors really used just a composite score for the neuropsychological results, in which case they should not refer to as a RCI as they have previously published (page 7). The relevance of this is that only a few of those 8 subjects might have achieved the cutoff that signifies change. I do not think that there is anything wrong with using only the neuropsychological composite score. I also recommend that the quantitative analyses be limited to the first follow-up visit i.e., 6 months because thereafter there are even fewer patients to make any sense of quantitative analyses. This could be a simple analysis of change from baseline using the composite neuropsychological score. It would be best, in my opinion, to qualitatively describe the additional time points as shown in the figure.
"We used the conventional terminology of reliable change index (RCI) as our change score was based on a similar methodology used for all reliable change indexes (as originally defined by Jacobson & Truax, 1991). However, the use of the RCI as a continuous variable should not preclude the use of this terminology. As we have previously stated, we used a multidimensional regression model that used the composite reliable change index as the outcome and as a continuous variable. This allowed testing the effect of VPA while controlling for duration of treatment (or time in the study) as well as variation in intake."

"Moreover, we believe that arbitrarily censoring some information at six months is not a valid methodological strategy as we would arbitrarily select the time line of the study while not being able to interpret the effect of this arbitrary selection on the VPA effect. It would also preclude any harmonious analysis of the cases that remain longer in the study as well as increasing the experimental-wise error rate for no gain. We opted for a statistical methodology that would remain more flexible to evaluate the effect of VPA in an observational cohort. Despite its limitations, we believe that this regression model is the most powerful to detect an effect."

"We believe that our data highlight the need for caution in the conduct of large trials to address the issue of VPA and its neurological effects. Combining our data with that of Schiffito et al's suggests that there may be a dose and time window - this will be critical to address as a trial design issue in the future."