Author's response to reviews

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

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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, October 12th 2006

Dear Dr Jo Appleford
Senior Assistant Editor
BMC-series journals

Thank you for considering our revised manuscript for a potential publication in BMC. Below are outlined the changes requested by the reviewers.

The editorial changes were made as requested by including a section on competing interest and a section for acknowledgements.

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)

Please clarify what RCI cutoff was used to determine cognitive impairment. In the previous published work by the authors (ref 9) it specified that an RCI of -1.5 to -1.96 was considered abnormal. What was the number of subjects that met these criteria, and was the proportion of subjects on VPA with such a score different than the rest of the cohort? In looking at the figure, it appears that perhaps 3 subjects would fall in that category. Beyond the 6 months evaluation the data are more difficult to interpret. Subjects 2, 3 and 6 both worsened and improved on VPA; subject 8 both improved and worsened off VPA and subject 7 improved on VPA.
Our regression model controls statistically the performance fluctuation that is a common feature of HIV-associated neurocognitive decline (e.g. Grant et al., 1999). We chose to use a regression model that allowed adjusting for variation in VPA intake as well as drop out. Overall, the model demonstrated that with factors controlled, there is a negative association between VPA and cognitive functioning. This model does not allow identification of individual cases with progressive decline, which is actually rare in the case of HIV-infection. We agree with the reviewer that larger studies are necessary to conclude definitively on the effect of VPA in HIV-infected individuals. However, we also believe it is important to get as much data as possible to the scientific community, while we are waiting for these large trials. In this regards, our results are consistent with those of Schifitto’s study. As we stated in the discussion, our patients were more advanced, the VPA dose was higher and the observation period longer than in the Schifitto study, however both studies agree on the need to assert additional caution on potential new trials with VPA.

It is recommended that the analyses be adjusted for history of AIDS diagnoses and cognitive impairment. We used a cohort of individuals with advanced HIV-infection which was quite homogenous in terms of AIDS history (see reference 1 & 9). We report in the revised version the proportion of AIDS-defining illnesses at baseline in both groups (See Methods, Subject section). There was no difference between the groups on and off VPA. In addition, across the study time one individual in both groups developed a new AIDS-defining illness. We therefore did not include this factor in the regression model as the distribution precludes further analysis.

It is not mentioned whether liver function was assessed as it would be relevant to VPA exposure and cognitive performance. Subjects with significant liver function abnormalities should probably be excluded from the analyses.
None of the patients had any significantly abnormal LFTs.

Because of neuropathy in 7/8 subjects, the analyses should take into account this prognostic factor as it may affect psychomotor test results. Because neuropathy (presence or absence) was not distributed equally additional analyses of relationships between neuropathy and the cognitive variables could not be conducted. However, we agreed with the reviewer that in a larger investigation the peripheral neuropathy should be evaluated as a factor in a multiple regression model. However, none of the participants had moderate to severe neuropathy in the upper limbs. Our participants reported mainly neuropathy in the lower limbs.

Reviewer: Robert Bornstein

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

The primary concern regarding this manuscript is the lack of consideration of the performance of the two groups at baseline. Although the VPA group may decline more, it may be related to the initial level of deficit. The manuscript notes that the VPA group had a higher incidence of HIV neurologic complications, so it would not be at all surprising if they had greater deficit at baseline. That being the case they might also be at higher risk for cognitive decline that has no relation at all to treatment with VPA. We agree with the reviewer. We therefore re-conducted the analysis using a sub-sample that of the individuals on no VPA that had comparable baseline neuropsychological performance. In the Methods, Subject section, we detailed our method to extract the 40 individuals on no VPA who had comparable baseline performance to the individuals on VPA. In addition, we included a paragraph to comment on this issue in the discussion.