Reviewer's report

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

Version: 2 Date: 28 September 2006

Reviewer: giovanni G schifitto

Reviewer's report:

General
Cysique et al. report on the cognitive effect of Valproic acid (VPA) in HIV infected individuals. This retrospective study is based on a longitudinal cohort of 101 HIV infected individuals. In the cohort, eight subjects were on VPA prescribed for either neuropathy or epilepsy (one case) at an average dose of 850 mg/d. The number of subjects on VPA decreased from 8/8 at six months to 3/5 and 2/4 at 15 and 27 months. The results of this investigation found greater cognitive impairment in subjects exposed to VPA, at least in the first 6 months of evaluation.

A significant limitation of this study, acknowledged by the authors, is that the data are derived from an observational cohort (not a randomized clinical trial) and as such not specifically designed to address the effect of VPA on cognitive function. In addition, the sample size, especially in the context of an observational study where no randomization has occurred and where inclusion/exclusion criteria are retrospectively imposed, is quite small.

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.

It is recommended that the analyses be adjusted for history of AIDS diagnoses and cognitive impairment. 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.

Because of neuropathy in 7/8 subjects, the analyses should take into account this prognostic factor as it may affect psychomotor test results.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No
Declaration of competing interests:

The results of this study are in part discordant with our recently published report on valproic acid.