EXPERT REVIEWS

Association of chronic divalproex sodium use and brain atrophy in Alzheimer's disease

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Divalproex sodium has been widely use for the treatment of bipolar disorder, behavioral control in schizophrenia, seizure and agitation in Alzheimer's disease. With the advent of other mood stabilizers and anticonvulsants, the use of divaplroex sodium has been slightly decreased; however, it has been a major mediation for the treatment of such medical conditions. Beyond symptomatic effects on such neuropsychiatric conditions, it has also been proposed to hold some neurotoxicity effects, including reversible brain atrophy (which may be a serious complication associated with substantial cognitive decline), although it has shown neuroprotective effects. Common adverse events include sedation, tiredness and gastrointestinal symptoms. According to a recent study, divalproex treatment was associated with accelerated brain volume loss over 1 year, which could possibly lead to greater cognitive impairment. Hence, this article will discuss clinical and further research implications of this study, as well as the potential limitations and significance of the research.

Keywords: adverse event • atrophy • cognitive decline • divalproex sodium

Divalproex sodium (the US adopted name vs valproate semisodium, which is the international nonproprietary name; thus, both terms of divalproex and valproate are used without differentiation), dissociates to the valproate ion in the GI tract. The mechanisms by which valproate exerts its therapeutic effects have not been clearly established. It has been suggested that its activity in approved indications is related to increased brain concentrations of γ-aminobutyric acid [1]. Beyond such a mechanism of action, it has been found to affect signal systems (e.g., Wnt/β-catenin and ERK pathways), and to alter inositol and arachidonate metabolism, although the scientific understanding on the direct relationship between such effects and the clinical relevance has not yet been established [1,2]. It also influences multiple gene expression, which plays a major role in transcription regulation, cell survival, ion homeostasis, cytoskeletal modifications and signal transduction [2]. Therefore, it may exert its therapeutic effects via both immediate biochemical and longer-term genomic alterations [2].

Beyond symptomatic effects on such neuropsychiatric conditions, a series of case reports suggested that valproate treatment may cause reversible brain atrophy, parkinsonism and cognitive impairment [3–7], although it has also shown neuroprotective effects [8–10]. The common adverse events include sedation, tiredness and gastrointestinal symptoms, while hepatotoxicity, pancreatitis and teratogenecity are presented as life-threatening adverse events.

Recently, in an MRI substudy of a 24-month, randomized, placebo-controlled clinical trial of divalproex sodium for mild-to-moderate Alzheimer's disease (AD) [11], conducted by the Alzheimer's Disease Cooperative Study [12], unexpected increased rates of brain volume loss were found to be associated with divalproex sodium. The authors found that divalproex

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treatment showed a greater rate of decline in the left and right hippocampal and brain volumes, and a greater rate of ventricular expansion.

Summary of methods & results

In the original study, patients were randomly assigned to double-blind treatment with either divalproex sodium or a placebo that was identical in appearance for 24 months [12]. Three hundred and thirteen patients with probable AD were recruited from multiple sites across the USA, of which 172 volunteers participated in the MRI study. Structural MRI scans were acquired at baseline and at 12 months to assess treatment and disease-associated changes in whole brain, hippocampal and ventricular volumes over time, as a planned secondary analysis in a subset of such population. Eighty nine patients had baseline and 12-month MRI results of sufficient quality to analyze the data. There were no significant between-group differences in baseline mean age, education, years since AD diagnosis or APOE ε4 carrier status, except for gender and BMI. Analyses of imaging measures revealed no statistical differences between treatment groups at baseline or 12 months for hippocampal, whole brain or ventricular standardized volumes.

The most pronounced difference was a change in ventricular volumes, the divalproex-treated group showed a significantly greater increase than the placebo group, with a magnitude of difference of 14.6% ($p < 0.001$). Brain volumes changed an average of -3.5% (±1.4) in the divalproex group compared with -1.4% (±1.1) in placebo-treated subjects ($p < 0.001$). Annual hippocampal volume reductions were -10.9% (±7.3) on the left and -12.4% (±8.8) on the right in the divalproex group, compared with -5.6% (±7.9) and -6.3% (±8.5), respectively, in the placebo group ($p < 0.001$). More rapid decline in Mini-Mental State Examination (MMSE) scores were noted in the divalproex treatment group through month 12 (placebo -2.0 vs divalproex -3.9; $p = 0.037$), which was also correlated with annualized hippocampal volume reduction, although there were no changes on other cognitive, behavioral or functional ratings at 12 and 24 months.

Discussion

The authors found that substantial brain volume loss associated with divalproex sodium treatment in patients with AD and the divalproex MRI subgroup led to a profound decline in MMSE scores in the first 12 months of the trial, without similar findings in other global cognitive tests [11]. The authors' conclusion was that additional divalproex treatment for patients with dementia, when considering the risks and benefit of the use of divalproex sodium, could not be recommended as routine therapy, although we cannot clearly conclude that the morphologic effects in association with divalproex treatment were caused by acceleration of AD pathology or nonspecific global neurotoxicity.

It is well known that patients with AD can be sensitive to neurotoxic insults. It should be assumed that similar potentially neurotoxic effects of divalproex associated with brain volume loss in the first 12 months of the original longitudinal study [12] also caused the initial rapid decline in MMSE scores observed in the present secondary MRI study [11]. However, clinical data concerning adverse events and laboratory test from the original study showed no clear evidence of significant neurotoxicity in any patients during the 24-month study, indicating that divalproex treatment is not directly associated with cognitive impairments in such a population (rather suggesting that divalproex may be more associated with reduction of brain volume than direct cognitive decline). In addition, the annual rates of cortical atrophy in the placebo-treated group corresponded to previously reported rates in similar AD cohort studies [13–15]. The power of the sample ($n = 66$ for whole-brain measures) was more than 0.8 for detection of 10% differences in the two treatments, although the size of the effect for the specific region of interest would be small to modest, ranging from 0.2 to 0.4 owing to small differences in each region of interest. Overall these findings indicate the strength of the authors' study. The study was the first well-controlled trial and conducted over a relatively long study duration for such a research field. These may also strengthen the Fleisher *et al.* study results [11].

However, interpretations of these results should also be cautious since many possible factors are involved in terms of clinical and pathologic implications in such patients with AD. We cannot completely exclude the possibility of underlying influences of comorbid late-life depression on brain atrophy and cognitive impairment, since late-life depression was associated with significant and direct subcortical and hippocampal neuronal loss and cognition, which may have substantially impacted on the study results [16,17]. Other pharmacological factors (e.g., antihypertensive medications and alcohol) should also be kept in mind because these are also known to cause substantial and independent decline in cognitive function and brain volumes [18]. Valproate may also induce delirium or confused states in patients with dementia, which may present significant and exaggerated cognitive decline [19]. As stated in divalproex prescribing information, divalproex is known to cause reversible brain atrophy and dementia. However, the underlying mechanisms are currently not established, although hepatotoxicity (e.g., encephalopathy), hyperammonemia (e.g., encephalopathy and urea cycle aberration), osmotic changes (e.g., alteration of myoinositol or glycine), neurotoxicity (e.g., mitochondrial damage or apoptosis) or acceleration of AD are possible explanation for these unresolved phenomena [1,12]. However, a body of evidence supporting neuroprotective effects of valproate may also exist. In fact, it has been consistently proposed that valproate may positively influence neuronal survival/apoptosis and proliferation/differentiation balance, as well as synaptic plasticity, by acting both directly on neurons and indirectly through glial cells, which possibly account for its beneficial effects on neuronal cell survival [20]. Hence, we are still in the process of working to prove how valproate exerts its function on the brain through biochemical, epigenetic and molecular level mechanisms. The study failed to acquire MRI data after 24 months of divalproex treatment or after discontinuation of medication, suggesting that we cannot fully exclude a possibility of transient effect of divalproex treatment on cognitive decline and brain atophy, which is one of the main pitfalls in the study. As seen in the results, divalproex treatment was associated with

a higher rate of decline in left and right hippocampal and brain volumes (-10.9 and -12.4% vs -5.6 and -6.0%, and -3.5 vs -1.4%, respectively), and a greater rate of ventricular expansion (24.5 vs 9.9%), compared with placebo treatment. The largest difference was noted in the ventricular volumes, which favored placebo treatment, with a magnitude of difference of approximately 15%, while other differences between the two treatment groups ranged only from 2 to 6%. Although the MMSE scores showed a more rapid decline with divalproex through month 12 (placebo -2.0 vs divalproex -3.9), no changes on other cognitive, behavioral or functional ratings were observed at 12 and 24 months. Therefore, we cannot conclude how much these differences would directly translate into our clinical practice. Other important questions still remain. Is valproate-associated atrophy seen in this study specific to AD or may it also occur in other clinical populations? How much of the natural clinical course of AD impacted changes of brain volumes in the study? Finally, the study duration of around 1 year also does not allow us to conclusively state the long-term effects of valproate on brain atrophy along with cognitive decline considering the long clinical course of AD.

Expert commentary & five-year view

Valproate should be used carefully as a preventive treatment option for agitation and psychosis in AD patients since the results indicate that valproate may possibly increase the brain atrophy along with substantial cognitive decline. In addition, the authors' study has also proved the importance of investigating the relevance of preclinical findings concerning neurotoxicity of valproate to humans, especially those who are vulnerable to such harmful effects. The atrophic changes associated with the use of valproate were also clearly correlated with significant cognitive impairments as measured by MMSE scores, from which we as clinicians may have to consider more conservative use of valproate balancing risk/benefit ratio in such patients with degenerative CNS diseases.

Recently, the American Psychiatric Association guidelines for AD (especially for those with agitation and psychosis) has not recommended valproate for treating such AD patients, while it also stated that antipsychotics and benzodiazepines could be possible treatments option but not routine use. When clinicians are confident with the clinical advantages of valproate treatment over other biological agents on control of agitation and psychosis by compiling reliable clinical and scientific evidence, the valproate treatment option would be reconsidered compared with its current place. Given the risks and potential detrimental findings of valproate as seen in the Fleisher *et al.*'s study and anecdotal evidences, we will need more accurate, clear and systematic clinical evidence supporting the use of valproate in such AD patients.

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Key issues

- The study by Fleisher *et al.* clearly demonstrated that divalproex treatment was associated with a harmful effect on brain volume over 1 year.
- Valproate-associated brain atrophy was also correlated with accelerated cognitive decline.
- Methodologically advanced researches will be needed to reveal a clear understanding regarding the beneficial and detrimental influences of valproate treatment for Alzheimer's disease patients.

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