**CLINICAL VIGNETTE**

# Valproate for Agitation in Dementia? Think Again!

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***Case Presentation***

A 78-year-old male with history of mixed Alzheimer's and vascular dementia presented to his neurologist due to concern for worsening behavioral disturbances. His cognitive complaints began more than five years ago. However, onset of his neuropsychiatric symptoms of dementia did not present until 3-4 months prior to this visit. First-line therapy was initiated with quetiapine. According to his wife, despite adherence to quetiapine, the patient became increasingly aggressive including pushing her when angered. She was so fearful for her safety that she had considered calling the police on more than one occasion. As such, the patient's neurologist added divalproex sustained action (SA) 250 mg once daily to his regimen. Labs obtained four days after starting the medication were unremarkable, including comprehensive metabolic panel, white blood cells (5.6), and platelets (149); the patient's hemoglobin was also at baseline in the setting of a known normocytic anemia (9.9 with MCV 95).

Two weeks later, the patient's neurologist increased his divalproex SA dose to 500 mg daily in an effort to wean him off of quetiapine, which was suspected to cause postural tremors. Laboratory tests obtained about two weeks later incidentally showed new-onset thrombocytopenia (platelets with a nadir of 97) and macrocytosis (MCV 100.6), with stable anemia (hemoglobin 9.5). The patient remained asymptomatic without increased bleeding or bruising, fever/chills, chest pain/ shortness of breath, GI symptoms, or fatigue. Tests for various etiologies of thrombocytopenia were unremarkable, including HIV, hepatitis C, LFTs, INR, fibrinogen, and hemolytic markers. Given the correlation between the timeline of divalproex dose adjustment and the patient's decline in platelets, the thrombocytopenia and macrocytosis were attributed to divalproex use.

***Discussion***

Valproate is an antiepileptic medication that has been FDA-approved for the treatment of bipolar disorder and seizure disorder, as well as for migraine prophylaxis. Despite limited evidence to support its use in Alzheimer's Disease, off-label valproate prescriptions have been increasing for patients with behavioral disturbances. A study of 973,074 nursing home residents with Alzheimer's disease and related dementias, reported 13.4% of subjects had received valproic acid in 2019.[1] A recent Cochrane Review involving five randomized controlled trials showed that valproate had no significant effect on the primary outcome of agitation among patients with dementia. However, it was associated with several adverse effects, including sedation, gastrointestinal symptoms, urinary tract infections, and thrombocytopenia.[2]

Thrombocytopenia is a dose-dependent side effect of valproate and reported in 5-18% of patients taking this medication.[3] The risk appears to be increased in female patients and elderly individuals and can develop soon after initiation of the medication, ranging from 8 days to 16 months after first exposure. The mechanism of valproate-induced thrombocytopenia is not yet known but is thought to be multifactorial. Valproate likely suppresses bone marrow platelet production and is associated with increased levels of circulating platelet-related immunoglobulin M, which might induce peripheral platelet destruction.[3,4]

Unfortunately, managing the behavioral and psychological symptoms of dementia remains a challenge for many practitioners and patients' families, which explains the increased use of antiepileptics like valproate.[2,5] Additionally, nursing homes have increased regulations to improve quality including the initiation of the Minimum Data Set (MDS). Part of the quality metrics also includes monitoring rates of antipsychotic use which has led many practitioners to rely on off-label medications as alternatives like valproate which are not as strictly monitored.[6,7] Agitation, depression, apathy, and inappropriate behaviors are common, and one study reported the five-year prevalence of at least one such symptom of 97%. These behavioral disturbances have a profound effect on both patients and families, resulting in increased morbidity, mortality, hospitalizations, costs of care, and nursing home placements.[5]

Non-pharmacologic approaches are considered first-line and include: 1) behavioral therapy such as music, reminiscence, or physical activity and 2) environmental interventions like establishing a routine; and caregiver training in stress reduction and patient redirection. Pharmacologic therapy should be reserved only for patients who pose a danger to themselves or others, similar to our patient. While antipsychotic medications have a black box warning of increased mortality, they are often used due to some efficacy in reducing aggression. In the Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD), there was a significantly longer time to discontinuation for lack of efficacy in the risperidone group compared to the placebo group, though time to discontinuation due to side effects, as seen in our patient with

quetiapine, favored the placebo.[4] Cholinesterase inhibitors and memantine are also approved for treatment of cognitive decline and behavioral issues in Alzheimer's dementia, but there is little evidence to suggest that they specifically reduce agitation.[2,4,5]

For our patient, valproate did not have any perceived benefit in improving agitation, as the patient's wife continued to note waxing and waning periods of aggression. The dose of divalproex was decreased back to 250 mg, and platelet count stabilized at 105 with return of MCV to 96. The patient was instructed to discontinue the medication one week later.

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