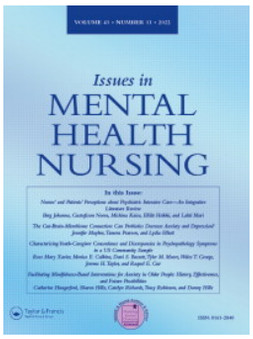

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PSYCHOTHERAPEUTICS COLUMN

Versatile Valproic Acid

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Historically, the indications for valproic acid have been seizure prevention, migraine headache prophylaxis, and manic episodes of bipolar disorder. From both literature review and anecdotal experience as an inpatient provider at a level 1 trauma center, however, I believe this agent is far more versatile than its FDA-approved indications. Let us briefly explore the history of valproic acid, as well as how this agent could have utility in other conditions as off-label uses.

History

Beverly Burton, an American chemist, discovered the chemical structure of valproic acid in 1886. However, it was originally thought to be inert since it was a liquid fatty acid. At one time, it was used as a solvent for pharmaceuticals and industrial chemicals. Valproic acid was not discovered to have antiepileptic properties until 1963, when George Carraz at Laboratoire Berthier in Grenoble, France identified that the compounds he and his colleagues were analyzing for anticonvulsant activity gave positive results when they were dissolved in valproic acid (American Chemistry Society, 2022). It went on the market for management of epilepsy in France in 1967, but the first controlled clinical trial did not take place in the United States until 1975 (Richens & Ahmad, 1975; Tomson et al., 2016). Valproic acid under the brand name of Depakene was approved by the FDA for use in 1978 and divalproex sodium as Depakote in 1983 (FDA Access Data, 2011).

Neurotransmitter actions

I teasingly refer to this medication as a weighted blanket for overexcited neurotransmitters such as glutamate. In truth, it has an impressive spectrum of neurobiological activity. At the chemical level, valproic acid inhibits voltage-gated sodium channels, suppresses NMDA-evoked depolarization, and upregulates GABA by inhibiting glutamate decarboxylase (Gean et al., 1994; Loscher & Schmidt, 1980; Zeise et al., 1991). It is also thought to impact monoamines: for example, valproic acid plays a role in regulating dopamine release (Huang et al., 2006).

Off-label uses from a psychiatric perspective

Hyperactive delirium, COVID-19 delirium

Valproic acid is a treatment option for hyperactive delirium since it manipulates complementary neurobiological pathways and can provide neuroprotection. Chemically speaking, delirium is thought to be an excess of dopamine, an excess of glutamate, a deficit of acetylcholine, and excessive NMDA receptor activity (Sher et al., 2015).

Valproic acid is particularly useful for patients with cardiac (specifically, QTc) issues, those with severe movement disorder concerns in which antipsychotics would be relatively contraindicated (such as Parkinson's disease), or those who experience side effects of antipsychotics such as akathisia (Woolley, 2021). Unlike antipsychotics, valproic acid does not decrease acetylcholine, which is noteworthy since delirium is thought to be at least in part a central cholinergic deficiency (Huang et al., 2006).

The refractory nature of COVID-19 delirium to typical medications used for agitation and psychosis make it particularly challenging to manage. In a piece written by Dr. Elliot Martin, director of medical psychiatry at Newton-Wellesley Hospital in Massachusetts, he described the struggle of finding medications that could squelch the "unwittingly violent" behavior of patients with COVID-19 delirium (Martin, 2020). As I described in my piece entitled "The COVID-19 conundrum: Where both the virus and its treatment contribute to delirium" published in *Geriatric Nursing*, valproic acid has been found to mitigate some of the agitation and impulsivity that accompanied hospitalized COVID-19 patients (Woolley, 2021). Theoretically, valproic acid might provide additional protection for COVID-19 patients, as this virus might increase one's risk for seizures and strokes; valproic acid also decreases neuro-inflammation (Woolley, 2021). After another year of anecdotal experiences treating COVID-19 delirium since that article was published, instead of citing valproic acid as a second-line or adjunctive treatment, I would now include it as an alternative first-line intervention alongside the antipsychotics.

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TBI-associated agitation, intermittent explosive disorder

Anti-epileptics with mood regulation effects (such as valproic acid and carbamazepine) are also considered to be first-line treatment for management of acute agitation in the setting of traumatic brain injury (TBI) (Luaute et al., 2016). Mood-regulating anti-epileptics act on neurotransmitters (simply speaking, by decreasing glutamate and NMDA and promoting GABA) involved in agitation and aggressiveness. More practically, the similarity found between manic state symptoms for which several anti-epileptics have a recognized indication can be similar to the manifestations in the setting of TBI (Siegel et al., 2007). Valproic acid is thought to be particularly useful in the setting of alert, labile, impulsive, and disinhibited brain injury patients (Showalter & Kimmel, 2000). Dr. Samuel Sears, a consult psychiatrist with whom I work closely, gave a good visual representation of valproic acid's ability to modify behaviors when he said it "lengthens the fuse but doesn't stop the explosion." By way of illustration, the brain is given a bit more time for the patient to make a different choice instead of immediate reactivity, which is often negative.

Parkinson's disease with non-motor symptoms

Non-motor manifestations of Parkinson's disease (PD) such as poor impulse control and agitation can hamper quality of life for both patients and caregivers. Impulse control disorder (ICD) is also one of the documented behaviors associated with behavioral and psychological symptoms of dementia. One study revealed that 42% of PD patients treated with an oral dopamine agonist developed ICD (Garcia-Ruiz et al., 2014). Impulse control disorder likely stems from chronic stimulation of dopamine due to the use of dopamine agonists such as levodopa or carbidopa (Lopez et al., 2017).

Due to anti-dopamine properties, antipsychotics are relatively contraindicated for patients with PD (studies looking at the use of clozapine or quetiapine for PD patients could be discussed in another piece). I have hypothesized that valproic acid could have value for this population in the instances where non-pharmacologic interventions have failed to address the behavioral disturbances and psychotropic intervention is warranted. Valproic acid's inhibition of glutamate decarboxylase and antagonistic actions on NMDA is why this drug may theoretically be helpful for PD patients with ICD since glutamate transmission is known to have a role in impulsivity and disinhibition (Pattij & Vanderschuren, 2008; Sukhotina et al., 2008). While valproic acid may have a small pro-dopamine impact due to increased prefrontal dopamine release by 5-HT1-A receptor activation, it would be clinically insignificant when compared to the pro-dopamine effects of the true dopamine agonists used for the treatment of PD (Ichikawa & Meltzer, 1999).

Future implications for valproic acid

In recent years, there has been a resurgence of scientific inquiry about valproic acid. Its ability to inhibit histone deacetylase has renewed scientific inquiry in valproic acid beyond traditional indications, such as for treatment of cancer (Tomson et al., 2016). Histone deacetylase is an enzyme that allows histone proteins to wrap DNA more tightly. It also has the ability to reduce the stability of certain proteins, including Cas9 (CRISPR-associated protein 9), which is an important part of prokaryotic adaptive immunity (American Chemistry Society, 2022).

Valproic acid is thought to halt the growth of tumor cells by killing the cells, preventing division, or stopping spread. Examples of cancer types in which valproic acid has been studied and found useful include prostate, breast, and gliomas (Iannelli et al., 2020; Vecht et al., 2014). There are three active clinical trials at M. D. Anderson Cancer Center in Houston, Texas, studying valproic acid's uses in various cancers including melanoma. I am particularly looking forward to results from their "MADNESS" trial, which is assessing the efficacy of antiepileptics and antipsychotics in hyperactive delirium among patients with advanced cancer (NIH, 2022).

Valproic acid also holds neuroprotective qualities. By way of illustration, it has been found to protect against ischemia-induced cerebral inflammation by decreasing brain infarct volume, suppressing microglial activation, and decreasing the number of microglia (Kim et al., 2007). It may also reduce inflammatory mediators such as nitric oxide, tumor necrosis factor, and reactive oxygen species. Another study described how valproic acid therapy significantly increased oligodendrocyte survival post-stroke and generated new oligodendrocytes, which was linked to increased myelinated axonal density, white matter repair, and ultimately neurogenesis (Liu et al., 2012).

Conclusion

To close, I can see why valproic acid has stood the test of time and has continued to be prescribed more than forty years after its FDA approval. It continues to be useful for its original indications in epilepsy, migraine prophylaxis, and manic episodes of bipolar disorder while having off-label utility for hyperactive delirium (including COVID-19 delirium), TBI agitation, intermittent explosive disorder, and ICD associated with PD and behavioral and psychological symptoms in dementia. I would expect future investigation to elucidate more uses for this versatile agent, even outside of the neurological and oncological settings for which it is presently being studied.

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