PHARMACOLOGY UPDATE

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Valproic Acid: Special Considerations and Targeted Monitoring

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ABSTRACT

Valproic acid (VPA) is a medication used to treat multiple neuroscience conditions. It is an inexpensive and useful medication, with a low incidence of adverse drug events. Nonetheless, optimal clinical outcomes require that a series of screening and laboratory steps be followed before the initiation of VPA therapy. An additional aspect of pharmacovigilance is to recognize clinical patterns signaling genetic traits that preclude VPA, background of the black box warnings, targeted assessments, and laboratory monitoring indicated while on VPA. The intention of this article is to provide a focused summary of published information clinically relevant to prescribing and monitoring these patients.

Keywords: adverse drug events, AED medications, clinical decisions with pharmacology, neuroscience pharmacology, valproic acid

Sodium valproic acid (VPA) is a prescribed medication for seizures, chronic epilepsy management, status epilepticus, and the treatment of psychosis and as a prophylaxis for migraines.[1,2] Interprofessional teams from neuroscience and psychiatry often provide care for patients on this antiepileptic (AED) medication. Typically, it is well tolerated with infrequent occurrences of serious adverse drug reactions (ADRs).[2,3] However, it is vital to identify host factors, which lead to ADRs. Genetic testing is now available to identify selected genes that impact the pharmacokinetics of VPA metabolism. Genetic testing for medications in clinical practice is a new choice and not yet widely used.[4] Safe prescription and monitoring require team members to be alert to assess for clinical manifestations of genetic factors leading to adverse VPA effects, identify special populations who need additional monitoring, and have a working knowledge of associated black box warnings (BBWs). Serious adverse effects include mitochondrial toxicity, hepatotoxicity, teratogenic, and drug-induced diseases.[1,3] The aim of this article is to outline clinically significant information for safe prescribing and monitoring of patients who receive VPA therapy.

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VPA: Pharmacokinetics (Absorption, Distribution, Metabolism, and Excretion)

Valproic acid is available in multiple oral dosage forms and is well absorbed. The bioavailability of oral VPA formulations is generally 90% to 100%. Valproic acid is highly bound to albumin once absorbed. Patients with hypoalbuminemia should be closely monitored because of the increased amount of unbound drug in the body. Valproic acid is distributed rapidly to the central nervous system through the use of fatty acid transport systems and other unidentified mechanisms.[5] Valproic acid has no significant first-pass metabolism but is metabolized by the liver via multiple pathways. The 3 primary pathways of elimination and metabolism are glucuronidation, mitochondrial dependent β-oxidation, and the minor pathway of Ω-oxidation. Most fatal ADRs associated with VPA are due to mitochondrial dysfunction, resulting in insufficient β-oxidation and accumulation of the toxic metabolite 4-*ene*-VPA, causing hepatotoxicity possibly leading to death.[1,3]

Assess for Genetic Mutations: Leading to Mitochondrial Toxicity With VPA

There are multiple genetic disorders of the mitochondria that lead to neurology problems, including seizures

and epilepsy. Mitochondrial myopathies are due to a mutation in the nuclear or mitochondrial DNA.[6] Mitochondrial DNA is inherited from the mother. In addition, 2 genetic intracellular mitochondrial metabolism defects also manifest VPA adverse events. Valproic acid is contraindicated in all known mitochondrial-related diseases.[3] However, because these diseases are often misdiagnosed or undiagnosed, VPA prescription can reveal the intracellular dysfunction. The administration of VPA to this subset of patients produces mitochondrial toxicity, causing a myriad of clinical problems. The most common presenting adverse effect upon administration is hepatotoxicity.[3,7] This occurs because of the drug's nearly exclusive hepatic metabolism. Selected information on the genetic basis of mitochondrial disorders, with published data relevant to VPA use, is included to increase awareness of this spectrum of seizure-related disorders.[8,9] Once diagnosed, patients can be excluded from VPA administration and referred for genetic testing (see Table 1 and Supplemental Digital Content 1, available at http://links.lww.com/JNN/A84).

Hyperammonemic Syndromes Genetically Linked: Primary Carnitine Deficiency-Metabolism Transport Gene

Primary carnitine deficiency is a gene mutation in *SLC22A5*, an autosomal recessive gene. *SLC22A5* allows the body to create a protein called OCTN2, which transports carnitine into the intracellular space. Carnitine is an amino acid component. It is believed to be essential to normal mitochondrial handling of ammonia and a cofactor required for VPA degradation.[3,10] Cells require carnitine as a cofactor to transport fatty acids into the mitochondria and to maintain the ratio of acetyl-Coenzyme A to free Coenzyme A in the mitochondria.[10,11] Dietary sources for this nutrient are red meat and dairy products. Carnitine is particularly important in cells that require a high oxygen and energy supply, such as the brain, heart, and liver. Carnitine is part of an intracellular transport system sometimes called the ''carnitine shuffle.'' Two metabolites of VPA diminish the amount of available carnitine for fatty acid intracellular transport (see Fig 1). The clinical presentation of this genetic pattern is variable with some persons being asymptomatic. Signs and symptoms of primary carnitine deficiency include headache, muscle weakness, and profound fatigue. Persons with this deficiency may report an aversion to protein because consumption triggers headaches. Overwhelming metabolic stress, such as nausea and vomiting, or extreme exertion, exhausts the alternative metabolic pathways in these patients. In primary carnitine deficiency, metabolic strain is manifested as cardiomyopathy, which can progress to death. Some presentations of sudden cardiac death are associated with this deficiency.[11] Several authors recommend carnitine supplementation for patients who take VPA chronically. Carnitine is also recommended for the treatment of VPA overdose.[10–12] Clinicians monitoring VPA patients who complain of fatigue may consider recommending carnitine supplementation to enhance mitochondrial function.

Ornithine Transcarbamylase Deficiency

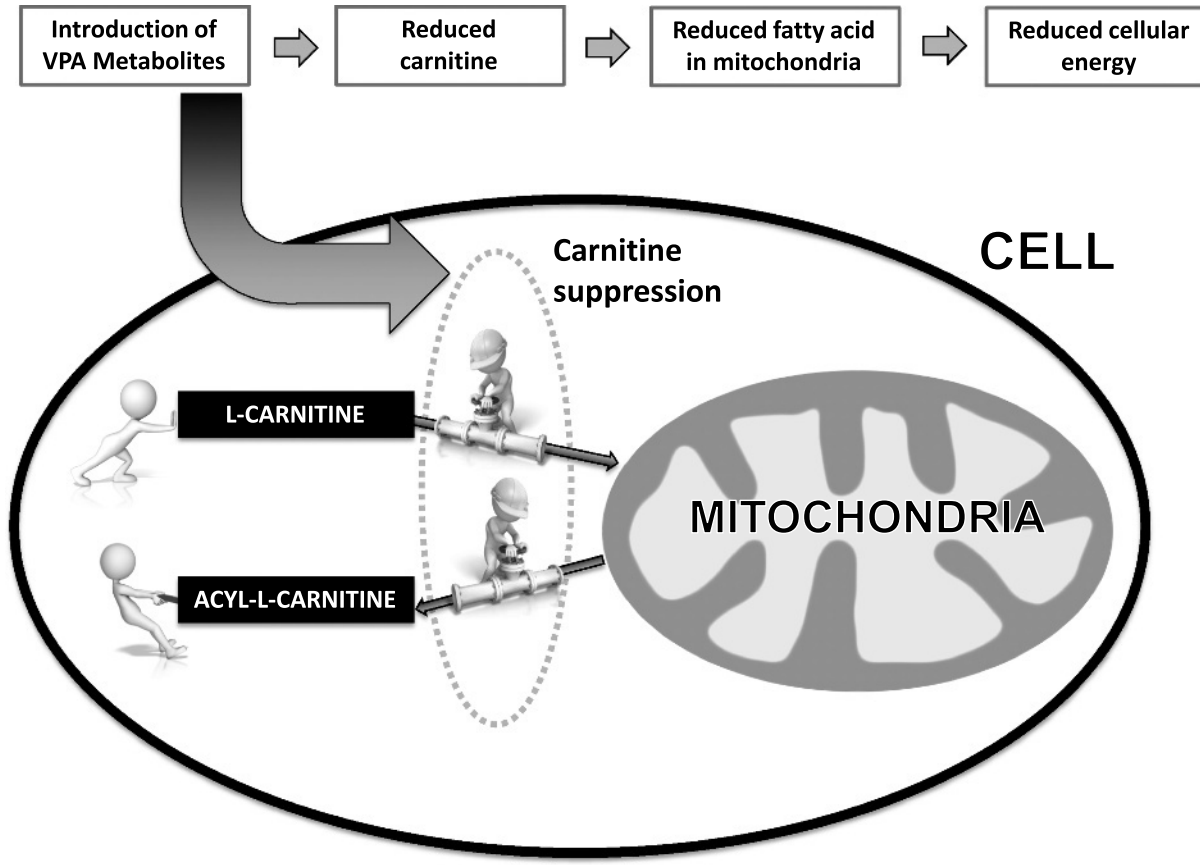
Ornithine transcarbamylase (OTC) deficiency describes an X-chromosomal linked disorder that has more than 200 known gene mutations.[13] The OTC gene mutation can be expressed as an OTC enzyme that is shorter than normal or the wrong shape. In some women, the enzyme is not produced at all. Male babies born with this defect do not survive infancy. This genetic disorder is categorized as one of the urea cycle disorders. The urea cycle describes a series of chemical reactions in hepatocytes that produce nitrogen from protein intake.[10,11] Excessive nitrogen is then processed into urea for kidney excretion. In OTC deficiency, excessive levels of nitrogen are produced because the urea cycle is dependent on this enzymatic component and prevent normal liver metabolism of protein. The end product is excess nitrogen, which leads to high serum ammonia levels in the affected patient. This genetic abnormality is often unrecognized before excessive protein intake or VPA administration. The drug-induced disease of VPA hyperammonemic encephalopathy (VHE) develops when patients with this inborn metabolic error are given VPA.[11,13] The clinical manifestations of VHE include a decreasing level of consciousness, focal neurological deficits, cognitive slowing, vomiting, drowsiness, and lethargy. Without prompt recognition and treatment of VHE, the patient develops fulminant liver failure. Treatments of this disease are carnitine administration, pharmacological agents to promote alternative metabolism of nitrogen, and withdrawal of the VPA. Machado and Pinheiro da Silva[13] recommend sodium phenylacetate, sodium benzoate, and sodium phenylbutyrate to provide alternative pathways to eliminate ammonia via renal excretion. Carnitine supplementation assists the mitochondria in producing energy from fatty acids required to metabolize VPA.[11,13]

Identifying Special Populations Requiring Additional Monitoring

Children 1–2 Years Old

According to multiple publications and medication labeling, VPA is not recommended for children younger than 2 years. This information is placed on VPA's Food and Drug Administration medication labeling under ''special populations.''[3] Infants have the greatest incidence of fatal hepatotoxicity with VPA, particularly when other AED medications are also used. This is believed to be due to the immaturity of liver metabolic processes

FIGURE 1 Two Metabolites of Valproic Acid Decrease the Amount of Carnitine Available for Fatty Acid Transport Into the Mitochondria



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and the vulnerability of the infant to handle multiple CYP inducer medications, such as phenobarbital and phenytoin concurrently.[3] If the provider elects to use VPA in this population, extensive monitoring of liver function and neurodegenerative acceleration is required. There are older case studies of a Reye syndrome of liver toxicity and failure in pediatric patients prescribed with VPA. Clinicians attribute the decline in these case reports to avoidance of VPA prescription in this age range.

Older Adults With Polypharmacy

Valproic acid is used for seizures and the management of psychotic mania in the psychiatric setting, for the older adults.[15] Variables that impact the ability of the older adults with the pharmacokinetics of VPA are declining liver function, polypharmacy, and concurrent use of herbal supplements.[12] The medication label states that somnolence is associated with the use of the medication in the older adults recommending a lower starting dose. Alder and Regenold[16] report a 2-fold incidence increase in hyperammonemic levels in the older adults in a psychiatric setting on VPA, compared with a control group without this medication. Hyperammonemia produced symptoms of decreased alertness when ammonia levels doubled from normal in 10% of the patients. Hyperammonemia can lead to encephalopathy presentation with declining mental status. Psychomotor tests are recommended to document decline in attention and motor speed. Polypharmacy, including herbal supplements in the older adults, requires that each medication taken be evaluated by the clinical pharmacist for potential impact on the therapeutic level of VPA.[5,16] Drugs, which modify, block, or induce changes within the enzymatic CYP pathways, can potentiate drug toxicity.[5] Selected medications that should trigger a clinical pharmacist evaluation are listed in Table 1.[17]

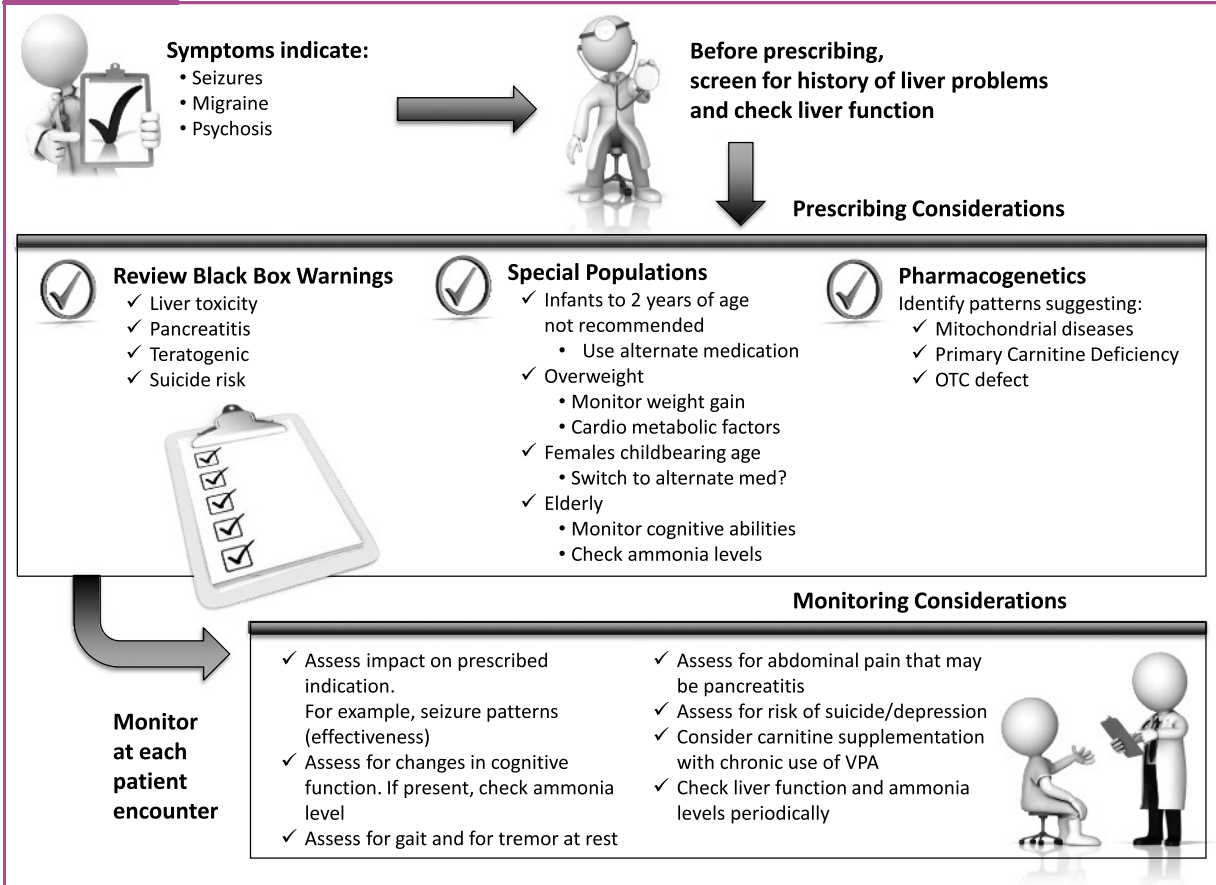
Tremors, nystagmus, and ataxia are common drug-induced adverse effects of VPA with a higher prevalence in the older adults. Tremors at rest, particularly of the eyelids, are associated with a drug-induced finding.[18] Valproic acid can also produce a drug-induced Parkinson disease in the older adults. A comprehensive review of the medical literature found 13 cases that were directly linked to VPA.[15] Symptoms improved after discontinuation of the medication. These researchers recommend careful monitoring of the older adults on VPA

TABLE 1. Selected Clinically Important VPA Drug-Drug Interactions With Polypharmacy Patients

Category	Medications With Drug-Drug Impact on VPA	Nature of Interaction
Antiseizure	Carbamazepine	Increased clearance of VPA resulting in lower serum levels. Seizures may occur.
	Phenobarbital Phenytoin	Phenytoin and VPA are both protein bound, and when administered together, the circulating phenytoin level is increased.[1]
Anticoagulants	Aspirin	Increases the concentration of VPA[1]
	Warfarin	VPA slows the rate of warfarin metabolism.[1]
Anti-infective	Carbapenems	Current theories of interaction: Disruption of the normal metabolism in the liver of VPA results in decreased serum level of medication.[17] There is decreased absorption of VPA due to the change in gut flora and inhibition of intestinal transporters.[6,17]
Sedation	Benzodiazepines (Beers Criteria for Potentially Inappropriate Medication Use)	This group of medications has synergy with VPA to increase sedation effects leading to a higher risk of falls.[12]

Abbreviation: VPA, valproic acid.

FIGURE 2 Flow Chart of Decision Checkpoints When Prescribing and Monitoring Valproic Acid



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for change in gait and reaction time because there were often many comorbidities linked to neurological decline present.[19]

Childbearing and Pregnancy

Valproic acid is considered one of the most teratogenic drugs. It crosses the placenta to the fetus, which can produce neural tube, cardiac, and facial defects. Use of this medication in pregnancy should be avoided.[20] There are scant published data relevant to the use of AEDs in pregnancy. Clinicians need data relevant to decreased AED concentrations in each trimester, optimal timing to monitor drug levels, incidence of breakthrough seizures, and seizure frequency.[20] Teratogenic effects are a BBW with this medication.[14] Many clinicians choose to administer other AED medications for female patients with seizures during their reproductive years.

Accelerating Insulin Resistance in People With Diabetes

There are 2 metabolic ADRs associated with VPA that can increase insulin resistance. These include an incidence of weight gain and metabolic syndrome. The body mass index increases upon initiation of VPA administration, and hyperinsulinemia is found in some patients.[3,21,22] Monitoring of glucose tolerance and changes in body weight are important once the patient is placed on this medication, to prevent the onset of type 2 diabetes. Women on VPA developed metabolic syndrome at a higher rate than men.[23] Obese patients may benefit from the choice of another AED medication.

Black Box Warnings

The 3 BBWs listed on the medication label are hepatotoxicity, teratogenicity, and pancreatitis.[14] There is also a general warning to watch for depression and suicide risk with all AEDs. Hepatotoxicity and teratogenicity were discussed in the previous section and linked to patients at greatest risk. The additional BBWs and general warning are discussed hereinafter.

Life-threatening pancreatitis is a rare, drug-induced complication of VPA. There are several case reports of pancreatitis while on VPA as a polytherapy.[23] How VPA induces pancreatitis is unknown. However, through biochemical pathology studies, the theory of the persistence of pancreatitis in these patients is believed to be associated with the suppression of histone deacetylases.[23] These enzymes are important in the regeneration of acinar cells after a pancreatic insult. When a patient is on VPA, a clinician must rule out elevation of pancreatic enzymes as the cause of significant back and abdominal pain.

The reasons for increased depression and suicide risk with AEDs are believed to be multifactorial and unique to each patient. The Food and Drug Administration added the warning in 2009 because of research reports that suggest a relationship between AED use and suicide. Hecimovic et al[24] discuss several areas of research examining factors that may create depression in epileptic patients, including AED use. Valproic acid's impact as an AED on the neurochemistry of depression is not yet clearly delineated. The current recommendation is to screen for depressive and suicidal manifestations at each patient encounter.

Conclusions

Each healthcare team member has a responsibility to identify, assess, and monitor, or discontinue, AEDs based on patient response. Valproic acid is a low-cost medication and generically available, with typically few adverse effects. However, matching the AED to the patient is critical to achieving optimal outcome for all patients. Presented hereinafter in flow diagram format is a suggested decision tree that summarizes the data presented here. It may be helpful to clinicians when prescribing, screening, and monitoring the patient on VPA (see Fig 2).

Early recognition and intervention of ADRs while on VPA therapy may lead to decreased length of stay in acute care. Further targeted assessment could reduce the incidence of drug-induced hepatic, pancreatic, hyperammonemic encephalopathy, or fetal malformation. Data pertinent to ADRs should be recorded within the EMR so that future team members can avoid stimulating the same response. Identified genetic presentations should be referred for genetic testing, allowing for an individualized medication plan. Future studies should incorporate past evidence, creating new insights to guide practitioners to optimal drug choices through targeted pharmacogenomics.

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