# Valproic Acid: Review

*Ácido Valpróico: revisão*

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## SUMMARY

Clinical pharmacologists, neurologists, and all health care givers must consider the efficacy, safety, and side effect profile of a given antiepileptic drug when determining which drug is best for a given patient.The purpose of this study was to investigate valproic acid with a detailed analysis of the different reports.


**Keywords. Anticonvulsants, Enzyme Inhibitors, GABA Agents.**

Citation. Fagundes SBR. Valproic Acid: review.


## RESUMO

Farmacologistas, neurologistas e todos os clínicos devem considerar a eficácia, segurança e efeitos colaterais das drogas antiepilépticas quando determina qual melhor droga a ser dada ao paciente. A proposta deste trabalho é investigar o ácido valpróico com análise detalhada de diferentes artigos.


**Unitermos. Anticonvulsivos, Inibidores Enzimáticos, Agentes GABAérgicos.**

Citação. Fagundes SBR. Ácido Valpróico: revisão.

**Trabalho realizado no Neuroinstituto Forel, Itapema, SC.**

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Recebido em: 10/05/05
Revisado em: 11/05/05 a 30/06/07
Aceito em: 02/07/07
Conflito de interesses: não

## BACKGROUND

The Valproic Acid (VA) is an endogenous fatty acid, and was synthesized by Burton (1882)[1] as an organic solvent. In 1963, Meunier et al, explored antiepileptic properties of new molecules and was surprised with this solvent's (VA) ability to protect experimental animals against seizures[2]. Its antiepileptic properties were recognized and in 1964, when Carraz et al[3] published the first clinical study which, moreover, was used in all of Europe. Its introduction for clinical use in the USA occurred in 1978, initially only to absence epilepsy and lately, in 1996, in partial seizures. In the beginning it was formulated in acid form, later as a salt (sodium or magnesium) and as an amid. After absorption, all of these different molecular structures are transformed into the valproate ion[4].

The difference in this formulation of VA is its solubility in water. VA is not sensitive to humidity, but sodium valproate is very hygroscopic and in the gastrointestinal tract is impossible for it to disintegrate in equal form, without constant fluctuations. For this reason, laboratories developed the sodium divalproate molecule (Figure 1, Tables 1 and 2)[4-6].

### Pharmacokinetic

In view of the diverse molecular and cellular events that underlie different seizure types, the combination of several neurochemical and neurophysiological mechanisms in a single drug molecule might explain the broad antiepileptic and other brain disease efficacy of VA[7]. Furthermore, by acting on diverse regional targets thought to be involved in the generation and propagation of seizures, VA may antagonize epileptic activity in several steps of its organization[7].

Its pharmacological effects involve increased gamma-aminobutyric acid (GABA)-ergic transmission, reduced release and/or effects of excitatory amino acids, blockade of voltage gated sodium channels and modulation of dopaminergic and serotoninergic transmission. These drug may regulate the expression of neuroprotective genes and protect against excitotoxicity. It is available in different dosage forms for parenteral and oral use. Sustained-release formulations are available that minimize fluctuations in serum drug concentrations during a dosing interval and can therefore be given once or twice daily. It is about 90% bound to plasma proteins, and the degree of binding decreases with increasing drug concentration within the clinically occurring range. It is extensively me tabolized by microsomal glucuronide conjugation, mitochondrial beta-oxidation and cytochrome P450-dependent omega, (omega–1) and (omega–2) oxidation[8].

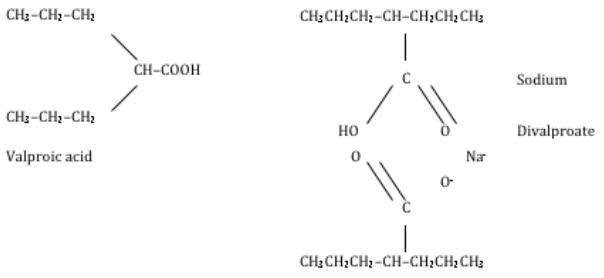


**Figure 1.** Valproic acid molecular structure[66].

VA, itself, is devoid of enzyme-inducing properties, but it has the potential of inhibiting drug metabolism and can increase plasma concentrations of certain coadministered drugs by this mechanism, including phenobarbital (phenobarbitona), lamotrigine and zidovudine[8-10].

It is rapidly absorbed in the gastrointestinal tract with a peak 1-4h after tablet ingestion,15-60min after oral solution and 3-7.5h after enteric tablets retard[4].

Elimination of the drug appears to follow a monophasic exponential course: biological half-life were 8 to15 hours, but shorter values (5 to 12 hours) are observed in patients medicated with enzyme-inducing agents. The drug appears to have a relatively restricted distribution: calculated relative distribution volumes ranged from 0.15 to 0.40/Kg. There were large individual differences in clearance rates. The therapeutic range was considered to be between 50 and 100 mg/l plasma. Determination of the plasma concentrations of drugs at accurately fixed times appears to be a reliable method for the pharmacotherapeutic monitoring of epileptic patients. The High Performance Liquid Chromatographic (HPLC) method was used, which determines diazepam as an internal standard (IS). The method is simple, rapid, accurate, and sensitive[8,11,12].

### Use

VA is a broad spectrum anti epilieptical drug (AED) being effective against all seizure types. In patients with newly diagnosed partial seizures (with or without secondary generalization) and/or primarily generalized tonic-clonic seizures, the efficacy of valproate is comparable to that of phenytoin, carbamazepine and phenobarbital. Valproate is generally regarded as a first-choice agent for most forms of symptomatic and idiopathic generalized epilepsies[8,13].

*Idiopathic generalized epilepsy* (IGE), sometimes in association with Lamotrigine[14].

*Generalized epilepsies* seem to be particularly vulnerable to seizure aggravation, and medications that are primarily effective against partial seizures are more commonly involved in seizure aggravation than other medications[15]. Broad-spectrum AEDs such as Valproate, Lamotrigine and Topiramate are extremely effective at controlling a variety of seizures without causing excessive seizure aggravation[14,15]. Sodium Valproate 400 mg-1800 mg daily is an useful addition to anti-convulsant therapy with beneficial effects in the majority of patients with grand mal, petit mal; myoclonus, and akinetic attacks. Temporal lobe epilepsy and other focal cortical seizures responded less well. The transition period, while other anticonvulsants were being withdrawn, was 7–10 days, when it becomes fully active,other anticonvulsants should be withdrawn only after the patient is established on a maintenance dosage[15,16].

*Lennox Gastaut Syndrome* (LGS), which appears in children aged between 2 and 8 years old, is characterized by a triad of epileptic seizures with different patterns, variable degrees of mental retardation, an electroencephalogram (EEG) with slow spike wave complex at 1.54 Hz and bursts of rapid centrotemporal activity, with a variable response in the control of the epileptic seizures[17].

*Landau-Kleffner Syndrome* is a rare, functional, age-related epilepsy with aphasia and epileptiform discharges on EEG.The aphasia responds poorly to most drugs. Valproic acid and benzodiazepines are most effective[18].

*West Syndrome*, some reports have indicated the possible efficacy of VA in regular large (40-100 mg/Kg/day) and very high (100–300 mg/Kg/day) doses[19].

*Neuropathy*. In the management of painful diabetic neuropathy[20].

*Peripheral nerve injury*. The potential clinical application for the treatment of peripheral nerve injury in humans[21].

*Anti-cancer*. It is associated with anti-cancer activity. VA not only suppresses tumor growth and metastasis, but also induces tumor differentiation in vitro and in vivo.VA increases the DNA binding of activating protein-1 (AP-1) transcription factor, and the expression of genes regulated by the extracellular–regulated kinase (ERK) AP-1 pathway; VA downregulates protein kinase C (PKC)activity; inhibits glycogen synthase kinase–3 beta (GSK-3 beta); VA activates the peroxisome proliferator-activated receptors (PPAR) gamma and delta; VA blocks HDAC (histone deacetylase) causing hyperacetylation.VA might also be useful as low toxicity agent given over long time periods for chemoprevention and/or for control of residual minimal disease[22-26].

**Table 1.** General characteristics of formulations of VA[5].

| | Valproic Acid | Sodium Valproate | Sodium Divalproate |
|---|---|---|---|
| Natural form | liquid | Power | power |
| Molecular weight | 144.16 | 166.21 | 155.18 |
| Solubility | high | Hygroscopic | not hygroscopic |

*Mood-stabilizing properties*. It has been reported to preferentially increase dopamine (DA) release in rat medial prefrontal cortex (MPFC), an effect partially or fully inhibited by WAY 100635, a selective 5-HT (1 A) antagonist. Ichikawa et al[9], suggest that the result indicate that not all mood-stabilizing agents, but only those which have anticonvulsant mood-stabilizing properties, increase DA release in the cortex and that the effect is dependent upon 5-HT(1A) receptor stimulation. Cheng et al[27] report that VA directly inhibits recombinant prolyl oligopeptidase (PO) activity, which would have the opposite effect on phosphoinositide (PIns) signaling inhibition of PO activity is reported to enhance PIns signaling consistent with the suggestion that mood stabilizers inhibit Pins signaling.This unexpected result suggests a model that could explain the dual action of VA in mood stabilizing: euthymic mood is dependent on stable PIns signaling and VA may limit mood swings to mania by decreasing PIns signaling, additionally, it may limit mood swings to depression by inhibiting PO and thus increasing PIns signaling[9,25,27].

*Alzheimer*. For symptomatic treatment of agitation in Alzheimer's disease[28].

*Migraine*. Intravenous valproic acid is one option for emergency treatment of migraine and prophylaxis[29,30].

*Panic attacks*. In patients with panic attacks not responding to antidepressants[31].

*Toxoplasma*. It inhibited the *Toxoplasma gondii* at a concentration below that found in the cerebrospinal fluid and blood of individuals being treated with this medication and displayed synergistic activity with haloperidol and with trimethoprim, an antibiotic commonly used to treat toxoplasma infections[32].

*Dyskinesia*. It has potential as an effective pharmacological tool in the treatment of tardive dyskinesia[33].

*Idiopathic olfactory hallucination*. The symptoms of some cases of Idiopathic olfactory hallucination may be controlled by sodium valproate[34].

**Table 2.** Availability of VA in Brazil[4].

| Generic name | Proprietary | Availability |
|---|---|---|
| Valproic acid | Depakene®, Epilenil® | Suspension 250 mg/5 ml<br>Capsules 250 mg<br>Tabs 300 and 500 mg |
| Sodium Valproate | Valpakine®<br><br>Valprene® | Caps 200, 500 mg<br>Suspension 200 mg/ml, 57.6 mg/ml<br>Caps 300 and 500 mg<br>Suspension 250 mg/5 ml, 288/5 ml |
| Divalproate | Depakote®<br>Depakote sprinkle® | Caps 250 and 500 mg<br>Caps 125 mg |

Caps = capsules; Tabs = tabletes.

*Infection*. VA is microbicidal against *Mycobacterium smegmatis* and *Staphylococcus aureus*. The mode of action may include the blockage of calcium channels and perturbation of membrane potential[35].

*Sydenham chorea*. Is a manifestation of rheumatic fever and occurs after a throat infection by group A streptococci. The disease is characteristic and consist of a combination of choreic movements, hypotonia and emotional lability. The clinical course is diverse.VA was prescribed of the chorea[36].

## Adverse Reaction

The most common side effects of ingestion or therapy are transient nausea, vomiting, abdominal cramps, and diarrhea. However, more serious adverse reactions can occur such as hepatotoxicity and pancreatitis. It has been proposed that, whenever possible VA not be used in younger children, children with a severe seizure disorder or other neurological disorders, mental retardation, developmental delay, organic brain disease,congenital abnormalities, or children who are taking multiple AEDs, as these factors may increase the likelihood of hepatotoxicity and/or pancreatitis[8,37,38].

In recent years, there has been a growing awareness of the potential aggravation of seizures disorders by AEDs. The aggravation of seizures occurred in a specific clinical context known to be linked to seizure aggravation, such as overdose, encephalopathy hepatopathy or metabolic disorders. However, no consistent evidence of pure pharmacodynamic aggravation in the absence of any the above quoted factors has been proven. VA appears to have a very low potential for pharmacodynamic paradoxical seizure aggravation[39].

Poor seizure control may result from the combinations of VA with methotrexate[26].

Episodes of non-convulsive status epilepticus presented as an acute confusional state with mild myoclonus due to a withdrawal effect of VA[40].

VA might favor proliferation of estrogen-dependent human tumors. VA, at concentrations of clinical interest, significantly enhanced the proliferative activity exerted by 17-beta-estradiol in the endometrial adenocarcinoma Ishikawa cell line. Similar effects of VA on cell proliferation were also observed in an ER alpha-positive Breast cancer cell line (MCF-7)[41].

This medication potentially produces iatrogenic parkinsonism[42].

The VA induces subclinical changes in both the intrinsic and extrinsic coagulation system. However, fatal bleeding is very rare. Induced neutropenia[43,44].

Teratogen-induced limb defects-effects on limb morphogenesis. The effects are mediated specifically by inhibition of Histone deacetylases[24,45,46].

Anomalies in neural tube, cardiovascular, craniofacial and skeletal. The nature of the abnormalities observed implies that this effect may be mediated by disruption of the genes that regulate pattern formation[8,45-47].

Infants of epileptic women treated with VA during pregnancy have a higher risk of developing spina bifida than those of the general population.VA induces exencephaly in experimental animal embryos.VAconsiderably reduced maternal plasma folate and B12 concentration. The plasma levels of FA and B12 have to be kept substantially elevated and maintained high throughout organogenesis period to protect embryos against VA-induced NTD[45-49].

Fetal Valproate Syndrome (FVS) is characterized by distinctive facial appearance, major and minor malformations, and developmental delay. This strongly suggests hereditary susceptibility to valproic acid induced adverse outcome. The risk for recurrence in a subsequent pregnancy may be high and should be taken into account in the conseling of pacient and in considering drug treatment[50].

Reversible neurotoxic symptoms[51].

Fanconi Syndrome has rarely been reported[52].

The association of dementia with valproate therapy is rare. The possible role of drugs should always be considered in patients with cognitive decline[53].

Anticonvulsant-induced Pseudolymphoma Syndrome (PLS) is relatively rare but can lead to death if there are extensive skin lesions, severe hepatitis, agranulocytosis, and neutropenia. PLS may also give rise to harmful effects if misdiagnosed as malignant lymphoma and patients with PLS are treated unnecessarily with chemotherapy, because it may mimic histologically other lymphomas, including mycosis fungoides (MF). PLS may show histopathological findings similar to MF and take a prolonged course even after the cessation of causative agents. Thus, a clear understanding and diagnosis of this disease is considered to have an important effect on treatment and prognosis[54].

Body weight gain, liver toxicity with an overall incidence of 1 in 20,000, but a frequency as high as 1 in 600 or 1 in 800 in high-risk groups such as infants below 2 years of age receiving anticonvulsant polytherapy[8,38,55,56].

VA may be associated with menstrual abnormalities and increased total testosterone levels in both bipolar and epileptic patients although women with BD did not show clinical features of hyperandrogenism: menstrual abnormalities, hirsutism, and truncal obesity as frequently as women with epilepsy[8,57].

Overrepresentation of polycystic ovary syndrome (PCOS) in woman with epilepsy has been described since the early 1980s. While some authors attribute this association to an effect of the seizure disorder on the hypothalamic control of reproductive function, others have reported a relationship with the use of the VA. On the whole these studies suggest that woman with epilepsy are at risk of developing reproductive endocrine disorders, even if there is not yet definitive evidence that PCOS may be over represented in these patients, nor that VA may be the cause of endocrine problems. It is likely that both the epileptic disorder and the antiepileptic treatment play different roles in the development of such disturbances. In the meantime women with epilepsy should be carefully monitored with regard to menstrual function, body-weight and hyperandrogenism, and evaluation of these parameters should became part of the routine evaluation in baseline and follow-up consultations[58].

VA-induced hyperammonemic encephalopathy (VHE). The pathogenesis is unclear, but it has been suggested that hyperammonemia can produce encephalopathy via the inhibition of glutamate uptake by astrocytes which may lead to potential neuronal injury and perhaps cerebral edema. Glutamine production is increased, whereas its release is inhibited in astrocytes exposed to ammonia. The elevated glutamine increases intracellular osmolarity promoting an influx of water with resultant astrocytic swelling. This swelling could compromise astrocyte energy metabolism and result in edema with increased intracranial pressure. Moreover, VHE seems to occur more frequently in patients with carnitine deficiency or with congenital urea cycle enzymatic defects[59].

Across a range of assumptions used,the risk of hospitalization for Stevens-Johnson Syndrome or toxic epidermal necrolylis in new users is low for VA[60].

Anticonvulsant hypersensitivity syndrome, characterized by fever, rash, and internal organ involvement is a rare but potentially fatal adverse event in several hypothesis, these include accumulation of toxic metabolites, graft versus host disease, antibody production and viral infections[61,62].

### Contraindications

Patients with succinic semialdehyde dehydrogenase deficiency[63].

Severely handicapped children may be at risk for sodium valproate-induced renal involvement[52].

Clinicians might avoid VA given some conflicting reports regarding its potential for increasing viral replication in seropositive patients[64].

This drug should be omitted in the treatment of seizures in patients with possible medium chain Acyl-CoA dehydrogenase deficiency, because it alters the neural membrane in these patients[65,66].

## CONCLUSIONS

VA is one broad-spectrum antiepileptic drug and has the longest clinical experience history and the largest body of published data. Its pharmacological effects involve a variety of mechanisms.

It is also an effective drug in migraine prophylaxis, in treatment of bipolar disorders and other uses. But its use is limited by two rare but potentially life-threatening side effects, teratogenicity and hepatotoxicity, and it is the least potent of the established AEDs. Thus, a clear understanding of its pharmacokinetics, uses and adverse reactions is considered to have an important effect on treatment and prognosis.

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