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Valproic Acid: A Summary of Indian Epilepsy Society-Consensus Document

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Introduction

Valproic acid (VPA) is a well established anticonvulsant drug for the last 40 years and is now a part of more than 130 national health care programmes. Since 1988, it has regularly featured as an anticonvulsant in the WHO Model List of Essential Medicines [1]. The current NICE Guidelines recommend Valproic Acid as the first-line of treatment for Idiopathic Generalized Epilepsies (IGEs) in children, young people and adults but should be used with caution in pregnant women. [2]

Mechanism of Action

- VPA stimulates glutamic acid dehydrogenase, the enzyme primarily involve in GABA synthesis, and increases GABA concentrations within the brain. Thus, reducing excessive neuronal firing. *[3]*, [4]
- VPA attenuates NMDA receptor mediated excitation and inhibits sodium and calcium channel function which reduces glutamatergic transmission with increased brain levels of GABA
- VPA produces weak inhibition of voltage-gated sodium channels, leading to prolongation of refractory period of high frequency neuronal firing thus limiting the frequency of neuronal depolarization. [5] The blockade of T-type calcium channels is also said to contribute to its anticonvulsant effects.
- VPA at lower concentrations is shown to diminish high frequency repetitive firing of action potentials of central neurons critically involved in its activity in generalized tonic-clonic seizures. *[6]*
- Putative mechanisms involved in early and late anticonvulsant effects *[7]* come from the quick accesses to extracellular sites e.g. ion channels and slow access to intracellular sites e.g. GABA synthesis following acute administration of VPA.

Pharmacokinetics

- VPA is almost completely absorbed with enteric-coated formulations are slowly absorbed - reaching peak levels 3 to 5 hours after intake.
- The therapeutic blood concentrations of VPA are 50-100 g/ml with a half-life of 6-15 hours.
- Being highly lipophilic, it concentrates in the liver and cross the blood brain barrier to give high concentrations in the brain.
- VPA is extensively metabolized through oxidative and conjugation mechanisms. The metabolites are biologically inactive.
- Its half-life in various age groups is different – neonates (in first week of life): 40-45 hours; neonates <10 days: 10-67 hours; infants and children > 2months: 7-13 hours; children and adolescents 2-14 years: 9 hours; and adults: 9-16 hours.

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Table 1
Guidelines for use of Valproic acid in epilepsy.

Type of seizure	ILAE (013) recommendations	NICE recommendations
GTCS	VPA is possibly efficacious as monotherapy	VPA as first line treatment
Absence seizures	VPA and ETM are efficacious as monotherapy as initial monotherapy for children with newly diagnosed or untreated absence seizures	VPA as the first line treatment
Benign childhood epilepsy with centretemporal spikes	VPA and CBZ are efficacious as monotherapy.	VPA as the first line treatment along with CBZ, LTG, OXC, LEV
Juvenile Mycoclonic Epilepsy	VPA and TPM are potentially efficacious/effective for patients with newly diagnosed JME	VPA as the first line treatment along with LTG, LEV, TPM
Partial Seizures	VPA is possibly efficacious/effective as initial monotherapy for children with newly diagnosed or untreated partial onset seizures.	• Offer CBZ or LTG as first line treatment • VPA can be offered as adjunctive treatment
Myoclonic	Not mentioned separately	VPA as the first line drug
Atonic seizures	Not mentioned separately	VPA as the first line drug
Other seizures/epileptic encephalopathies where VPA has been found to be effective: 1. West Syndrome 2. Dravet Syndrome 3. Benign myoclonic epilepsy of infancy 4. Lennox-Gastaut syndrome 5. Myoclonic astatic epilepsy 6. Continuous spike and wave during sleep 7. Landau Klefner syndrome		

Table 2
Interaction of VPA with other commonly used drugs.

Drugs that may decrease Valproic acid levels	Carbapenems, Ethosuximide, Mefloquine, Protease inhibitors, Rifampicin
Drugs that may increase Valproic acid levels	Chlorpromazine, Felbamate, Salicylates, Topiramate
Drugs whose levels may increase with Valproic acid intake	Barbiturates, Carbamazepine, Lamotrigine, Lorazepam, Risperidone, Rufinamide, Zidovudine
Drugs whose levels may decrease with Valproic acid intake	Phenytoin/Fosphenytoin, Olanazipine Oxcarbazepine

Valproic Acid in Idiopathic Generalized Epilepsy (IGE)

- As per AAN Guidelines, VPA is effective in the treatment of Absence seizures, primary generalized-onset tonic-clonic seizures especially Juvenile Myoclonic Epilepsy.
- VPA considered as the drug of choice in patients with IGEs, especially when given as the sole anti-epileptic drug. [8,9]
- While the other AEDs like carbamazepine, Oxcarbazepine, Lamotrigine and phenytoin may aggravate seizures in certain cases, VPA has very low risk of seizure aggravation.
- VPA is found to be more effective than Lamotrigine and better tolerated than Topiramate in generalized or unclassified epilepsy. [10]
- It is believed that if the daily dose of VPA does not exceed 40 mg/kg or 2.5 g, then it is singularly free from serious side effects. [11]
- It can also be recommended as first-line monotherapy in IGEs with multiple seizure types. [12]
- It can also be prescribed as an initial conservative treatment option in newly diagnosed patients in whom the nature of epilepsy syndrome is still undetermined. [13]
- However, it should be avoided in women of childbearing age due to its safety profile with concerns of teratogenesis and weight gain.

Valproic Acid in Absence Seizures

- VPA monotherapy was found to be effective in controlling absence seizures and should be given adequate trial before adding or switching to another AED. [14]
  Combination therapy with ESM and VPA should be considered for patients whose absence seizures do not respond to standard therapeutic measures. [15]
- Its combination with a low dose Lamotrigine appears to have synergistic effect in typical absence seizures. [16]
- The patients with primary generalized epilepsy responds better than those with diffuse cerebral damage or generalized epilepsy with focalization. Therefore, VPA is the drug of choice for the prevention of ASE recurrence. [17]

Valproic Acid in Generalized Tonic-Clonic Seizures (GTCS)

- A study shows non-statistical trend towards a better response with VPA compared with CBZ. [18]
- VPA monotherapy is very effective for both seizure outcome control and photosensitivity reduction in adolescents with epilepsy with generalized tonic-clonic seizures only. [19]

Valproic acid in Juvenile Myoclonic Epilepsy (JME)

- VPA is among the most efficacious drug in JME but may be poorly tolerated by some.

Table 3
Effects of Valproic Acid on other antiepileptic drugs.

Anti-epileptic drug	Effect on its level on co-administration with VPA
Lamotrigine	Lamotrigine levels increase by 85%
Topiramate	Topiramate levels stay unchanged
Felbamate	Felbamate levels increase by 27%