Indian Epilepsy Society

Valproic Acid: Indian Consensus Document

Editor-in-Chief

Man Mohan Mehndiratta

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Core Committee and Contributors

Man Mohan Mehndiratta – Convener
Director; Professor & Head,
Department of Neurology,
Janakpuri Super Speciality Hospital,
New Delhi

Sanjeev V. Thomas – Convener
Professor of Neurology and
Head of R. Madhavan Nayar Centre for
Comprehensive Epilepsy Care,
Department of Neurology, Sree Chitra Tirunal
Institute for Medical Sciences and Technology,
Thiruvananthapuram

Neeraj N. Baheti
Consultant Neurologist and Epileptologist,
Central India Institute of Medical Sciences,
Nagpur 440010, Maharashtra

Atma Ram Bansal
Neurologist and Epileptologist,
Medanta—The Medicity Gurgaon,
Haryana

Sanjeev Bhoi
Assistant Professor, Department of Neurology
Sanjay Gandhi Post Graduate medical Sciences,
Lucknow

Deepanshu Dubey
Senior Resident, Department of Neurology
Sanjay Gandhi Post Graduate medical Sciences,
Lucknow

Sheffali Gulati
Professor of Pediatrics,
Chief of Child Neurology Division,
Department of Pediatrics,
All India Institute of Medical Sciences,
New Delhi

Satish Jain
Director, Indian Epilepsy Centre, New Delhi

Sita Jayalakshmi
Senior Consultant Neurologist,
Krishna Institute of Medical Sciences,
Secunderabad, Telangana

Jayantee Kalita
Professor, Department of Neurology
Sanjay Gandhi Post Graduate medical Sciences,
Lucknow

Parampreet S. Kharbanda
Additional Professor Neurology & In-charge
Comprehensive Epilepsy Program,
Department of Neurology,
Postgraduate Institute of Medical Education &
Research (PGIMER), Chandigarh

Chanda Kulkarni
Advisor – Department of Clinical Pharmacology,
SAKRA World Hospital; Bangalore, India

Bindu Menon
Senior Consultant Neurologist,
Apollo Speciality Hospitals, Nellore

Usha Kant Misra
Professor & Head, Department of Neurology,
Sanjay Gandhi Post Graduate Institute of
Medical Sciences,
Raebareli Road, Lucknow

P. Satishchandra
Director/Vice Chancellor and Senior Professor of
Neurology, National Institute of Mental Health &
Neuro Sciences (NIMHANS),
Bengaluru, Karnataka

Vinod S. Saxena
Life Trustee Indian Epilepsy Association –
18th International Epilepsy Congress Trust, Delhi

Suvasini Sharma
Assistant Professor,
Department of Pediatrics,
Lady Hardinge Medical College and
Associated Kalawati Saran Children's Hospital,
New Delhi

Gagandeep Singh
Professor & Head,
Department of Neurology,
Dayanand Medical College, Ludhiana

Sanjib Sinha
Professor of Neurology,
NIMHANS, Banglore

Manjari Tripathi
Professor, Department of Neurology,
Neurosciences Centre,
All India Institute of Medical Sciences, New Delhi

Sudhindra Vooturi
Department of Neurology, Krishna Institute of
Medical Sciences, Minister Road,
Secunderabad - 03, Telangana,
India

Nandan Yardi
Consultant Epileptologist & Pediatric Neurologist
Associate Professor,Pediatrics ,
BJ MEDICAL COLLEGE(MUHS)
Yardi Epilepsy & sleep clinic, Kothrud, Pune
KEM hospital, Jehangir Hospital, Deenanath
Mangeshkar Hospital Pune
Member, Task force on pediatric
Epilepsy Surgery (2004-)
Member, ILAE Treatment Strategies Commission
(2004-2009)

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CONTENT

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OPERATIONS

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EDITORIAL OFFICE

Elsevier, a division of Reed Elsevier India Private Limited
14th Floor, Building No. 10B, DLF Cyber City, Phase-II,
Gurgaon, Haryana – 122002, India.
Telephone: + 91-124-4774444
Fax: + 91-124-4774100

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Statement of Need and Introduction

Man Mohan Mehndiratta

Neurology, as a branch of medicine, is a superspecialty that requires knowledge of a wide range of clinical presentations. Because of the diversity of clinical conditions encountered and the modification of the presentation of these at various stages of growth and development, it takes longer to acquire the pattern recognition and to be able to recognize presentations of the common and rare conditions. Epilepsy is a common neurological disorder with 65 million People with Epilepsy (PWE) worldwide and approximately more than 12 million in India. Two-third of PWE live in resource-limited countries.

In this age, where at times there seems to be an overabundance of information, it is important for the practicing clinician to have an authoritative source of quality advice and genuine practice wisdom. Keeping in mind the requirements of the society, the practitioners need to update themselves on the current approaches and the wide variety of choices now available. India has a distinct need for comprehensive programs about the drugs and disease conditions that fit into the Indian context of the situation. It has to be a continuous process that aims at updating the clinicians on the current scenario and clear the apprehensions based on scientific evidence and approaches the problem on the basis of the experience of the specialists in India who are among the stalwarts in this field.

This document provides a useful basis from which to view new and existing perspectives in usage and position of Valproic Acid in the management of epilepsy, coupled with the more traditional protocols. It will be a valuable update tool and reference point for the many professionals engaged in the field of Neurology.

Historical Aspect of Valproic Acid

Vinod Saxena

Introduction

The description of epilepsy dates back to antiquity. Written texts have been found in Akkadian language in Mesopotamia in 2000 BC, in Sanskrit in Charaka Samhita in 600 BC, in the Greek classic *On the Sacred Disease* and in the Hippocratic collection of medical writings in 400 BC.[1] Shrouded as it has been in superstition, dogmatism, mysticism, or even star constellations, the treatments remained similarly obscurantist. Alchemy was some relief till modern chemistry brought in a series of specific anti-epileptic drugs (AEDs).

In such a scenario, one compound, valproic acid (VPA) stands out as singularly unique.

It came into therapy in 1960's, through an illustratively piquant expression: serendipity. By now, it occupies an exalted position in the Pantheon of AEDs. It remains the subject of perpetual research into its ever expanding clinical horizons. VPA is now a part of more than 130 national health care programmes. Since 1988, it has regularly featured as an anticovulsant in the WHO Model List of Essential Medicines.[2]

VPA is even considered for a 'marooned island drug list'. It will protect against seizures, could be useful for analgesia, preventing migraine and stabilizing the mood particularly if one becomes mentally unbalanced on the island. It might even help to prevent the development of cancer. A simple chemical yet, it has so much to offer.[3]

Treatment Before Valproic Acid (Sixteenth to Early Twentieth Century)

Valerian (*Valeriana officinalis*) root was used in 1592 by Fabio Colonna to cure his own epilepsy. It remained the best treatment for the next three centuries. Valerian yields isovaleric acid, which is analogous to valproic acid and hence could be considered as the first (AED).[4]

Bromides came next. The Royal Medical and Chirurgical Society of London met under the chairmanship of Sir Charles Locock then the obstetrician for Queen Victoria. He must have been very busy having delivered her nine children yet he presided over scientific meetings of consequence. In one such meeting on 11th May 1857, Dr. Edward Seiveking[5] reported positive outcome with potassium bromide in 52 women. Locock endorsed the idea for treating more cases as he cited the observations of another German physician who had seen similar benefit with valerian.

As a group of chemicals with medicinal use barbiturates had existed for four decades before, phenobarbitone was recommended in 1912[6] to sedate agitated patients suffering from epilepsy. Three decades later in 1938, phenytoin became the first AED supported with specific experimental proof. There were demonstrable EEG changes and positive results on a cat experimental model,[7] leading to an established clinical use of phenytoin ever since.

Then stepped in VPA to fulfil its greatest promise as an AED.

The discovery of VPA came out of 'serendipity' a word attributed to Horace Walpole for its coinage. Walpole was referring to a collection of short stories which were published in 1557 titled ***The Three Princes of Serendip***[8] (set in an island Serendip or Swarandeep in Sanskrit and present day Sri Lanka). The original Persian fairy tales were put together as *Hasht-Bihisht* by Amir Khusrau's (1253-1325, born in Etah, UP), who is more famous as a musicologist and who wrote his songs in a language combining Persian, Hindi and Awadhi.

Fig. 1: Horace Walpole (1717-1797)

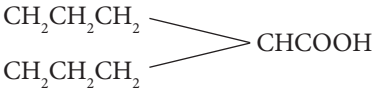
Walpole called these stories as "silly fairy tales" where the three princes by "accidents and sagacity" discern the nature and make

continuous discoveries in their travels. The example of serendipity: "they discovered that the mule that had recently covered the same road was blind in the right eye because the grass was more worn out on the left side."

Valproic Acid as a Chemical Entity

VPA as an analogue of valeric acid was first synthesised in 1881 in by an American chemist Beverly S. Burton.[9] It is a simple branched – chain carboxylic acid di-*n*-propylacetic acid or 2-propylpentanoic acid or 2-propylvaleric acid.

The molecular formula is $C_8H_{16}O_2$ and the molecular weight is 144.21 g/mol. It is water-insoluble (1.27 mg/mL), weakly acidic (pKa = 4.8) but the sodium salt is freely water soluble and very hygroscopic.



The year 1881 saw another co-incidence of paramount consequence as Sir William Gower[10] fully described epilepsy in the same year.

The First Evidence of VPA as an Anticonvulsant (1962-1963)

Khelline has been a valuable herbal source for diverse therapeutic areas (e.g. amiodarone and chromolyn). One, Mr. Pierre Eymard, a doctoral student in the University of Lyon, France had synthesised a number of compounds from khelline. While wanting to test these further, he found these to be water-insoluble. He sought advice from Laboratoire Berthier in Grenoble who recommended valproic acid as a lipophilic vehicle. To Eymard's surprise all the compounds synthesised showed activity in the anticonvulsant screen. Two pharmacologists who worked along, H. Meunier and Y Meunier suspected the solvent vehicle to be active. They checked VPA on the standard anticonvulsant models. Pentylenetetrazole seizure (PTZ) test was applied to experimental groups of four rabbits each who were given the recommended anticonvulsant protective dose of PTZ 30 mg/kg intravenously. Forty minutes later, varying doses of VPA were administered intraperitoneally. Their contention was indeed proved correct as dose levels of 250 and 420 mg/kg proved to be anticonvulsant in all animals while lower doses were only partially effective.

These positive results were first presented at the French Society of Therapeutics and Pharmacodynamics on December 19, 1962 and later published in 1963.[11]

Towards a Drug Candidate in Europe (1963-1973)

Mention of VPA includes valproic acid and its sodium, magnesium and calcium salts in various formulations.

Chemically VPA is one of the simplest drugs currently available in our therapeutic arsenal with eight carbons and no nitrogen atom or cyclic ring. It was been found that increase in carbon atoms from 8 to 9 enhanced the sedative activity. Straight chain acids had mild to no activity. Amide compound valpromide had greater liposolubility and helped cross the blood-brain barrier compound. It was also twice as potent in anticonvulsant activity.

Screening with PTZ led to tests on other models e.g. seizure induced by maximal electroshock (MES) and seizures induced by strychnine, bicuculline and picrotoxin in mice and audiogenic seizures in rats. All these test models also gave positive results.

The group of researchers was getting wider as Georg Carraz then contacted Sergio Berselli and Pierre Lambert in the Hôpital Psychiatrie, Bassens, France. Carraz got help from the School of Medicine and Pharmacy and from Berthier Laboratories both at Grenoble. The joint publication[12] aroused pharmaceutical interest. Later, Laboratoire Azidique (Azide Laboratory) took over the research and renamed itself Labaz having decided to develop VPA as an AED in Europe.

Consequently, more extensive work on pharmacology, pharmacokinetics, monitor of interactions with other drugs, biochemical and its possible adverse effects began along with chronic toxicity studies. The regulatory environment was becoming tighter in most countries following ban on thalidomide marketing in early to mid-1960 with increased controls on introduction of new drugs.[13] The developing company was required to

produce extensive basic scientific and clinical data with particular emphasis on safety. To commit to additional scientific, toxicity and clinical evidence in the renewed regulatory environment with possible legal responsibilities entailed huge financial risks.

Labaz seemed willing to take up this challenge with a remarkable foresight. The first few clinical trials to establish VPA and its role in various types of epilepsies, with valpromide then with a combination of VPA with phenobarbitone. Encouraged with positive clinical indicators they tested VPA alone. There was indeed reduction in the number of seizures with VPA and "…the patients felt themselves more; the mental stickiness, viscosity that had sometimes been the standard with the older agents, was less. We saw the disappearance of the tendency to depression, sometimes even a mild euphoria".[14]

So far the pharmacological work was mostly limited to rodent models using PTZ, MES etc. These were not adequate to elicit range of activities where VPA could be used e.g. in absence attacks where clinical evidence was very encouraging. So primates, which replicate human response more accurately, were used despite their high cost. Rhesus monkey was a good model for eliciting focal fits by alumina gel implant but it required animals to be maintained over several months and negative outcome wasted time and resource. Ciba-Geigy Research Centre, Bombay (Dr. RS Grewal and Dr. Joy David) despite their earlier success on rhesus monkey model for focal seizures and interictal EEG abnormalities[15]; they had novel primate models including one for absence attacks in rhesus monkey but those remained unpublished.

Meldrum[16] found baboon (Papio papio) to be a very useful photosensitivity model as seizures could be produced 'on order'. This model was even more expensive and the susceptible species was exclusive to certain part of Senegal. The prospect of faster response encouraged Labaz to explore this model further in this erstwhile French colony. This model closely resembled the human photoconvulsive seizure model and for instant response on EEG. Herein once again VPA was proved very effective.

So far most clinical trials with VPA were carried out as add-on to existing therapy using refractory cases The first placebo controlled double blind trials was published by Meinardi in 1971.[17] The drug was first launched in France in 1967 followed by Holland and Belgium in 1971, Switzerland, Finland, Denmark and Italy in 1972 and in Germany in 1973, for use in refractory cases or as add-on therapy.

Towards Drug Approval in the United Kingdom (1973-1977)

Labaz prepared itself for wider introduction of VPA after achieving good success in Europe. A joint venture called Reckitt-Labaz was found in the UK in 1973 with Reckitt & Colman UK as the latter operated in at least 60 Anglophone countries where Labaz did not have a direct reach. The new company Reckitt-Labaz was then headed by a physician Dr. Richard Smith (latterly Chief Editor British Medical Journal). He sponsored Dr. V.S. Saxena in 1973 to work with Prof. Paul Turner, St Bartholomew Hospital, London for pharmacokinetics of VPA and another CNS-active drug. Afterwards Dr. Saxena worked under Dr. Alan Richens, Cardiff and Dr. Harry Meinardi from the Instituut voor Epilepsiebestrijding, Meer-en-Bosch, Heemstede, Holland. Dr. Meinardi had the longest experience since 1965 with VPA in Europe in its kinetics, blood level estimation,[18] EEG correlation and clinical work and he invited Dr. Saxena for work on the kinetics of VPA.

In the UK, Dunlop Committee was replaced by the Committee on Safety of Medicines (CSM) as an independent advisory entity to the UK Licensing Authority on the quality, efficacy and safety of drugs. On their first review on VPA of data submitted by Reckitt-Labaz they insisted on further animal teratogenicity data. This was then carried out in comparison with phenobarbitone, phenytoin and carbamazepine in the Toxicology Laboratories of Reckitt and Colman, Hull.[19]

Clinical Trials

Prof. Peter Jeavons Aston University, Birmingham since 1964 was working on photoconvulsive model in children with or without absence attacks (then mostly called petit mal) collaborating with an ophthalmologist Prof. Graham Harding[20] at the same University. They were impressed with the very positive clinical response they got with VPA. Prof Jeavons then agreed to conduct the first clinical trial

Fig. 2: Leading early investigators (1973-75) for valproate who associated with Dr. V.S. Saxena

(1) Prof. Paul Turner, Head Clinical Pharmacology Dept., St. Bartholomew's Hospital, London. **(2)** Prof. Harry Meinardi, Instituut voor Epilepsiebestrijding, Heemstede, Holland with Dr. V.S. Saxena on his right. **(3)** Dr. F.E. Dreifuss, Comprehensive Epilepsy Centre, Univ. of Virginia, USA. **(4)** Dr. P. Jeavons on the right with Dr. V.S. Saxena in the middle at Aston Univ., Birmingham. **(5)** Dr. M.C. Maheshwari, Dudley Road Hospital, Birmingham. **(6)** Dr. A. Covanis, Aston Univ., Birmingham. **(7)** Dr. D. Chadwick, Liverpool, UK.

with VPA at the Dudley Road (now City) Hospital, Birmingham, where he was assisted by Dr. M.C. Maheshwari for adult patients and Dr. A Covanis for children.[21] Other clinical trials were initiated since 1973 with Dr. Edward Reynolds (London), Dr. Robert Elwes (London) and Dr. David Chadwick (Liverpool).

The data generated on pharmacodynamics, pharmacokinetics, toxicology and clinical trials carried out in the UK became part of the dossier submitted to the CSM. Based on this Reckitt-Labaz received Product License to market VPA as Epilim in the UK and Ireland in 1975.

Roll out in Other Markets (1975-1978)

Reckitt-Labaz did not have an adequate representation or infrastructure to file new drug application with FDA, USA. Meanwhile, Reckitt-Labaz was taken over by Sanofi who in 1975 sold their rights to Abbott for development of VPA in the American markets.

There was urgent requirement to carry out more trials to introduce the drug. National Institutes of Health (NIH), USA had designed new parameters for controlled clinical trials with AEDs. The awareness of beneficial effects of VPA was coming into the US through press and television shows. Some patients started getting VPA from Mexico or travelling to Ireland, UK or Europe for treament. Many neurologists tried to reason and persuade for its early introduction. Prof. FE Dreyfuss had just then established a Comprehensive Epilepsy Centre in Charlottesville, Virginia with the aid of

NIH. He established radiotelemetry for the first time and he obtained excellent results in absence seizures with VPA. He tried impressing upon FDA, for its introduction. One complicating information came out in early 1978 as four out of five fatalities resulting from hepatitis with VPA.[22] Prof. Dreiffuss as President of the American Epilepsy Society in 1978, and as Chairman of the Professional Advisor Board of the Epilepsy Foundation of America at the same time put up the correct scientific perspective of mitochondrial disorders in those cases. VPA was finally approved in the USA in mid-1978 and marketed by Abbott as Depakene.

South Asia, South East Asia and Pacific Rim countries (1977-1985)

When Reckitt-Labaz was taken over by Sanofi, Dr. Saxena was assigned to the associate company, Reckitt & Colman India in 1977, to review the regulatory situation and progress to introduction of VPA in South Asia and Southeast Asian countries, Japan, Australia and New Zealand.

Japan curiously got stuck on rat spermatogenesis data which they wanted to be repeated locally. Australia and New Zealand needed local clinical trials. All these requirements were complied with based on the data submitted in the UK and some additional local trial data which led to marketing of VPA by1978/79.

In Singapore, Thailand, Malaysia, Hong Kong and Philippines the regulatory authorities were willing to work on the basis of the dossiers submitted to the CSM in the UK as long as the product was sourced from the manufacturers in the UK. These countries needed minor labelling changes and use of local language in addition in Thailand. South Korea and Taiwan registered the drug in 1979 for import with data with labelling in local languages and English. China at that point in history was a closed market.

Pakistan and Sri Lanka had freedom of import after registration so VPA/Epilim was introduced in 1981 in these markets. In Indonesia, the local regulatory body had an expert who was also a member in the essential drugs group of WHO. Hence they were eagerly watching the progress on the Essential Medicines List. However, by 1985 Indonesia approved VPA for the local market.

The political environment during 1970's to 1980's in India and Bangladesh favoured local industries rather than multinational companies (MNCs). Foreign companies faced stringent conditions on manufacture, marketing, pricing, profits etc. Imports were virtually impossible except by individual patients who needed foreign exchange to pay more than 120% import duty.

By then the drug laws were amended in India as it was decided that the first sponsoring company must conduct local clinical trials. The trials with VPA were then started in 1978 in six major centres. These were completed by 1980 and published.[23] The new drug laws also required obtaining industrial licensing for local manufacture as import was not permitted. These functions were outside Dr. Saxena's area of responsibility. Yet pressure was faced from the neurologists and needy patients. The advantages of continued treatment were obvious just as denial had increased seizures in some patients. Knocking on many official doors and sharing actual patient master charts seemed to melt bureaucratic hearts. Finally, in November 1981, VPA/Epilex was approved for marketing and manufacture in India. VPA/Epilex was launched in India in February 1982.

Conclusion

On the basis of usage VPA perhaps remains the Number One AED the world over. Yet the molecule could be modified to a more effective, neuroprotective and site-specific targeted drug. Patients are still looking for better tolerance and safety during pregnancy. The continuous development of VPA may hold encouragement for future and it will be a while before the last word is written about the history of valproic acid.

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Clinical Pharmacology of Valproic Acid

Chanda Kulkarni

Introduction

Valproic acid [VPA] is regarded as a first generation anti-epileptic drug with its derivatives as second generation or follow up compounds [valrocemide and valnoctamide]. The reasons for design and development of this new group is **a**] to enhance brain penetration **b**] to eliminate toxic metabolites **c**] to avoid teratogenicity seen with parent compound.[1,2]

Chemistry

Valproic acid (VPA) is chemically an achiral, unique, simplest branched short chain fatty acid molecule derived from naturally occurring valeric acid and is devoid of a nitrogen atom or a cyclic ring. A weak acid insoluble in water but its sodium salt is freely water soluble. VPA is well established as an anticonvulsant for the last 40 years and subsequently approved by FDA and EMA for the treatment of migraine and bipolar disorder. VPA is a simple isooctanoic acid. Many of the derivatives have been synthesized as CNS active follow up compounds which are currently under investigation for non-neurological disorders and appear to have a huge therapeutic potential.[2,3]

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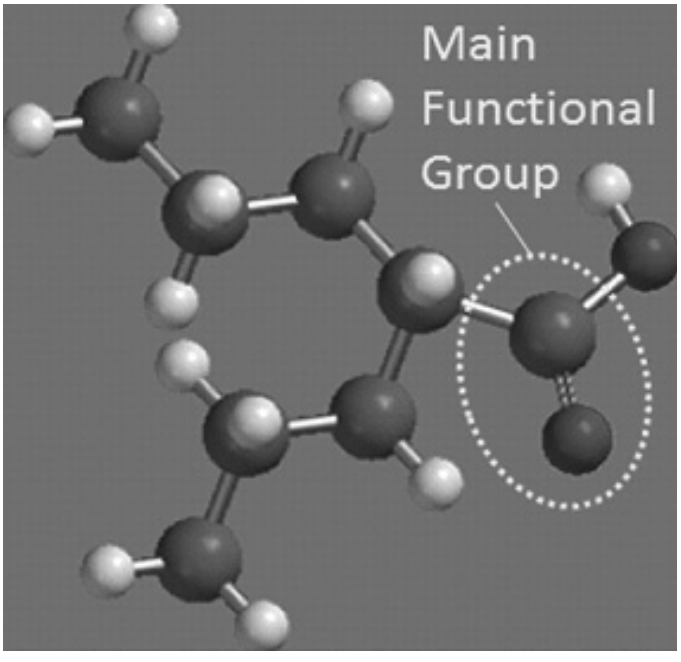

Fig. 1: Valproic acid structure (2 propyl-pentanoic acid), a unique simple small monocarboxylic acid (fatty acid), was discovered accidentally when being used as a solvent in previous antiepileptic drug (AED) testing. It is postulated that the main functional group responsible for the antiepileptic activity is the C=O (circled). This region provides the initial electrostatic interaction between VPA and the target protein causing reversible inhibition (Comelli *et al.*, 2012)[4].

Clinically Relevant Drug-Drug Interactions of VPA

Table 1: Influence of Co-administered Drugs on VPA

Drug Group	Interaction	Comments
1. Influence of co-administered antiepileptic drugs on VPA		
Phenobarbital /Primidone	Double the VPA clearance	Monitor the levels of VPA and concomitantly used drugs whenever enzyme inducing drugs are introduced or withdrawn
Phenytoin		
Carbamazepine	May decrease plasma VPA levels. Discontinuation of carbamazepine may increase levels of VPA	Close monitoring of VPA concentration whenever carbamazepine is initiated or discontinued
Clonazepam	May precipitate absence status in patients with a history of absence type seizures.	Use the combination with caution
Felbamate	May increase mean peak plasma levels of VPA	Decrease in dosage of VPA
2. Influence of chemotherapeutic agents on VPA		
Carbapenems - ertapenem, imipenem, meropenem	May reduce concentration of VPA leading to loss of seizure control	Avoid concomitant use, or monitor VPA levels, or consider alternative anti-infective
Acyclovir	May decrease levels of VPA, an increase in seizure frequency and worsening in EEG	Use concomitantly with caution
3. Influence of other drugs on VPA		
Aspirin	VPA free fraction increased by four-fold due to decreased protein binding and inhibition of its metabolism	Caution to be observed during concomitant use
Rifampin	May increase VPA clearance	VPA dosage adjustment
Alcohol	Additive effects with VPA	Caution when used concomitantly
Chlorpromazine	May increase trough levels of VPA	Avoid concomitant use

Extracted from – Reference

http://www.drugs.com/ ›*Professionals* › *FDA PI* Valproate – FDA prescribing information, side effects and uses Drug Interactions

Table 2: Influence of VPA on Co-administered Drugs

Drug Group	Interaction	Comments
1. Influence of VPA on antiepileptic drugs		
Phenytoin	VPA increases plasma free phenytoin concentration, displaces phenytoin from binding sites with increase in seizure frequency and phenytoin intoxication	Monitor plasma phenytoin concentrations when VPA is added or withdrawn
Clonazepam	Possible but not common	Precipitates absence status in patients with absence seizures. Caution to avoid administration
Diazepam, Phenobarbital/ Primidone or CNS depressants	VPA increases free fraction of diazepam by displacing from binding sites and inhibits metabolism of phenobarbital	Excessive somnolence/ depressant effect. Monitor patients closely for neurotoxicity
Lamotrigine	VPA inhibits metabolism of lamotrigine and increases elimination half-life.	Possibility of increased risk of rash, [SJS, TEN]. Reduce dose of lamotrigine and use slower lamotrigine titration rate
Topiramate	Concurrent administration VPA leads to hyperammonemia with/without encephalopathy	Measure blood ammonia, discontinue VPA if symptoms appear
2. Influence of VPA on psychotropic agents		
Amitriptyline/ Nortriptyline	VPA reduces clearance and increased levels of amitriptyline/nortriptyline	Consider close monitoring and dosage reduction of amitriptyline
Monoamine oxidase [MAO] inhibitors	Potentiation of effects of MAO inhibitors	Consider dosage reduction of MAO inhibitors
3. Influence of VPA on chemotherapeutic agents		
Zidovudine	VPA inhibits metabolism of zidovudine and its clearance, hence increases its bioavailability	Altered efficacy and toxicity of zidovudine. Close monitoring is recommended
4. Influence of VPA on other drugs		
Oral anti-coagulant [warfarin]	VPA may increase unbound fraction of warfarin	Monitor coagulation tests when used concomitantly

Extracted from – Reference
http://www.drugs.com/›*Professionals* › *FDA PI* Valproate – FDA prescribing information, side effects and uses Drug Interactions

Mechanisms of Actions of VPA

The identification of appropriate therapeutic strategies often depends on mechanisms underlying epileptogenesis. Evaluation of these is not only important for treatment of epilepsies, but also to help in developing new targets for treating seizures[1]. A variety of experimental animal models of seizure have demonstrated VPA as a broad spectrum anti-epileptic drug[2]. Extensive literature supports involvement of multiple mechanisms which explains its wide spectrum of anti-epileptic activity. The following paragraphs summarize neurochemical and neurophysiological mechanisms implicated primarily in anticonvulsant activity of VPA in animals as well as in humans. Lastly, a note on the basis for possible diverse therapeutic effects of VPA in other neurological and non-neurological disorders is included.

Mechanisms of Anti-epileptic Actions of VPA

Neurochemical effects on the γ-aminobutyric acid [GABA] system[3]

Enhancement of GABAergic transmission by VPA, an inhibitory neurotransmitter as a primary mechanism was postulated as early as 1968 and is supported and explained through its –

a. Inhibitory effect on GABA degradation
b. Enhancement of GABA synthesis and its release through stimulation of glutamic acid decarboxylase, the enzyme instrumental in GABA synthesis
c. An indirect effect on presynaptic GABA levels by potentiation of postsynaptic GABAergic function leading to feedback inhibition of GABA turnover leading to increases in nerve terminal GABA
d. Increase in GABA concentrations within the brain is also said to be via multiple enzyme systems such as – GABA transaminase, α-ketoglutarate dehydrogenase and succinic semialdehyde dehyrdrogenase, thus reducing excessive neuronal firing[4] and increase release of GABA, possibly through stimulation of glutamic acid dehydrogenase, the enzyme primarily involved in GABA synthesis.[5]

Glutamate antagonistic action

VPA induces its anticonvulsant effects both by direct and indirect mechanisms such as:

a. Attenuation of NMDA receptor mediated excitation
b. Inhibition of sodium and calcium channel function which reduces glutamatergic transmission with increased brain levels of GABA.
c. Most recently, animal experiments have provided robust evidence that supports involvement of PIP3 depletion with seizure activity that is attenuated by VPA producing reversal of these effects, thus providing a novel mechanism of action for VPA in epilepsy treatment.[1]
d. Other possible undefined mechanisms include reduction in excitatory neurotransmission, modulation of monoamines namely dopaminergic and serotonergic transmission.[6]

Effects on ion channels[3]

a. 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.[7]
b. The blockade of T-type calcium channels is also said to contribute to its anticonvulsant effects.

Neurophysiological effects on neuronal membranes[8]

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.

Neurochemical and neurophysiological effects of active metabolites[8]

Several pharmacologically active metabolites of VPA have been identified and explored for anticonvulsant activity following its rapid metabolism *in vivo*. One of the most active, potent and major metabolites identified is the trans isomer of 2-en-valproate [E-2-en-valproate]

Putative mechanisms involved in early and late anticonvulsant effects[8]

Carrier mediated active transport of VPA is proposed to be involved in both extracellular [e.g.

ion channel] and intracellular [e.g. GABA synthesis] sites of action. The quick accesses to extracellular sites following acute administration of VPA and slow access to intracellular sites is reported to explain its immediate and late anti-convulsant actions respectively in pre-clinical and clinical studies.

Summary of Newer Novel Mechanisms of Actions and Possible Indications for VPA in Other Neurological and Non-neurological Conditions

Non-epileptic and Neurological conditions

The use of VPA in the prophylaxis of migraine headaches is approved by US – Food and Drug Administration [FDA] and EME due to its ability to inhibition of glutamatergic hyperexcitability of cortex. However, there is only moderate evidence for efficacy of VPA in the treatment of neuropathic pain where it produces altered pain sensitivity for which it is being explored in - diabetic neuropathy, post-herpetic neuralgia and in trigeminal neuralgia[9, 10]. VPA is also under investigation for use in Alzheimer's disease.[11]

Non-neurological conditions

The blocking of sodium channels as a mechanism, appears to be implicated in a psychiatric condition namely — bipolar affective disorder.[12,13,14] The amplifying dopaminergic activty aggravates schizophrenia is proposed to improve the symptoms by potentiating GABA activity.[15] Further, conditions like cocaine craving, alcohol withdrawal[16] and impulsivity/aggression are hypothesized due to glutamate-induced synaptic plasticity. VPA by reducing glutamate transmission and increasing GABAergic 'lagging' of pathological firing is known to have beneficial effects.[16] The use of VPA in conditions such as fibromyalgia and extra-pyramidal dysfunction are being investigated.[17]

The mechanism of action of VPA such as histone deacetylase [HDAC] inhibition is said to offer opportunities for its use in cancer treatment.[18] Many Phase III studies are underway to evaluate its activity against breast, glioblastoma, endometrial and prostate cancer.[19,20,21]

The conditions like – asthma due to hyperactivity of central nervous system and to induce delay in aging related to degenerative changes are under investigation.[22]

Conclusions

The above literature appears to support VPA with multiple mechanisms of actions to have a huge potential for its utility in wide variety of therapeutic indications.

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PK – Parameters of VPA[1, 2]

ABSORPTION				DISTRIBUTION			ELIMINATION		
Bioavailability	**Peak concentration**	Food delays absorption of oral preparations **but not extent** of absorption	Therapeutic concentration range – 50-100 mcg/mL Toxic - > 150 mcg/mL **[Concentrations DO NOT correlate well with its therapeutic effects]**	Distributed Rapidly Detected in CSF and saliva	Protein binding is concentration dependent	Detected in CSF & saliva Crosses placenta & eliminated in milk	Metabolism in liver by beta & omega oxidation and glucuronidation Half-life 5-20 hrs	Mainly in urine as metabolites Small amounts in feces & expired air	Increased clearance in children 3 months to 10 yrs. Decreased clearance in neonates & geriatric population. Reduced clearance in hepatic and renal impairment.
Rapid & complete absorption oral Valproic acid from GI tract	1 – 4 hrs								
Oral divalproex sodium	3 – 5 hrs								
Oral divalproex sodium-Delayed Release[DR]	-								
Oral divalproex sodium-Extended Release [ER]	6 – 14 hrs								
Valproic acid IV injection	Similar to above	-							

NOTE - Divalproex Sodium Extended Release [ER]

- Dosing frequency of ER is – once a day compared to delayed release [DR].
- Twice a day ER dosing, increases steady state trough concentration to higher values making it efficacious and safer by reaching plateau levels.

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Preparations of VPA with storage instructions

Routes	Dosage Forms	Strengths	Storage
Oral	Solution	250 mg (of valproic acid) per 5 mL*	Tight containers at <30°C; avoid freezing
Parenteral	Injection, for IV use	100 mg (of valproic acid) per mL*	15–30°C. Discard unused portions of the solution
Oral	Capsules, delayed-release	125 mg	25°C; may be exposed to 15–30°C Tight containers at 15–25°C.
		250 mg	
		500 mg	
	Capsules, liquid-filled	250 mg*	
Oral	Capsules (containing coated particles)	equivalent to valproic acid 125 mg*	<25°C
	Tablets, delayed-release	equivalent to valproic acid 125 mg*	Tight, light-resistant containers at a temperature <30°C
		equivalent to valproic acid 250 mg*	
		equivalent to valproic acid 500 mg*	
	Tablets, extended-release	equivalent to valproic acid 250 mg*	25°C, but may be exposed to temperatures ranging from 15–30°C
		equivalent to valproic acid 500 mg*	

REF: Adapted from - http://www.drugs.com/monograph/valproate-sodium.html
*available from one or more manufacturer, distributor, and/or re-packager by generic (non-proprietary) name

Valproic Acid – Role in Idiopathic Generalized Epilepsy (IGEs)

Sanjib Sinha, P. Satishchandra

Introduction

VPA has been used extensively as an antiepileptic drug (AED) over the past four decades, and occupies an important place as a first-line therapy for many epilepsy syndromes in adults, notably Idiopathic Generalized Epilepsy (IGEs).[1,2] In spite of the lack of randomized, double-blind studies in JME , the efficacy of valproic acid monotherapy has been documented in many clinical series. Despite availability of newer AED like levetiracetam, the efficacy of VPA in JME is unparalleled. Valproic acid is of particular interest in IGEs as AEDs like carbamazepine, oxcarbazepine, lamotrigine and phenytoin may aggravate seizures in certain cases and thus these AEDs should only be used with caution in generalized epilepsies.

This position has been acquired because valproic acid has been recognized as a generally safe and effective therapy. A workshop was held in Goteborg in June 2005 in which epilepsy experts from around the world discussed the place of valproic acid in treating adult epilepsies, evaluating the epilepsy types for which the drug is most suitable and addressing issues in the use of valproic acid in women of child-bearing age, in men and in patients with psychiatric comorbidity. This issues discussed and the consensus positions of this meeting have been summarized in an article by Ben-Menachem *et al.*[3]

The objective is to develop consensus guidelines for the use of valproic acid (VPA) in IGEs. The objective was to provide useful and shared information for physicians, healthcare professionals, patients and their caregivers.

Data Sources

Data were retrieved from PubMed and Cochrane review; the terms used were: Idiopathic Generalized Epilepsy; Idiopathic Generalized Epilepsy and Valproic acid; treatment of Idiopathic Generalized Epilepsy, and, for MeSH terms in PubMed, Epilepsy, Generalized; Epilepsy, Idiopathic Generalized; Diagnosis and Therapeutics

Classification of Clinical Trial Evidence

Evidence of AED efficacy in the literature is divided into four classes::

- Class I evidence requires results from randomized controlled studies. They are of 2 types:-
  - Class IA: It is a meta-analysis of double blind, randomized controlled trials (RCTs).
  - Class IB: It is at least one RCT in a series.
- Class II evidence requires results from matched, controlled, but not randomized trials.
- Class III evidence comprises uncontrolled comparisons involving groups of patients and case studies.
- Class IV evidence comprises additional efficacy information, including expert opinions.

Treatment of IGE

So far, no AED has Class I or Class II evidence regarding efficacy or effectiveness in adults with IGEs.[4] Recently, four RCTs which examined initial monotherapy of adults with IGEs were considered class III studies because of either an open-label design[5,6], too brief treatment duration[5,7] or lack of an adequate comparator.[8]

VPA in the treatment of IGE: VPA is the most effective anti-epileptic drug (AED) in patients with IGEs and is considered to be the drug of choice.[6] This is especially true if it is given as the sole antiepileptic drug.[9,10] There is Class III evidence that VPA is more effective than lamotrigine and better tolerated than topiramate in generalized or unclassified epilepsy.[6] There is also Class III evidence that if the daily dose

does not exceed 40 mg/kg or 2.5g, it is singularly free from serious side effects.[11] Valproic acid is of particular interest in IGEs, as many other AEDs such as carbamazepine, oxcarbazepine, lamotrigine, vigabatrin and phenytoin may aggravate seizures in certain cases and thus should only be used with caution in generalized epilepsies.[12] Valproic acid can also be recommended as first-line monotherapy in IGEs with multiple seizure types.[13] In addition, valproic acid could be prescribed as an initial conservative treatment option in newly diagnosed patients in whom the nature of the epilepsy syndrome (i.e. focal vs. generalized) has not yet been determined[14], as the risk of seizure aggravation is low and the chances of improving seizure control are relatively good. There is also Class III evidence that VPA reduced seizure-related morbidity and improved educational and occupational functioning in patients with IGEs.[15]

Problems with VPA: Valproic acid rates lowest with respect to favorable pharmacokinetic characteristics, mostly because of its non-linear pharmacokinetics, extensive hepatic metabolism, and its high propensity to interact both with other AEDs and non-AEDs.[16] VPA is also well known to have teratogenic side effects. It causes dose dependent damage to the fetus related to the exposure to AEDs during pregnancy.[17,18] However, failure to prescribe valproic acid for IGEs, particularly when another first-line treatment has failed, may not be in a young woman's best interests, particularly when they are most vulnerable to sequelae from uncontrolled seizures.[15]

According to the ILAE Classification of Epilepsies and Epileptic Syndromes (1989) (19), there are Eight IGE Syndromes

1. Benign Myoclonic Epilepsy In Infancy (BMEI)
2. Generalized Epilepsy With Febrile Seizures Plus (GEFS +)
3. Epilepsy With Myoclonic Absences (EMA)
4. Epilepsy With Myoclonic-Astatic Seizures (Doose Syndrome; DS)
5. Childhood Absence Epilepsy (CAE)
6. Juvenile Absence Epilepsy (JAE)
7. Juvenile Myoclonic Epilepsy (JME)
8. Epilepsy With Generalized Tonic–Clonic Seizures Only (IGEs With GTC Only)

This document deals with guidelines for CAE, JAE, JME, IGEs with GTC Only and IGEs NOS.

Absence Epilepsy (AE)

VPA and Ethosuximide (ESM) are established (level A) and lamotrigine (LTG) is possibly (level C) efficacious as initial monotherapy for children with newly diagnosed or untreated absence seizures.[4] This was indicated by a Class 1A superiority trial comparing VPA, ESM, and LTG in 446 children with absence seizures.[20] The initial report focused on the short-term (16–20 weeks) freedom from failure rate, an effectiveness outcome measure defined as seizure freedom without intolerable side effects; the rate was 58% for VPA and 53% for ESM (no significant difference between VPA and ESM), both of which were higher than the rate for LTG (29%; $p < 0.001$ for both comparisons). These findings persisted over the first 12 months of double-blind therapy, allowing this study to qualify as a successful Class IA study.

A Class 1B trial done on the EEG readings of 25 patients with absence seizures treated with valproic acid (VPA) in doses of 17–62.5 mg/kg/day showed that 19 (76%) patients experienced a reduction in spike-and-wave charges, and 11 (58%) of the 19 had a spike-and-wave discharge reduction of >75%, a statistically significant ($p < 0.02$) reduction. Twenty-one (84%) patients had a reduction of the total time of spike-and-wave discharge, and 19 (76%) patients had fewer absence seizures. The authors noted that clinical improvement occurred in the patients when plasma levels of VPA reached 50–60 µg/ml.[21] In a multicenter, open study was conducted on patients with IGEs on VPA monotherapy. In this study, 21 patients had absence seizures and were given a mean daily dose of 20 mg/kg of VPA. After 18 months receiving VPA monotherapy, 20 (95%) of the 21 patients remained seizure free. The authors concluded that VPA monotherapy was effective in controlling absence seizures and should be given an adequate trial to ensure that patients derive the greatest possible benefit before adding another AED or switching to a different AED.[22] However, a case study reported a patient with early-onset absence

seizure with onset at age 11 months, whose seizures increased in frequency after the introduction of valproic acid (VPA) treatment and substantially improved upon cessation of treatment.[23]

Combination therapy with ESM and VPA should be considered in patients whose absence seizures do not respond to standard therapeutic measures.[24] Low-dose lamotrigine added to valproic acid appears to be effective in typical absence seizures. A therapeutic interaction of the two drugs seems likely.[25]

A study assessed the value of VPA in 25 patients (11 males and 14 females, aged 14–73 years) with recurrent ASE who had failed to respond to other anticonvulsants, including ethosuximide and CZP (clonazepam).[26] All of the patients had absence status demonstrated by EEG and were grouped according to EEG criteria as having primary generalized epilepsy, generalized epilepsy with cerebral damage, or generalized epilepsy with focalization. The frequency of absence status in these patients before treatment with VPA was retrospectively determined and compared with the frequency observed during treatment with individually titrated doses of VPA. The most frequently administered dose was 1,500 mg/day, given in an open and unblinded manner. Among the 25 patients, 18 had primary generalized epilepsy with a mean frequency of 5.7 absence status attacks per year. After a mean follow-up period of 4.4 years, the frequency of attacks was reduced to 0.6 per year. Fourteen patients had no recurrence, three had rare attacks with noncompliance, and one had an incomplete response, probably due to gastrointestinal intolerance. The response to treatment by patients with diffuse cerebral damage or generalized epilepsy with focalization was not as good as that of patients with primary generalized epilepsy. These findings suggest that VPA is the drug of choice for the prevention of ASE recurrence.[26]

Generalized Tonic-Clonic Seizures (GTCS)

A meta-analysis by Marson *et al.* specifically reviewed the use of VPA and CBZ (carbamazepine) in GTCS. There was a non-statistically significant trend toward a better response with VPA compared with CBZ (carbamazepine), and the authors concluded that trials should be conducted with VPA in GTCS management.[27] Class IV evidence suggests that CBZ (carbamazepine) and PHT may precipitate or aggravate generalized-onset tonic–clonic seizures.[28-30]

Juvenile Myoclonic Epilepsy (JME)

Among anticonvulsants, valproic acid still stands out as the most efficacious drug in JME, but may be poorly tolerated by some, and is considered unsafe for the fetuses of pregnant women. The interest of valproic acid in treating this epilepsy syndrome is reinforced by the fact that most other AEDs available, including phenytoin, carbamazepine, lamotrigine, oxcarbazepine, vigabatrin, tiagabine and gabapentin may aggravate myoclonic seizures.[31] The open case-series that has been published using VPA shows a 41–88% seizure-free rate for patients receiving VPA, either as an add-on medication or as monotherapy.[32,33]

A Class III randomized open label trial compared topiramate (TPM) and VPA monotherapy in both newly diagnosed and previously treated JME patients.[34] There were only 16 newly diagnosed previously untreated patients among the 28 children in the study. These 16 children were randomized between TPM (n = 12) and VPA (n = 4). The low number of previously untreated patients prevents drawing conclusions from this study. Case studies have also shown that a low, once-daily dose (500 mg) of VPA can effectively control JME and keep patients seizure free for as long as 2 years.[35, 36]

Acute treatment for most myoclonic seizures starts with a BZD, such as CZP (clonazepam) or nitrazepam. Another BZD, clobazam, was found to be less effective.[37] As a second step, intravenous VPA (i.v.-VPA) can be administered at a high loading dose to rapidly achieve therapeutic levels.[38] Sheth and Gidal described two female patients, aged 15 and 28, with JME that presented with myoclonic status.[39] One was on baseline therapy with phenytoin (PHT), and the other was on lamotrigine (LTG). When they presented with SE, both were successfully treated with 500 mg i.v.-VPA given over 30 min, a relatively modest dose and a fairly slow infusion rate. Within 5 min. of the end of the infusion, both patients were seizure free, their myoclonic jerks stopped, and follow-up EEG readings were normal.

Epilepsy With Generalized Tonic–Clonic Seizures Only (IGE With GTC Only; EGTCS)

VPA monotherapy is very effective for both seizure outcome control and photosensitivity (PS) reduction in adolescents with EGTCS.[40]

Studies Looking at VPA Efficacy in Multiple IGE Groups

Of 84 children having a diagnosis of IGEs [33 (35%) of the children having Childhood Absence Epilepsy (CAE)], 48 (57%) became seizure-free on valproic acid monotherapy and another 10 patients became seizure-free but discontinued VPA because of adverse effects. The mean dose in seizure-free children was 15.7 mg/kg/day and over 95% of IGEs patients will respond below 25 mg/kg/day.[41] A study done prospectively to assess the response to low-dose valproic acid (VPA) treatment (<1000 mg/day) together with plasma VPA levels in a cohort of 44 patients with IGEs [23 (42.6%) having JME, 17 (31.5%) having JAE and 14 (25.9%) having GTCS only] found that low-dose VPA was a highly effective treatment for the majority of those with JME and GTCS only. The seizures in JAE tended to be more resistant to treatment, usually requiring higher doses of VPA or polytherapy.[42]

There is Class III evidence that VPA treatment in patients with IGEs (1) reduces spontaneous generalized spikes and waves but not photo paroxysmal reactions[43]; (2) decreases EEG synchronization in the delta and theta frequency bands in a use-dependent manner[44]; (3) normalizes EEG functional connectivity.[45]

Place of valproic acid in children with idiopathic generalized epilepsy

A study was done to test the efficacy and innocuousness of a single dose of VPA for the treatment of IGEs, as compared with 3 daily doses. It was found that twenty patients (57.14%) who were well controlled with 3 daily doses had no fits with the single dose treatment. Ten patients (28.57%) who had had one fit every 6 months during the observation year had no convulsions during the year on a single dose: however, 5 (14.28%) others who had had one fit every 6 months with 3 doses, had fits with the same frequency with the single dose treatment. There were no side effects.[46] They concluded that the efficacy of a single dose might result from the action of VPA, which increases the intra-cerebral levels of GABA, which are delayed and prolonged.

Cochrane Reviews

1. Relationship between valproic acid, lamotrigine and topiramate and IGEs prognosis
   Valproic acid may be the most effective antiepileptic drug in the treatment of the IGEs. Combination therapy should be initiated if an adequate trial of valproic acid monotherapy is not effective, rather than switching to alternative monotherapy. Antiepileptic drug treatment needs to be lifelong in many adult patients with IGEs.
2. Primary outcomes of SANAD study
   Time to treatment failure: valproic acid was significantly better than topiramate (hazard ratio 1·57 [95% CI 1·19–2·08]), but there was no significant difference between valproic acid and lamotrigine (1·25 [0·94–1·68]).
   For patients with IGEs: valproic acid was significantly better than both lamotrigine (1·55 [1·07–2·24] and topiramate (1·89 [1·32–2·70]).
   For time to 12-month remission: valproic acid was significantly better than lamotrigine overall (0·76 [0·62–0·94]), and for the subgroup with IGEs [0·68 (0·53–0·89)]. But there was no significant difference between valproic acid and topiramate in either the analysis overall or for the subgroup with IGEs.
   But there was no significant difference between valproic acid and topiramate in either the analysis overall or for the subgroup with IGEs.

Current NICE Guidelines

Treatment of IGEs in children, young people and adults

- First line treatment: valproic acid, lamotrigine (if valproic acid is not suitable)
- Cautions: be aware of potential effect of valproic acid in pregnancy. If the person has myoclonic seizures or may have juvenile myoclonic epilepsy lamotrigine may worsen myoclonic seizures

- Alternative first line: carbamazepine, oxcarbazepine
- Cautions: be aware that these drugs may worsen myoclonic or absence seizures
- Adjunctive treatment (if 1st line treatment is ineffective or not tolerated): clobazam, lamotrigine, levetiracetam, topiramate
- Cautions: be aware of potential effect of valproic acid in pregnancy. If the person also has absences or myoclonic seizures, or may have juvenile myoclonic epilepsy do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

AAN Guidelines

- Valproic acid is effective in the treatment of primary generalized-onset tonic–clonic seizures especially Juvenile Myoclonic Epilepsy.
- Topiramate is effective for the treatment of refractory generalized-onset tonic–clonic seizures in adults and children (recommendation level A).
- A small study with lamotrigine used as add-on therapy in patients with refractory IGEs and a combination of seizure types is mentioned in the guidelines.
- AAN cautions about use of VPA like FDA.

Conclusions

- Valproic acid has been demonstrated to be the most efficacious and safe AED in adult males and post-menopausal with IGEs and multiple seizure types.
- VPA is considered as 1st line therapy for many epilepsy syndromes in adults, notably IGEs – JME, Absence Epilepsy
- Although VPA is highly efficacious in women with IGEs, it should be used with caution in young women and those in childbearing age.
- Valproic acid is often said to be more suitable in children with epileptic encephalopathies and in those with multiple seizures
- Valproic acid is of particular interest in IGEs as AEDs like carbamazepine, oxcarbazepine, lamotrigine and phenytoin may aggravate seizures in certain cases and thus these AEDs should only be used with caution in generalized epilepsies
- Despite availability of newer AED like levetiracetam, the efficacy of VPA in JME is unparalleled
- Combination with lamotrigine: only proven synergistic combination

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Table showing choice of AEDs in patients with IGE syndromes as NICE guidelines

Preferred AEDs	GTCS	Absence seizures	Myoclonic seizures
1st line AEDs	Valproic acid	Ethosuximide /lamotrigine	lamotrigine
Alternate 1st line AEDs	lamotrigine	lamotrigine	levitiracetam topiramate
Adjunctive AEDs	clobazam, levetiracetam, or topiramate		Any of the above
Avoid AEDs	carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin	carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin	carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

Valproic Acid in Focal Epilepsy

Manjari Tripathi

The International League Against Epilepsy (ILAE) published their updated ILAE evidence review of anti-epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes in 2013.

The below table summarises the role of valproic acid (VPA) clearly in partial onset seizures (POS):

Seizure type or epilepsy syndrome	Class I	Class II	Class III	Level of efficacy and effectiveness evidence (in alphabetical order)
POS: Adults	2	1	30	Level A: CBZ, PHT, LEV Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB
POS: Adults	1	0	17	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA
POS: Elderly	1	1	2	Level A: GBP, LTG (CBZ CR) Level B: None Level C: CBZ

Based on this VPA would not be the drug of first choice.

Seizure type or epilepsy syndrome	Class I	Class II	Class III	Level of efficacy and effectiveness evidence (in alphabetical order)
BECTS	0	0	2	Level A: None Level B: None Level C: CBZ, VPA

The summary of recommendations for syndromes put this as one of the options for benign rolandic epilepsy with centrotemporal spikes (BECTS).

One of the more recent multicenter studies **KOMET** by Trinka *et al.* in 2012 which was an unblinded, randomised, two parallel-group, stratified trial compared the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release valproic acid as monotherapy in patients with newly diagnosed epilepsy. The results showed that in a study design where the clinician decided whether VPA or CBZ (carbamazepine) would be the standard 1st line treatment. Within the VPA stratum, pts were randomised (1:1) to treatment with LEV or VPA-ER. 1698 patients were randomised 1266 patients were still taking the drug at the end of the study. The primary outcome measure was the time to withdrawal from study medication (treatment withdrawal). This was calculated from randomisation to the day after the last intake of study medication for the overall comparison of LEV with standard AEDs. The secondary outcome measure was time to first seizure calculated from randomisation, treatment withdrawal and seizure freedom rates at 6 and 12 months. Time to treatment withdrawal was longer in patients treated with LEV compared with standard AEDs, but the difference was not significant. Time to first seizure was significantly longer for patients in the standard AEDs group compared with the LEV group.

About 30% of the patients received levetiracetam versus valproic acid for focal seizures. Time to treatment withdrawal was similar for LEV and VPA-ER (HR 1.02, 95% CI 0.74 to 1.41). When comparisons were done according to seizure type, no significant differences were found, but trends favoured LEV in those with focal seizures (HR 0.73, 95% CI 0.37 to 1.44). Estimated seizure freedom rates at 6 and 12 months were higher with VPA-ER than LEV, for all patients. Discontinuation of treatment due to AEs was similar in patients treated with LEV (6.1%) and VPA-ER (4.7%). The study found LEV to be non-superior to both VPA-ER and CBZ-CR (carbamazepine) for the global outcome and time to treatment withdrawal.

Nolan in the Cochrane review studying the role of valproic acid versus phenytoin monotherapy in

focal seizures. Outcomes were time to (a) treatment withdrawal (b) 12-month remission (c) six-month remission and (d) first seizure post randomisation. Individual patient data were available for 669 individuals out of 1119 eligible individuals from 5 out of 11 trials, 60% of the potential data. The results did not suggest that valproic acid was better in focal seizures.

Conclusion

There should be no reason to use valproic acid as a drug of choice for focal seizures at all with better treatment options available for the same.

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Valproic Acid in Epileptic Syndromes with Special Reference to Juvenile Myoclonic Epilepsy

Satish Jain, Manjari Tripathi

The International League Against Epilepsy (ILAE) published a review of all relevant studies that were aimed to provide evidence based answers to the specific question: "For patients with newly diagnosed or untreated epilepsy, which anti-epileptic drugs (AEDs) have the best evidence for long term efficacy or effectiveness as initial monotherapy.[1] This review article has been updated by the ILAE subcommission of AED guidelines, mainly based on the impact of the initial publication and the information that was made available in several of the published randomized controlled trials (RCTs) on the efficacy and effectiveness of AEDs in patients with new-onset epilepsy.[2]

Juvenile Myoclonic Epilepsy (JME)

A review of the evidence available at the time of initial publication in 2006 revealed that there were no RCTs that had studied the efficacy and effectiveness of AEDs as initial monotherapy for patient having JME. The two RCTs that had not reported on the efficacy and effectiveness as the primary outcome measure were not included in this report.[1] Subsequently, one RCT compared the role of topiramate (TPM) and valproic acid (VPA) monotherapy in only 16 newly diagnosed children having JME. This study (Class III DB, n=1) was interpreted to show that VPA and TPM are potentially (level D) efficacious/effective for patients with newly diagnosed JME.[3]

In one of the largest study of phenotypic analysis of JME among Indian families, information on clinical and EEG features, family history and response to AEDs was collected on 500 probands with JME. The seizures among majority of patients having JME were successfully treated with VPA alone (447 of 500, 89%), and 28 (6%) required another AED in addition to VPA, 24 (5%) were never treated with VPA and had good seizure control on other AEDs, and the current information on AEDs of one patient was not available. Additionally, 41 of 42 JME patients who had a photo-paroxysmal response on the EEGs had responded very well to VPA alone.[4]

The International league Against Epilepsy (ILAE) published their updated ILAE evidence review of anti-epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes in 2013.

The below table summarises the role of VPA in generalised seizures tonic-clonic (GTC) and other generalised seizure types/syndromes:

Seizure type or epilepsy syndrome	Class I	Class II	Class III	Level of efficacy and effectiveness evidence (in alphabetical order)
GTC: Adults	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA
GTC: Children	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Absence seizures	1	0	7	Level A: VPA Level B: VAL Level C: LTG
JME	0	0	1	Level A: None Level B: None Level C: None

- One of the more recent multicenter studies **KOMET** by Trinka *et al.* in 2013 which was an unblinded, randomised, two parallel-group, stratified trial compared the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release VPA as monotherapy in patients with newly diagnosed epilepsy. This study showed that in the stratum comparing LEV and VPA-ER, the HR (95% CI) for time to treatment withdrawal was 1.02 (0.74 to 1.41), suggesting similarity between the two. Subgroup analysis of only the patients classified with generalised seizures gives an HR for treatment withdrawal of 1.16 (95% CI 0.79 to 1.71) suggesting a non-significant advantage for VPA-ER. For time to first seizure in the VPA stratum, (HR 1.19) results were similar to the overall results, suggesting an advantage for VPA-ER.
- Nolan in the Cochrane review studying the role of VPA versus phenytoin monotherapy in generalised seizures. Outcomes were time to (a) treatment withdrawal (b) 12-month remission (c) six-month remission and (d) first seizure post randomisation. Individual patient data were available for 669 individuals out of 1119 eligible individuals from 5 out of 11 trials, 60% of the potential data. The results suggested that there was no evidence against or for the use of VPA in generalised seizures.

Conclusion

VPA is an effective anticonvulsant for generalized seizures in terms of efficacy and should be used where there are no contraindications and side effect profile is acceptable to the patient after a shared decision making process.

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Valproic Acid in Status Epilepticus

Usha Kant Misra, Jayantee Kalita, Sanjeev Bhoi, Deepanshu Dubey

Status epilepticus (SE) is a common neurological emergency second only to acute stroke. The management of SE has been evolving. Benzodiazepines have now been established as the first line treatment of SE. There are many drugs like phenytoin (PHT), levetiracetam (LEV), valproic acid (VPA) and lacosamide as possible second line agents for SE. **An ideal antiepileptic drug (AED) for SE should act rapidly without cardiorespiratory depression, with a half-life long enough to prevent relapse, protein binding such that the pharmacokinetics** are not affected by systemic illness, metabolism not affected by renal or hepatic impairment and a linear dose response relationship.

Pharmacokinetics

VPA potentiates γ-aminobutyric acid (GABA) inhibitory effects in the central nervous system. In addition, it also acts through attenuation of N-methyl D-aspartate (NMDA) receptor mediated excitation, although this does not explain the effect of valproic acid on absence seizures. It has also been proposed that VPA exerts its effect via blockade of voltage dependent sodium channels.[1] VPA is about 90% bound to plasma proteins, and the degree of binding decreases with increasing drug concentration within the clinically occurring range. VPA is extensively metabolized by microsomal glucuronide conjugation, mitochondrial beta-oxidation and cytochrome P450-dependent oxidation.[2] Elimination of VPA appears to follow a monophasic exponential course: biological half-life is 8 to15 hours, but shorter values (5 to 12 hours) are observed in patients receiving enzyme-inducing agents. Valproic acid appears to have a relatively restricted distribution ranging from 0.15 to 0.40/Kg. There are large individual differences in clearance rates. The therapeutic range of VPA is between 50 and 100 mg/l.[2,3]

For treatment of status epilepticus, lorazepam 4 mg or diazepam 10 mg followed by phenytoin (PHT) 15-18 mg/kg IV or equivalent dose of fosphenytoin is recommended.[4] Each of the recommended treatment has its advantage and disadvantage. Benzodiazepines although are highly effective, result in sedation, hypotension and respiratory suppression whereas PHT (Phenytoin) though has no sedating effect but has serious side effects such as cardiac arrhythmia, hypotension and phlebitis. The first line AED fails to control 25-45% of patients with SE.[5] Additional treatment therefore is needed though high quality evidence is lacking. Valproic acid (VPA) acid has been elevated second line antiepileptic drug (AED).[6-10] US FDA has approved IV SVA in 1996 and since its introduction several case studies and uncontrolled studies have been published evaluating the role of VPA in SE.[11] Intravenous VPA is an emerging alternative in SE patients who are resistant to 1st line drugs (BDZ). The safety data has also been encouraging for VPA.

The First Case Series Reporting Efficacy of VPA in SE was by

Vajda *et al.* who administered VPA per rectum in 6 patients resistant to diazepam and/or amobarbital were administered SVA 200-800 mg per rectum. The plasma levels of SVA reached the therapeutic level within 36 hours. SE was controlled in 5 patients and a 75% reductions in seizures was noted in the 6th patient.[12]

The review of published literature including randomized controlled trials (RCT), non RCT prospective and retrospective case series received and presented to the group of experts. The conclusions opinion is summarized in the following section

Randomized Controlled Trials

There are 3 RCTs comparing VPA with PHT (Phenytoin) [8,9,10] and 2 with diazepam[13,14] and 1 with phenobarbitone.[15] These studies include 361 patients,

183 were randomized to VPA. The dose of VPA was 20-30 mg/kg.

In the study by Misra *et al.* seizure cessation at the end of infusion was significantly higher in VPA (66%) compared to PHT (Phenytoin) (42%; P=0.06). 15 of the non-responses were treated to the other study drug. 15 out of 19 (79%) non-responds to PHT (Phenytoin) responded to VPA compared to 3/12, (12%, P<0.001). 24 hour seizure freedom was obtained in 29 patients irrespective of treatment group or sequence.[8] Gilad *et al.* in 2007 found no significant difference in seizure cessation after infusion of VPA or PHT (Phenytoin) after 20 min. infusion (13/18, 72.2% Vs 7/9, 77.8 NS). Seizure freedom was obtained in all the patients in both the groups.[9] Agarwal *et al.* compared seizure cessation clinically and EEG was done within 20 minutes of VPA or PHT (Phenytoin) infusion and rate of seizure recurrence within 12 hour in 50 patients was noted. There was no significant difference in seizure cessation between VPA and PHT (Phenytoin) (88% vs. 84%). Seizure cessation was high if patients were treated within 2 hours (P<0.005).[10]

The efficacy of VPA was compared to diazepam: in generalized convulsive SE in 66 patients. Significant difference between diazepam (56%) and VPA (50%) with respect to seizure cessation was not observed. Relapse of seizure in 24 hour occurred in 25% in diazepam and 20% in valproic acid group which was also not significant.[14]

In a study on children comparing VPA and diazepam, the median time to abrogation of seizures were shorter with valproic acid (5 min.) compared to diazepam (17 min.) (P<0.0001).[13]

In a systematic review IV VPA and IV PHT (Phenytoin) comparing PHT (Phenytoin) to VPA there was no significant difference in seizure cessation (RR 1.31 95% CI 0.3–1.84) and in 24 hour seizure freedom (PR 0.96, 95% CI 0.80-1.06).[11]

Valproic Acid Compared to Phenobarbitone

In the study comparing IV VPA vs. phenobarbitone in children, seizure termination was higher in those receiving IV VPA (27/30, 90%) compared to IV phenobarbital (23/30, 77%) (P=0.189). A significantly higher relapse rate in 24 hour was observed (12/23) in phenobarbital compared to VPA group 4/27.[15] (Table 1).

Controlled Non-randomized Studies

Four studies have compared VPA with PHT (Phenytoin) and LEV[16-19]. Tripathi *et al.* compared LEV with VPA in refractory SE (>1 hour) in the patients who had received benzodiazepine or PHT (Phenytoin). Clinical seizure cessation occurred in 26/41 (68.3%) in VPA group and 28/41 (73.2%) in LEV group which was not significant. Seizures were refractory to VPA in 31.7% and to LEV 26.8% and patients required mechanical ventilation and anesthetics.[17] In a retrospective study, VPA was compared with PHT (76%) as first line drug. SE was controlled by VPA in 75% and by PHT in 46%.[16]

In a prospective study 65 patients received VPA and 52 PHT for SE. Seizures of 56% on VPA and 44% on PHT were controlled. Crossing over the patients with uncontrolled seizure resulted in seizure control in 41 additional patients whereas 35 (30%) patients remained refractory to both VPA and PHT.[18] A retrospective analysis of VPA vs. PHT or LEV as 2nd line AED revealed failure by VPA in 25.4%, PHT 41.4% and LEV 48.3%. In this study even without statistical power LEV was less effective than VPA to control SE resistant to benzodiazepine.[19](table 2)

The results of two published trials, one evaluating the efficacy and safety of VPA and PHT (group I) and the other LOR and LEV (group II) were compared. Group I had 117 and Group II 79 patients. As first choice, LOR controlled SE in 75.1%, LEV in 76.2%, VPA in 55.4% and PHT in 44.2%. As second choice, LEV was effective in 88.9%, LOR in 70%, VPA in 74%, and PHT in 28%. Refractory SE was more commoner in group I (27.9%) than group II (10.5%). The complications and death were more in group II. LOR and LEV combination was better than PHT and VPA in reducing refractory seizures but at the cost of higher complications and death.[20]

There are a large number of uncontrolled studies and case reports which have little importance in light of the above mentioned studies.

VPA in Different Types of SE

VPA has been evaluated mainly in generalized convulsive SE. Evaluation of 10 studies (both retrospective and prospective) has revealed a response rate of 71.7%.[21] In simple and complex partial SE, the response to VPA was 77.6% (83/107). In absence SE, the experience is limited and based 16 patients 12 (75%) of whom responded. In 2 patients, valproic acid was given in absence SE after benzodiazepine failure and both responded.[16] In myoclonic SE response rate to VPA was 71% (5/7) and post anoxic myoclonus 60% patients responded.[21]

Order of VPA and seizure outcome

2 randomized and 1 non-randomized trials have evaluated VPA as first line AED instead of benzodiazepine. SE was controlled in 66%-72% patients in randomized and 68.3%-75% in non RCTs. 4 randomized studies evaluated VPA as 2nd time drug. SE was controlled in 50%-90% in RCT and 56% patients non RCT.[21]

Treating SE with One or Two Drugs in the Beginning

There is evidence that LOR alone, PB (Phenobarbitol) alone or PHT plus diazepam can be used of treatment of SE.[5] This study compared LOR 0.1mg/kg, with PHT+diazepam 0.15 mg/kg. Since LOR is several times more potent than diazepam hence the comparison was between LOR and PHT with ineffective dose of diazepam. Hence, the question whether to administer 2 drugs simultaneously or sequentially remains unanswered. Some authorities recommend 2 drugs with different mechanism of action because of the following reasons: 1) The time dependent loss of potency of BDZ documented experimentally[22] hence the drugs acting on GABA receptors should not be used when SE is treated more than 30 min. after the onset of seizure. This time is sufficient to cause a decline in the potency of BDZ.[23] 2) SE is a heterogeneous disorder and attacking two mechanisms of action may have a better chance of success. In such a situation VPA or PHT may be used in addition to BDZ especially in the patients with long standing or established SE.

Safety

There are a large number of dedicated safety studies, adverse event responding in efficacy studies, case reports and pharmacovigilance reporting which provide information about the safety and side effects of VPA.

Dedicated safety studies revealed safety of IV VPA. Though all the patients were not of SE but the information is relevant to evaluate the safety of VPA in SE. In a study of 318 adults and children with seizures VPA in a dose of 15 mg/kg/6 hourly was evaluated. The median dose was 375 mg injected in 1h .Transient adverse events were noted in 54 (17.5%) and included headache, injection site reactions, nausea, somnolence, vomiting, dizziness and altered taste. There was no change in hematological parameters, serum chemistry and vital signs.[24] In another study on 1.5 mg vs. 3 mg/kg/min infusion was compared in 112 children. There was no change in their mean BP, 2 patients on 3 mg/kg/min had transient hypotension. The commonest side effects were somnolence, paresthesia, dizziness and nausea. The possibility of treatment related encephalopathy was reported in 1 patient receiving VPA at the rate of 3 mg/kg/min which resolved on discontinuation of VPA. A study on 40 patients receiving 20-30 mg/kg/min at the rate of 6 and 10 mg/kg/min resulted in asymptomatic hyperammonemia in 30 out of 40 patients 1 hour after infusion. None of the patients had any alteration of consciousness or increase in serum transaminase.[25] On rapid infusion of VPA, BP changes and adverse events were evaluated in 36 patients who were infused VPA at the rate of 3 mg/kg/min up to a maximum of 15 mg/kg. 24 patients were infused at the rate of 3 mg/kg/min upto 30 mg and 6 patients 6 mg /kg up to 15 mg/kg and did not reveal any increase in adverse events at higher dose or at faster infusion rate and no change in BP was observed. Later infusion rate up to 11 mg/kg/min have been reported in paediatric patients without any toxicity.[26] Hypotension is a concern in IV AEDs in treatment of SE. A retrospective analysis revealed that IV VPA was used to control SE in 13 patients, revealed hypotension or cardiovascular instability 12 of these patients who were above the age of 64 years, mean dose of VPA was 25.1 + 5 mg/kg infused at rate of 36.6 + 25 mg/kg/min. All of these but one patient received vasopressors; no significant change

in BP was observed during or after VPA infusion and increase in vasopressor dose was not required. No other cardiovascular adverse event or arrhythmia was observed.[6] In an open labeled study, VPA infusion in 40 patients with epilepsy who received VPA in a dose of 20 or 30 mg/kg/min at the rate of 6 or 10 mg/min. VPA was well tolerated without any cardiac arrhythmia or cardiovascular side effects and there was no alteration in consciousness although 7.5% patients reported sedation and 2.5% had nausea.[27] Local irritation with VPA infusion was also less than that in PHT (18% vs. 25%) in a retrospective study in head injury patients.[28]

Randomized controlled trials: There are 6 RCTs including 183 patients in whom the side effects of VPA have been reported in comparison to diazepam, PHT and phenobarbitone. They revealed lower incidence of serious side effects following VPA administration (Table 3).

Valproic acid therefore seems to have better toxicity profile compared to other 1st line AEDs. In a metaanalysis VPA has significantly lower risk of adverse events (RR 0.31) (95% CI 0.12-0.85).[11] Controlled non-randomized trials also document cardiovascular and respiratory safety of VPA compared to other AEDs.[17] A case report has reported to association of VPA with acute pancreatitis.[29]

Conclusion

1. Intravenous valproic acid seems to be effective and safe in SE patients who have failed IV benzodiazepine
2. The recommended dose of VPA is 15-45 mg/kg bolus (6mg/kg /min) followed by 1-3 mg/kg in infusion
3. The incidence of adverse reaction is below 1% and includes, dizziness, mild hypotension which is independent of infusion rate. VPA has good cardiovascular and respiratory tolerability.
4. High quality RCTs of VPA in SE are needed.

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Table 1: Randomised controlled trials comparing efficacy of VPA with other drugs

Author	No. of patients	Patients	Type of seizures	Statistical difference
Misra *et al.*[8]	VPA=35, PHT=33	Adults and children	Convulsive SE	NS
Agarwal *et al.*[9]	VPA=50, PHT=50	Adults and children	Generalized SE	NS
Gilad *et al.*[10]	VPA=18, PHT=9	Adults > 18 yrs	Generalized SE	NS
Chen *et al.*[14]	VPA=30, D=36	Adults and children> 15 yrs	Generalized SE	NS
Mehta *et al.*[13]	VPA=20, D=20	Children (B12 y)	Generalised SE	NS
Malamiri *et al.*[15]	V: 30, B: 30	Children ([2 y)	Convulsive SE	NS

B: phenobarbital, D: diazepam, PHT: phenytoin, SE: status epilepticus, VPA: valproic acid

Table 2: Non-randomized trials of SE using i.v. Valproic acid

Author	N	Age	Type SE	Outcome
Tripathi *et al.*[17]	VPA 41, Lev 41	>14	Ref GCSE	VPA 68.3% vs Lev 73.2 NS
Tiamkao & Sawanyawisuth[16]	VPA 12, PHT 37	>15	GCSE	VPA 75% PHT 46% NS
Kalita *et al.*[18]	VPA 65 PHT 52	Ad & ch	GCSE,NCSE	VPA 56% PHT 44%
Alvarez *et al.*[19]	VPA 59, PHT70, Lev 58	>16	All	Failure VPA 25.4%, PHT 41.4, Lev 48.3%

VPA: Valproic acid, Lev: levetiracetam, PHT: phenytoin, GCSE: Generalized convulsive status epilepticus

Table 3: Reported incidence of serious adverse events of VPA compared to PHT

Severe adverse events	VPA	PHT	Diazepam	PB
Hypotension (%)	0.5	8.7	21.4	0%
Respiratory impairment (%)	0.5	4.3	25.0	3.3%
Liver failure (%)	3.8	2.2	-	-

Efficacy of Valproic Acid – Comparison with other Anti-Epileptic Drugs

SudhindraVooturi, Sita Jayalakshmi

Abstract

Valproic acid (VPA) is one of the most widely prescribed anti-epileptic drugs (AED) globally. Among available AEDs, VPA is distinguished by its broad spectrum of efficacy against all seizure types and syndromes. It has low risk of causing paradoxical seizure exacerbation and good CNS tolerability. In all types of epilepsy, the efficacy of VPA is comparable with that of alternative AEDs, and it is mainly the differences in tolerability profile that determine which drug has to be preferentially used. The current review aims to summarize the efficacy of VPA in comparison to other AEDs in the management of partial and generalized epilepsies and also in childhood epilepsies.

Introduction

Nearly half a decade since its introduction, valproic acid (VPA) is one of the most widely prescribed anti-epileptic drugs (AED) globally. Increased gamma aminobutyric acid (GABA) – ergic transmission, blockage of voltage-gated sodium channels and modulation of dopaminergic and serotoninergic transmission are the established pharmacological effects of VPA.[1-3] Clinical and electrophysiological studies have reported a wide spectrum action of VPA against different types of seizures suggesting a combination of mechanisms involved. Different dosages of VPA are available both for parenteral and oral use (with almost complete bioavailability).[4] Among available AEDs, VPA also has the advantage of good central nervous system (CNS) tolerability and low risk of paradoxical seizure exacerbation.[5] The current review aims to summarize the efficacy of VPA in comparison to other AEDs in the management of epilepsy.

The earliest reported trials on efficacy of VPA date back to 1960s in patients with epilepsy that was refractory to other AEDs available at that time;[5] where VPA reportedly reduced the incidence of both generalised and partial seizures. Pinder *et al.* in 1977 reported that VPA used as adjunctive therapy reduced seizure frequency by >75% in nearly two-thirds of the patient.[6] Similar findings were reported by Davies,[7] in 70% of the patients who received VPA mono-therapy for a variety of seizure types. However, both the above reviews were based on non-comparative and non-randomized trials.

Efficacy of VPA in Partial Seizures

Randomised trials comparing VPA, phenytoin and carbamazepine as initial monotherapy in adults with previously untreated epilepsy reported that, no major differences in efficacy were found between the drugs.[8] However, phenytoin was more frequently associated with idiosyncratic adverse reactions leading to withdrawal.[8, 9] Additionally, complete seizure control was observed less commonly in the carbamazepine group.[9] Moreover, response rates to VPA were higher in patients with generalised tonic-clonic seizures (GTCS) than in those with partial seizures.[9] These findings were consistent with the reports from randomised follow-up trial in 243 patients, randomised to treatment with VPA, carbamazepine, phenytoin or phenobarbital and followed up for 3 years.[10] The reported discontinuation due to adverse effects were found in 3, 5, 11 and 22% of patients randomised to phenytoin, VPA, carbamazepine and phenobarbital, respectively.[10]

Similar findings of efficacy were reported in children where no major differences were identified between VPA, carbamazepine and phenytoin, but withdrawals as a result of adverse effects were

more common in the phenytoin group (9%).[11] The findings were consistent with reports from paediatric study carried out in India where tolerability findings tended to favour VPA.[12] Three additional, larger scale randomised monotherapy trials focused on a comparison of valproic acid with carbamazepine. Verity *et al.*, in 260 children at 63 centres in the UK and Ireland, reported a trend for superiority of valproic acid in the 12- and 24-month remission rates.[13] The same study also reported that increased appetite was more common in the VPA group, whereas somnolence and dizziness were more common in the carbamazepine group. The Veterans Administration (VA) Collaborative Group,[14] in a double-blind trial that included patients with complex partial seizures and secondary GTCS reported that mean dosage of VPA was as effective as carbamazepine in controlling generalised tonic-clonic seizures, but carbamazepine provided better control of complex partial seizures and had fewer long-term adverse effects. The conclusions of this study, however, have been largely debated, in view of the high dosages used, high number of patients (about one-third) lost to follow-up in the first 12 months and recruitment of patients with a more severe partial epilepsy. The Cochrane Collaboration Group in a meta-analysis of randomised, controlled, comparative trials of VPA, phenytoin and carbamazepine given as monotherapy to patients with newly diagnosed partial and primarily generalised tonic-clonic seizures, reported no overall difference between the drugs for the main outcomes examined.[15] For primary GTCS, efficacy endpoints tended to favour VPA.

On comparison of VPA monotherapy with oxcarbazepine monotherapy in the management of patients with newly diagnosed, previously untreated, partial and primarily GTCS, followed up for 12 months, the two drugs were found to have comparable efficacy, and no significant differences were found in their overall tolerability.[16] The Standard And New Antiepileptic Drugs (SANAD) trial,[17] reported VPA as the first choice treatment in patients with either partial or generalised onset seizures. When evaluating for time to treatment failure, VPA was the most effective drug and topiramate was least effective. Furthermore, VPA was least likely to be associated with treatment failure for inadequate seizure control, followed by topiramate, with lamotrigine being most likely.

Aldenkamp *et al.*,[18] compared the tolerability and prevention of cognitive dysfunction of VPA or TPM given as first-line add-on therapy to steady-state treatment with CBZ (carbamazepine), in a multicenter, randomized, observer-blinded, parallel-group clinical trial. The authors reported that, none of the mood tests or the test for subjective complaints shows statistically significant differences between the treatments, although more scores are in the negative direction for TPM during titration.

Other adjunctive therapy trials, evaluating efficacy of VPA in the management of refractory partial seizures reported VPA superior to placebo.[19] In patients with refractory epilepsy, the best responses are often found when VPA is combined with either carbamazepine or with lamotrigine.[20] Zonisamide, is relatively a new AED with a broad spectrum of anticonvulsant activity, usually used in treatment of refractory epilepsy, very often as an add-on therapy. Furthermore, the updated ILAE report has established level A efficacy/effectiveness evidence for zonisamide as initial monotherapy for adults with partial-onset seizures.[21,22] However, the data on polytherapy is still inconsistent and needs further investigation.

Efficacy of VPA in Generalised Seizure Types

The effectiveness of VPA in patients with generalised epilepsies is supported by decades of extensive clinical experience, even though controlled comparative trials are rarely conducted in these patients. In idiopathic and symptomatic generalised epilepsy syndromes associated with multiple seizure types, prescription of a broad-spectrum drug such as VPA becomes a reasonable choice.[5] In fact, in patients with idiopathic generalised epilepsy syndrome, VPA has been shown to be significantly better than both topiramate and lamotrigine for seizure control.[17] The same study also concluded that based on cost per seizure avoided, VPA should remain the first choice drug for idiopathic generalised or unclassified epilepsy.

In patients with typical and atypical absence seizures, the efficacy of VPA has been demonstrated

by reduced frequency and duration of discharges in the EEG;[23,24] suppressing seizures in at least 80% of patients with childhood or juvenile absence epilepsy.[23,24] However, VPA is usually considered the drug of choice as it is also effective in preventing generalised tonic-clonic seizures, which may coexist or develop at a later time in these patients and also prevents recurrence of absence status.[25] Valproic acid is efficacious against all types of seizures associated with juvenile myoclonic epilepsy, where it is treatment of choice for this condition. Other syndromes where VPA has been found to be useful include the Lennox-Gastaut[26] and West syndromes.[27]

The SANAD trial identified VPA as the first line of drug in generalized epilepsies.[17] Subsequently, the Keppra vs. Older Monotherapy in Epilepsy Trial (KOMET), compared the effectiveness of extended release VPA (VPA-ER) versus levetiracetam (LEV).[28] The study reported that, time to treatment withdrawal was similar for LEV and VPA-ER. Furthermore, the authors reported trends favouring VPA-ER in patients with primary generalised seizures. The estimated overall withdrawal rates as reported by the authors at 12 months were 22.0% (18.0–26.7) with LEV and 21.6% (17.7–26.4) with VPA-ER. However, time to first seizure favoured VPA-ER over LEV. Importantly, estimated seizure freedom rates at 6 and 12 months were higher with VPA-ER than LEV, both for all patients and in those with generalised seizures only.[28] Moreover, serious adverse events were reported by 11.3% patients treated with LEV and 5.8% with VPA-ER.[28] Although VPA might be the most efficacious drug in idiopathic generalized epilepsies, it should be avoided in women of childbearing age due to its safety profile with concerns of teratogenesis and weight gain.[29]

VPA in Childhood Epilepsies

Most idiopathic generalized epilepsies (IGEs) begin in childhood and treatment with the first prescribed antiepileptic drug fails in approximately 20% and 40%.[30] Guerrinni,[31] in a review of literature on VPA in children reported that "valproic acid remains a gold standard antiepileptic drug for the treatment of children". The author further stated that; VPA can increase plasma concentrations of concomitant drugs, such as phenobarbital and lamotrigine, by inhibiting their metabolism. Moreover, as a result of its broad spectrum of efficacy in a wide range of seizure types and epilepsy syndromes, VPA is a drug of choice for children with newly diagnosed epilepsy, idiopathic generalized epilepsy, epilepsies with prominent myoclonic seizures or with multiple seizure types, and photosensitive epilepsies.

Dudley *et al.*,[30] in 48 children with idiopathic epilepsy compared VPA and carbamazepine to evaluate failure of treatment with first AED. The authors reported that, treatment failure was due to adverse effects in 12/30 children (40.0%), due to lack of efficacy in 11/30 (37.9%), and due to both adverse effects and lack of efficacy in 7/30 (24.1%). Furthermore, approximately one third of children newly diagnosed with epilepsy experienced treatment failure with the first antiepileptic drug used. Lack of efficacy and unacceptable adverse effects contributed equally to these treatment failures. The authors also reported that, AED choice, maximum drug dose, etiology of epilepsy, and particular epilepsy syndromes had no effect on treatment failures.

Importantly, when compared to carbamazepine, phenytoin, and phenobarbital in focal epilepsy and with ethosuximide in absence epilepsy, VPA was as effective and showed a favorable tolerability profile.[31] Intravenous VPA may be effective for the treatment of convulsive and non-convulsive status epilepticus that is refractory to conventional drugs.[31] The reviewer cautioned that, in infants, potential benefits should be carefully weighed against the risk of liver toxicity, gastrointestinal intolerance.[31]

Conclusions

Among available AEDs, VPA is distinguished by its broad spectrum of efficacy against all seizure types and syndromes, low risk of causing paradoxical seizure exacerbation and good CNS tolerability. In all types of epilepsy, the efficacy of VPA is comparable with that of alternative AEDs, and it is mainly the differences in tolerability profile that determine which drug has to be preferentially used.

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Valproic Acid – Adverse effects and Tolerability Profile

Bindu Menon, Gagandeep Singh

Valproic acid (VPA) is a widely used antiepileptic drug (AED) for generalized and partial seizures in adults and children. The broad range of effects and clinical efficacy with a wide therapeutic window makes it a broad-spectrum antiepileptic drug. Adverse effects of antiepileptic drugs remain the most common cause of treatment failure. However, the most common adverse effects are dose dependent and reversible.

The knowledge of side effects also plays an important role in choosing the AED of choice. The possible effects of AED could be divided as side effects, adverse effects and idiosyncratic reactions. The side effects could also be acute and long-term side effects.

Definitions

Side effect: Unintended effect occurring at normal dose related to the pharmacological properties.

Adverse event: Medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related.

Adverse reaction: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.

Unexpected adverse event: Not consistent with applicable product information or characteristics of drug.

Serious adverse event or reaction. Any untoward medical occurrence at any dose.

- Results in death
- Life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

Idiosyncratic reactions: Adverse effects not straightly related with pharmacodynamic mechanisms of the drug and can take place on unpredictable way by abnormal interaction between the drug and the organism, usually mediated by immunologic or cytotoxic effects triggered by the drug or its metabolites. Some of the most important idiosyncratic reactions also occur at the start of AED treatment. Idiosyncratic reactions after the start of treatment, such as hypersensitivity reactions and hepatic adverse effects, are most likely to occur within 2 to 8 weeks.

For practical purposes the use of word side effects and adverse effects are used as one.

The side effects profile of valproic acid can be divided as follows:

1) General Effects
2) Gastrointestinal
3) Dermatological
4) Neurological
5) Metabolic
6) Hematological
7) Hepatic and Pancreatic
8) Reproductive and Endocrine
9) Teratogenic effects

General

Common symptoms are asthenia, back pain, deafness, ear disorder, ear pain, facial edema, fever, malaise, arthralgia, arthrosis, leg cramps, myalgia, twitching.

Weight gain is a frequent side effect which may lead to drug withdrawal. Weight gain has been found to occur in 57% of adults[1] and 58% of older children and teenagers[2] treated with VPA. Weight gain was more in women as compared to men.[3] Weight gain is an important risk factor for the development of non-alcoholic fatty liver disease and endocrine

abnormalities in women. Caloric restriction does not necessarily eliminate the problem.[4] Potential risk factors for VPA induced weight gain are puberty, females, long duration of treatment, pre-treatment overweight status, moderate intellectual disability, physical inactivity and physical disabilities, excessive eating in individuals.

Gastrointestinal

Gastrointestinal side effects are the most common for AED's. Dose-dependent side effects are nausea, vomiting, dyspepsia, dry mouth, eructation and indigestion. Rarely diarrhea, abdominal cramps and constipation also occur. These effects are usually at initiation of treatment. They are usually transient and do not generally require discontinuation of treatment. The effects could be minimized by using an enteric-coated formulation or by administering the drug slowly or at meal times.[5]

Dermatological

Alopecia has been reported in 12-28% in a dose dependent manner.[6] Abnormal hair texture, abnormal hair growth, hair color changes, sweating are also reported. Mechanism of hair loss is still debated. Deficiencies of trace elements like copper, zinc, and magnesium and inhibition of metallic enzymes that are essential for hair growth and keratinization have been suggested. Increased synchronization of hair maturation is the other presumed mechanism.[7] Hair growing back tends to be curlier.

Allergic skin rash is the lowest with VPA.[8] Discoid lupus erythematosus, dry skin, ecchymosis, furunculosis, maculopapular rash, petechia, pruritus, rash, seborrhea, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis have been rarely reported.[9]

Ethnicity has been shown to be a contributing risk factor regarding antiepileptic drug. A study analyzing 154 patients with AED-induced severe cutaneous adverse drug reactions (SCARs) found none with VPA.[10]

A case report with DRESS with fulminant hepatic failure has been reported.[11] Stomatitis and cutaneous leukoclastic vasculitis has been reported.[12]

Neurological

Neurological side effects are very common. Drowsiness occurs at the beginning and is usually transient. Patients also experience giddiness, headache, drowsiness, ataxia, disturbance in attention and dysarthria. Confusion and irritablity can also occur. Tremor is an important dose related side effect. It occurs in about 10% of patients. The character of the tremor resembles essential tremor. Usually appears within a month of starting therapy, or else 3 to 14 months after the start of therapy. In some patients, when the tremor has a 'flapping' pattern, an underlying VPA-induced hyperammonemia may contribute to its etiology. Tremor is seldom severe enough to warrant treatment withdrawal. Propranolol has the most therapeutic value.[13] Extrapyramidal side effects are rare. There are only few reports and a few case series of VPA-induced reversible parkinsonism and cognitive decline. The first report was by Lautin *et al.* in 1979.[14] The cases of VPA-induced parkinsonism probably go unnoticed and unreported and hence the actual prevalence is not known. VPA induced parkinsonism is likely to be dose related. There is a cause effect relationship as the side effect is reversed after either dose reduction or stopping the drug. Hence the effect is called reversible parkinsonism. The exact mechanism is unknown, however oxidative stress and mitochondrial dysfunction has been postulated.[15] Parkinsonism usually responds to levodopa but drug withdrawal or substitution remains the best strategy.

Cognitive problems for VPA have also been reported. A study done on 76 adult patients showed that cognitive domains involved were memory (17%), speech (7%), attention (10%), psychomotor slowing (3%), confusion (3%), language (7%) or other (3%).[16] However few other studies failed to demonstrate any cognitive effects. [17]

A study on 453 children showed that attention dysfunction was more common with VPA than with ethosuximide (in 49% of the children vs. 33%; odds ratio, 1.95; 95% CI, 1.12 to 3.41; P = 0.03).[18] A reversible, dementia like syndrome has been reported. This syndrome is at times associated with magnetic resonance imaging (MRI) of the

cortical atrophy. The syndrome is rare. Treatment is reduction or discontinuation of VPA which results in reversal of mental and MRI changes.[19]

VPA induced encephalopathy is an important and severe side effect of AED-therapy and is seen to occur early in the course of treatment. This rare side effect is in most cases associated with hyperammonemia. Rarely, it is associated without hyperammonemia. A study reviewed 19 cases of valproic acid induced encephalopathy between 1994 and 2003 and found that this side effect is also prevalent in adults. Clinical manifestations are varied and patients present with irritability, agitation, lethargy, drowsiness, coma, and occasionally paradoxical seizures.

They proposed that VPA induced encephalopathy could be four types:[20]

1) Encephalopathy with normal ammonia, a direct effect on neurotransmitters.
2) Encephalopathy with hyperammonemia without liver failure, an inhibition of urea cycle.
3) Encephalopathy with hyperammonemia and liver failure.
4) Encephalopathy without hyperammonemia but liver failure.

There is a temporal relation between VPA administration and the development of encephalopathy and its reversal following VPA withdrawal establishes the diagnosis.[21]

Metabolic effects

Valproic acid produces an increase in glucose-stimulated pancreatic insulin secretion. This can lead to an increase in body weight and obesity. The metabolic disturbances associated with the weight gain include hyperinsulinemia and insulin resistance, hyperleptinemia and leptin resistance.[22]

Metabolic syndrome (MS) has been seen to occur in 41% of women treated with VPA.[23] MS as indicated by centripetal obesity, glucose intolerance, hypertension, elevated triglycerides, low high-density lipoprotein cholesterol, and hyperandrogenism/ polycystic ovaries. It was seen to occur exclusively in those who develop obesity during VPA use.[4] Longer duration of treatment appears to be a risk factor for developing MS.

Hyperammonemia is a rare and serious side effect of VPA. This often gets missed especially in the setting of normal liver function tests and VPA levels. This may be present in 20-50% of patients on VPA therapy. In some patients, it is asymptomatic, but in others elevated ammonia can be associated with encephalopathy. Symptoms include acute confusional state, lethargy, drowsiness, ataxia, reduced cognitive abilities, stupor, triphasic waves in EEG, and increased seizure frequency.[24] In chronic therapy, onset can be insidious.

Hyperammonemia without clinical or laboratory evidence of hepatoxicity is an

important idiosyncratic side effect of VPA treatment.[25] Timely diagnosis can reverse the condition and hence a high index of suspiion is required. Changes in mentation especially after addition of topiramate should prompt the clinician to think of this condition. Untreated, this can progress to life-threatening coma.

Several mechanisms have been proposed to explain VPA-induced hyperammonemic encephalopathy. There is inhibition of the mitochondrial carbamoyl phosphate synthetase enzymes in the liver by active metabolites of VPA, which is necessary for ammonia elimination via urea cycle. Chronic VPA therapy increases the amount of VPA oxidation and production of active metabolites in the liver. These metabolites interfere with several biochemical pathways in the mitochondria, leading to disruption of the urea cycle and thereby causing hyperammonemia.[26] Chronic VPA therapy enhances urinary excretion of L-carnitine, resulting in depletion of blood carnitine stores leading to reduced capacity of ammonia metabolism.[27]

In the acute stage hyperammonemia produces excessive activation of

NMDA receptors. The increased ammonia conjugates with glutamate to form glutamine. The increased glutamine level in the astrocytes increases intracellular osmolarity leading to astrocyte swelling and cerebral edema.[28]

Increase in activation of gamma-aminobutyric acid (GABA) by ammonia induces somnolence.[29] Risk factors of developing hyperammonemia is mental

retardation, carnitine deficiency, urea cycle defects, concomitant use of other AEDs, young age, multiple neurological disabilities, and poor nutritional intake.[30]

Treatment consists of supportive care, dose reduction or at times stopping the drug. Complete recovery often occurs within few days. L-carnitine supplementation can help in faster resolution of symptoms.[31] VPA has also been reported to cause a syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatraemia.[32] VPA may also cause a decrease in plasma carnitine levels.[33]

L-carnitine supplementation is currently recommended for VPA-induced liver toxicity, VPA overdose, other acute metabolic disorders associated with carnitine deficiency and primary plasmalemmal carnitine transport defect.[34] Alterations in lipid metabolism and reduced bone mineral density have been reported.[35, 36]

Hematological

Valproic acid–associated thrombocytopenia is generally mild and asymptomatic. The incidence varies from 5% to 60% is more often seen in children than in adults.[37] Most patients recover completely after dosage reduction or discontinuation of VPA. Recovery is seen within 1 week in most patients. Thrombocytopenia is usually transient and self-limiting. The interval between the initiation of VPA treatment and platelet nadir is variable among patients with thrombocytopenia, ranging from 8 days to 16 months.[38] Thrombocytopenia is dose related and often pronounced with intercurrent viral illness. Mechanism of thrombocytopenia is either a direct toxic effect on bone marrow[39] or formation of autoantibodies against platelets.[40]

Acquired Von Willebrand disease has been reported and in such cases desmopressin, a synthetic arginine vasopressin analogue is recommended before surgery. Deficiency of vitamin K–dependent coagulation factors has also been reported. Hemorrhagic symptoms may range from mild bruising to severe ecchymoses, serious mucous membrane bleeding, suffusions, or post-traumatic bleeding. Laboratory findings include prolonged PT and aPTT.

Hypofibrinogenemia occur because of decreased synthesis (inherited hypofibrinogenemia, liver disease) or increased consumption (fibrinolytic therapy, protein loss). There are usually no bleeding symptoms. Routine coagulatin tests may show pathologic PT, aPTT.[41] High serum concentration of VPA is associated with bone marrow suppression. Aplastic anemia, pure red cell aplasia, macrocytosis, and leukopenia are some of the hematological adverse effects of valproic acid therapy. Some of these effects can lead to life-threatening complications.

Liver and pancreas

Idiosyncratic reactions to VPA includes pancreatitis and liver failure. They are rare complications, however are serious.[35,42] Serious hepatic dysfunction following VPA use is a Type B (idiosyncratic) reaction, i.e., it is unpredictable and occurs in genetically predisposed individuals only.

Overall, the risk of VPA induced serious hepatic dysfunction is low – about 1 in 100,000 people using the medication.[43,44] However, in at-risk, predisposed individuals (see below), the risk may be as high as 1 in 500. The predisposed individuals are less than two years of age and harbour the polymerase gamma 1 (POLG1) mutation. The mutation is a feature of Alpers-Huttenlocher syndrome, a mitochondrial disorder with progressive downhill course. VPA-induced hepatitis in children less than two years of age is invariably fatal. Hence, screening of high-risk individuals for the POLG1 mutation before commencing VPA treatment should be considered.[45]

There has been mild increase in serum transaminases without any evidence of liver disease in 10-15%. The complication has been noted to occur more in children younger than 2 years receiving polytherapy, the risk of valproate-induced liver toxicity is as high as 1: 600 or 1: 800, but the incidence decreases with increasing age.[46,47]

Risk factors for developing hepatitis are age below 2 years, use of VPA as polytherapy, children with mental retardation, evidence of any pre-existing liver disease or elevated liver enzyme levels, coexistence of certain metabolic defects (e.g. β-oxidation disorders and mitochondrial diseases.

The mechanism of VPA induced hepatic failure has now been elucidated. The failure is characterised by microvesicular steatosis and is related to the accumulation of 4-en valproic acid instead of 2-en valproic acid, which is ordinarily formed as a result of VPA metabolism.[48,49] VPA largely undergoes glucoronidation in the level; however, a small proportion of the molecule is also oxidised. This oxidation preferentially occurs in the mitochondrion and requires the transport of VPA to the mitochondrial matrix from the cytosol. When this does not occur as a result of carnitine deficiency or due to the mitochondrial defect associated with POLG1 mutation, VPA oxidation occurs predominantly in the cytoplasm leading to the formation of 4-en valproic acid.

Symptoms include apathy, somnolence, anorexia, nausea, vomiting and increased seizure frequency, especially in the presence of febrile infections. In some patients there will be jaundice and bleeding tendency. These warning signs should immediately prompt the clinician for the withdrawal of the drug.

Management involves rapid discontinuation of the offending drug, and the use of intravenous carnitine has also been advocated.[50] Liver transplantation has been undertaken in the past for irreversible hepatic failure due to VPA but the outcome is invariably poor as the patients succumb to the widespread effects of mitochondrial dysfunction associated with the POLG1 mutation.[51]

VPA induced hepatotoxicity can be avoided if the drug is used as monotherapy whenever possible especially in children under 3 years, to keep minimal possible dose required for seizure control, salicylates to be avoided, avoiding use of VPA in patients with liver disease or metabolic disorders involving the urea cycle, organic acidaemias, mitochondrial disorders, free radical scavenger deficiencies, carnitine or medium chain acyl coenzyme A deficiency. Screening for POLG mutation should be performed in the required setting. Children with suspected hereditary mitochondrial disorder over two years should be treated with VPA only if other antiepileptics have failed. Further patients should always be asked to report if they have any nausea, vomiting, icterus. Regular clinical and laboratory assessment for older patients for noting any signs of liver injury must be done.

Pancreatitis

VPA induced acute pancreatitis is a severe idiosyncratic adverse effect. The common symptoms are abdominal pain, nausea, and vomiting. It is noted during the first year of therapy but can occur after years of treatment.[52]

The mechanism of pancreatitis postulated was there is depletion of free radical scavengers such as superoxide dismutase, catalase, and glutathione peroxidase. The free radicals accumulation results in endothelial permeability and lipid peroxidation, ultimately leading to tissue damage.[53]

VPA induced mitochondrial oxidation is another theory for VPA-induced pancreatitis.[54] Acute pancreatitis can be fatal. Patients with acute abdomen should undergo serum amylase and lipase as well as radiology imaging in suspect cases.

Endocrine, reproductive and teratogenic effects are discussed elsewhere.

Table 1: Effects of VPA according to severity

Minor	Moderately severe	Severe
Gastrointestinal side effects Somnolence Tremor Hair loss or thinning	Thrombocytopenia Bone marrow suppression Neutropenia Red cell aplasia Hyperammonemia Excessive weight gain Polycystic ovaries Decreased bone mineral density	Fatal hepatitis Pancreatitis Teratogenesis Hyperammonaemic encephalopathy

Table 2: Common and rare effects of Valproic acid

Common	Rare
General/Dermatological Weight gain, hair loss, Arthralgia, leg cramps, myalgia, bronchitis pharyngitis, acne **Gastrointestinal** Nausea, vomiting, dyspepsia, dry mouth, eructation and indigestion, diarrhea, Abdominal cramps, constipation. Hyperammonemia, hypercarnitenemia, elevated liver enzymes (asymptomatic) **CNS** Tremor, drowsiness, Lethargy, giddiness, ataxia, asthenia, headache. **Metabolic** Hypocarnitinemia hyperglycinaemia, hyperammonaemia **Hematological** Anemia, thrombocytopenia **Reproductive and Endocrine:** Polycystic ovary morphology, hirsutism, menstrual abnormalities, overweight , obesity, polycystic ovary syndrome, anovulary cycles **Teratogenic**	**General/Dermatological** Rash, Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome Facial and limb edema, Nocturnal eneuresis (not life threatening) **Gastrointestinal** Hepatotoxicity with liver failure Pancreatitis **CNS** Reversible dementia, brain atrophy parkinsonism, asterixis, chorea, sensorineural hearing loss, encephalopathy **Metabolic** Insulin resistance, hyperleptinemia and leptin resistance **Hematological** Neutropenia Bone marrow depression (life threatening) Von Willebrand disease type 1, decreased factor XIII, abnormal platelet function, bleeding, haemolytic anaemia, leukopenia, leucocytosis, eosinophilia, thrombocytosis, prolonged prothrombin and thromboplastin times, fibrinogen and hematoma **Reproductive and Endocrine** Hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased) and Syndrome of Inappropriate Secretion of ADH (SIADH) **Teratogenic** Major and minor malformations, including a 20-fold increase in neural tube defects, cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, limb defects, and autism. Fetal valproic acid syndrome Learning disability and behavioural problems in offsring

Common means 1 in 100 to 1 in 10 people will get it.
Rare means 1 in 1000 will get it.
Very rare means less than 1 in 10,000 people will get it.

Table 3: Early and late side effects of Valproic acid

EARLY	LATE
1. Gastrointestinal (42%). Higher in children. Anorexia, nausea, vomiting, indigestion, abdominal discomfort. 2. Elevated SGPT (5%) and SGOT (25%), four fold increase in GGT. (Dose related with no increase in serum bilirubin) 3. Acute liver failure. 4. Somnolence, tremors. 5. Drowsiness, lethargy, acute or subacute encephalopathy. 6. Asymtomatic hyperammonemia.	1. Reversible dementia with brain atrophy and Parkinsonism. 2. Psychiatric and cognitive side effects emotional upset, depression, psychotic reactions, aggression, hyperactivity and behavioral deterioration, insomnia, hypersomnia, lassitude, and hyperactivity. 3. Hearing loss. 4. Metabolic: Hyperinsulinemia, polycystic ovaries, hyperandrogenism. 5. Endocrine and reproductive dysfunction: Irregular mensus, secondary amenorrhea, breast enlargement, galactorrhea and parotid enlargement.

Table 4: Dose related and idiosyncratic side effects of Valproic acid

Dose related	Idiosyncratic
Tremor	Thrombocytopenia
Weight gain	Hamehorrhagic pancreatitis
Anorexia	Acute hepatic failure
Nausea and vomiting	Bone marrow aplasia
Dizziness	
Drowsiness	
Alopecia/hair loss/curly hair	
Encephalopathy	

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Pharmacoeconomics of Valproic Acid

Param S. Kharbanda

Pharmacoeconomics essentially deals with scientific comparison between the value of different pharmaceutical drugs or drug regimens, with focus on the cost. In the present day scenario, when pharmacotherapy is becoming increasingly expensive, this discipline has gained even more importance. Whether the medicines are state subsidised or the patient pays out of pocked, society has to bear the huge cost burden. Though the per capita (PC) income of our country has been steadily going up (~ INR 90,000/annum), a large population still lives below the poverty line, due to the huge disparity between different economic groups. In addition to this, most of the people here pay out of pocket; and antiepileptic medicines require a long term commitment.

Overall it is the cost-effectiveness which would guide the choosing of one treatment modality over another; where effectiveness consists of efficacy and tolerance. However, this can be a complex process. When we discuss the relative Pharmacoeconomics of Valproic Acid (VPA) here, we will confine ourselves to the economics of it all; as the comparative effectiveness of valproic acid to other similar antiepileptic drugs (AEDs) in different settings will be dealt with in the other write-ups in this monograph.

Valproic acid is a broad spectrum AED and is effective in both focal and generalized seizures. The cost analysis can be done both against drugs used for focal epilepsies and those used for generalized epilepsies. In our country, the cost of VPA differs depending on the price set by various manufacturers. It also varies with the preparation – whether it is immediate release or sustained release; the latter being more expensive (this is significant, as VPA is a long half life molecule).

The below mentioned table shows the average cost of some of the commonly used AEDs in comparison to VPA, namely Carbamazepine (CBZ), Oxcarbazepine (OXC), Phenytoin (PHT), Phenobarb (PB), Levetiracetam (LEV) and Lamotrigine (LTG). The daily cost was calculated depending on the defined daily dose of the drugs, as prescribed by the World Health Organization. To get as accurate a cost as possible, the price was averaged from the various brands available on the internet; with some counterchecking from the printed prices on the strips on a given day (subject to change anytime).

Table 1: Comparison of VPA with other AEDs

Drug	Defined daily dose (mg)	Ave. daily cost (INR)	Annual cost (INR)	% of PC income
VPA-sustained release	1,500	33	12,045	13.4
VPA-immediate release	1,500	24	8,760	9.7
LEV	1,500	36	13,140	14.6
LTG	300	39	14,235	15.8
CBZ	1,000	8	2,920	3.2
OXC	1,000	27	9,855	10.95
PHT	300	5	1,825	2
PB	100	5	1,825	2

As mentioned in table, the average daily cost of VPA was around INR 24 for the immediate release and INR 33 for the sustained release. Compared to this the other commonly used AEDs for generalized epilepsies, LEV and LTG had an average daily expenditure of INR 36 and 39 respectively. As for focal epilepsies cheaper AEDs like CBZ (carbamazepine) and PHT are available for use.

This cost analysis however has to be viewed in concurrence with the efficacy and tolerability analysis. The best choice of AED may also depend upon other factors in addition to the type of epilepsy, e.g. special situations like pregnancy, allergies, co-morbidities, co-medication etc.

Box Points:

- VPA is a relatively economical AED for Generalized Epilepsies
- Immediate release preparation is significantly cheaper than the sustained release
- More economical AEDs are available for treatment of Focal Epilepsies
- For best choice of AED-specific setting, efficacy and tolerability to be viewed in concurrence to the cost

Valproic Acid – A Paediatric Perspective

Nandan Yardi, Sheffali Gulati, Suvasini Sharma

Introduction

The story of antiepileptic drugs (AEDs) began on 11th May 1857, when Sir Charles Locock used potassium bromide in a young women with hysterical epilepsy and reported it in Lancet. This was followed by serendipitous discovery of antiepileptic properties of phenobarbitone in 1912 by Alfred Hauptmann, a young resident psychiatrist, who lived above a ward of people with epilepsy. The patients used to fall out of bed during the night due to tonic-clonic seizures, thereby keeping him awake. Phenobarbitone, marketed the previous year as a hypnotic (Luminal) by F. Bayer and Company was used by Hauptmann to sedate his patients, so that they could get a good night's sleep. His patients responded by reducing their seizures not only during night but also during daytime, so Phenobarbital created history by being recognized and used as a potent AED. More than 20 years later, in 1936, Tracy Putnam and Houston Merritt carried out a series of experiments on cats with electrical seizures and the result was launching of phenytoin in 1938.[3] The next major AEDs to be launched were carbamazepine (mid 1960s) followed by valproic acid thereafter benzodiazepines. Valproic acid since then has grown in stature and is currently on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system.

The modern era of AED development was ushered in after 1975 with the developemnt of Anticonvulsant Drug Development Programme by the National Institute of Neurological Disorders and Stroke in the United States, resulting in the licensing of an increasing list of AEDs.

Valproic acid (VPA, di-n-propylacetic acid) was first synthesized in 1882 by Burton as a lipophilic solvent to dissolve the water insoluble substrates. There was no known clinical use of VPA until P. Eymard serendipitously discovered its anticonvulsant activity in the lab of C. Carraz in 1962. In the experiment, VPA was being used as a solvent carrier to dissolve the water-insoluble khelline derivatives (synthesized by Eymard) to test them to abort seizures in rabbits. When all the compounds were found to abort seizures "surprisingly", it was found that the solvent per se (VPA) possesses anticonvulsant activity. Similarly Meunier found VPA's anticonvulsant activity at the rabbit test after dissolving coumarin derivatives in VPA. VPA's first clinical trial was published in 1964 and in 1967. It was approved for marketing in France and marketed worldwide. VPA was approved by the US-FDA in 1978.

Chemistry

Valproic acid is n-propyl pentanoate (di-n-propyl acetate), a branched chain fatty acid. It is marketed in free acid form or the corresponding sodium salt, and also as divalproex sodium, a combination of valproic acid and valproic acid. VPA is water-insoluble {(water solubility - 1.27 mg/mL) weak acid pKa = 4.8)} whose sodium salt is freely water soluble and very hygroscopic. Chemically, VPA is one of the simplest drugs currently available in therapeutic arsenal with eight carbons and without any nitrogen atom or cyclic ring.

Mechanism of Action

VPA potentialising the inhibitory activity of GABA through several mechanisms, including inhibition of GABA degradation, inhibition of GABA Transaminobutyrate (ABAT), increased GABA synthesis, and decreased turnover by altering the activity of the neurotransmitter Gamma Amino Butyrate (GABA).

VPA also attenuates N-Methyl-D-Aspartate-mediated excitation[8, 9] and blocks Na+ channels, Ca2+ channels (voltage-dependent L type CACNA1

type C, D, N, and F), and voltage-gated K+ channels (SCN).[10] Also, more recently VPA has been described as an HDAC inhibitor.

Pharmacokinetics

All formulations of VPA are completely absorbed with enteric-coated formulation slowly, with a 2-3-hour time lag and peak levels from enteric-coated tablets occur 3-5 hours after intake. After rectal administration peak plasma levels have been comparable to those after oral intake. Valproic acid has high affinity for plasma albumin and so a small volume of distribution with a free fraction value of 10%, at higher total valproic acid concentrations. The therapeutic blood concentrations of VPA are 50-100 æg/ml with a half-life of 6-15 hours. Being highly lipophilic, it concentrates in the liver and crosses the BBB to give high concentrations in the brain.

Clearance is increased at high doses, due to the higher free fraction of valproic acid and is higher in patients receiving CYP enzyme inducers. Neonates have a low and immature microsomal drug metabolizing system, but eliminate valproic acid at the same rate as adults, despite having a larger circulating free fraction.

Valproic acid is extensively metabolized, through oxidative and conjugation mechanisms. Conjugation with D-glucuronic acid is the major pathway of biotransformation, accounting for 30-40% of the dose. Similar to fatty acids, valproic acid is sequentially oxidized by mitochondrial beta-oxidation to yield 3-oxo-valproate. Other pathways are also involved, yielding numerous metabolites. Omega and omega-1 oxidative pathways have been described. The metabolites are biologically inactive.

Since valproic acid is a protein bound drug, its volume of distribution closely parallels the serum albumin concentration and also the body weight of the child. Also, since it is primarily metabolized in liver via the Cyp450 system, the maturation of liver enzymes improves valproic acid clearance. The major study by Cloyd in 1993 showed that half-life of valproic acid in various age groups is different.

- Neonates 1st week of life: 40 to 45 hours
- Neonates <10 days: 10 to 67 hours
- Infants and Children >2 months: 7 to 13 hours
- Children and Adolescents 2 to 14 years: 9 hours (range: 3.5 to 20 hours)
- Adults: 9 to 16 hours

An almost concurrent study showed that the metabolites of VPA are also different in different age groups. Here Leppik and colleagues[12] demonstrated that relative amount of VPA metabolized to 4-ene is more than twofold less in adults than in children, which explains the different profile of hepatotoxicity seen by age. In addition, metabolism of valproic acid is influenced by several cytochrome P450 and uridine diphosphoglucuronosyltransferase (UGT) polymorphisms.

Clinical Indications

VPA has been approved for the following clinical settings (Table).

Seizure Disorders: VPA is a broad spectrum AED that has been used for almost all types of seizures. The recommendations and guidelines for use of VPA in epilepsy have been illustrated in Table.

Epilepsy: Valproic acid is the drug of choice for the idiopathic generalized epilepsy, absence seizures (along with myoclonic seizures, juvenile myoclonic epilepsy, and atonic seizures. It is effective against focal less so than carbamazepine. VPA has even been found to be effective in febrile seizure prophylaxis but is not recommended for the same due to the self-limiting and benign nature of the disease.

Epileptic Encephalopathies: For management of children with West syndrome, the drug of choice is ACTH (non-tuberous sclerosis complex) or Vigabatrin (tuberous sclerosis complex). However, in limited literature, valproic acid has been effective for treating infantile spasms (Class IV evidence stiripentol along with valproic acid and clobazam has been proposed as the most effective therapy for Dravet syndrome. VPA has also been reported be effective in children with Lennox-Gastaut syndrome (LGS). It has been suggested as the first line treatment for children with LGS myoclonic astatic epilepsy. Among patients with continuous spike and wave during sleep (CSWS; First line – clobazam, corticosteroids), and Landau Klefner syndrome (First line-corticosteroids), VPA has been proposed as an adjunctive AED.

Status Epilepticus: Limited data have shown

efficacy of valproic acid in children with status epilepticus. In one retrospective study, an initial loading dose of 25 mg/kg was effective in stopping seizure activity within 20 minutes after the end of the infusion in all 18 patients treated epilepticus. A separate retrospective trial found a higher efficacy rate in paediatric patients who received an initial loading dose of 30 mg/kg (73.3%, n=15) compared to 20 to 30 mg/kg (46.2%, n=26) or >40 mg/kg (40%, n=10) (24). In an open-label, randomized comparative trial, loading dose of 30 mg/kg was administered (n=20; age range: 7 months to 10 years of age; mean age: 3 years); a repeat bolus of 10 administered if seizures were not controlled within 10 minutes; mean required dose: 37.5 ñ 4.4 mg/kg; median required dose.

Dosing of Valproic Acid

Seizure disorders: It is started at a dose of 10 mg/kg/day in two divided doses. The drug is then increased in increments of 10 mg/kg/day every 3 days to reach the maintenance dose of 20-40mg/kg/day. In special circumstances of refractory epilepsy doses up to 60 mg/kg/day have also been administered. However, caution is advised at doses above 40 mg/kg/day with regular monitoring of liver function tests and plasma ammonia.

Status epilepticus: Loading dose of VPA, 20-30 mg/kg, is administered by intravenous infusion @ ó 6 mg/kg/min, which should be followed by maintenance VPA administration at a dose of 20 mg/kg/day. VPA maintenance is initiated 12 hours after the loading dose.

Migraine prophylaxis: In children aged 7 years and adolescents aged 16 years, VPA is initiated at 10 to 15 mg/kg/day in 2 divided doses (maximum initial mg/dose). Thereafter, it can be titrated as needed over 4 to 6 weeks to 40 to 45 mg/kg/day in 2 divided doses (maximum daily dose: 1,000 adolescents >16 years). VPA is started at 250 mg twice daily and increased based on patient's response to maximum of 1000 mg/day. Bipolar disorders: VPA is started at 10-15 mg/kg/day in two divided doses and increased to 60 mg/kg/day for desired effects.

Potential Therapeutic Targets: Apart from the aforementioned clinical settings VPA is being tried in various other disorders as well.[4] They have been listed in the Table.

Drug Interactions

To date a total of 606 drugs are known to interact with VPA, 12 major, 546 moderate, and 48 minor interactions (http://www.drugs.com/). List of commonly used drugs that can alter serum valproic acid levels have been depicted in table 4.[6] Co-administration of VPA with other AEDs can influence pharmacokinetics both VPA and other AEDs (Table 5 Adverse Reactions).

The adverse effects of VPA have been illustrated.[28] The most common adverse effects include sleep disturbances, dizziness,abdominal pain/ dyspepsia, rash, increased appetite/ weight gain, tremors, alopecia, and hirsutism. The more serious adverse effects include hepatotoxicity (idiosyncratic Reye's like syndrome), hyperammonemic encephalopathy, mitochondrial toxicity, pancreatitis, Stevens Johnson syndrome/toxic epidermal necrolysis and aplastic anemia.

Hepatotoxicity

5 to 10% of persons develop asymptomatic and naturally resolving ALT elevations during long-term valproic acid therapy, needing no discontinuation of drug as shown by several prospective studies.

Besides this simple aminotransferase elevation, three clinically distinguishable forms of hepatotoxicity can occur with valproic acid. All three forms of valproic acid hepatotoxicity have features of mitochondrial injury and liver histology, usually demonstrate microvesicular steatosis with variable amounts of inflammation and cholestasis. Young age (<2 years), presence of other neurological conditions and concurrent use of anticonvulsants appear to be important risk factors for acute liver failure due to valproic acid.

The first syndrome is hyperammonemia with minimal or no evidence of hepatic injury. Syndrome typically presents with progressive and episodic confusion followed by obtundation and coma. The time to onset is often within a few of starting valproic acid or increasing the dose, but it can

present months or even years after starting the medication. The diagnosis is made by finding of elevations in serum ammonia with normal (or near normal) serum aminotransferase and bilirubin levels. Valproic acid levels are usually normal or minimally high. The syndrome resolves within a few days of stopping valproic acid, but may reverse more rapidly with carnitidine supplementation and or renal hemodialysis. The second form of injury from valproic acid is an acute hepatocellular injury with jaundice, typically accompanied by hepatocellular or mixed pattern of enzyme elevations. This acute liver injury pattern usually has its onset within 1 to 6 months of pattern of serum enzyme elevations, can be hepatocellular or mixed; sometimes the serum aminotransferase levels are not markedly elevated, despite the severity of injury. Prospective studies using historical controls suggest that carnitine (particularly intravenously) may be beneficial if given soon after presentation.

The third form of hepatic injury due to valproic acid is a Reye-like syndrome described in children on valproic acid that develop fever and lethargy (suggestive of a viral infection) followed by confusion, stupor and coma, with raised ammonia levels and marked ALT elevations but normal or minimally elevated bilirubin levels. Metabolic acidosis is also common and the syndrome can be rapidly.

Valproic Acid and Liver : 4 Clinical scenarios and manifestations:

Characteristics	Common	Confusion-coma	Hepatocel-luar	Reye's Like (children)
Liver Enzymes (ALT/AST)	Mild to moderately raised	Near normal	Raised minimally or significantly	Markedly raised
Ammonia	Normal	Raised	Normal	Raised
Bilirubin	Normal	Normal	Raised	Near nor-mal
Clinical presentation	Normal	Confusion/ coma	Signs of he-patocellular failure	Confusion/ coma and metabolic acidosis
Action	Continue VPA	Stop VPA	Stop VPA	Stop VPA
Treatment	Nil reassure parents / doctors	ORAL/IV Carnitine or hemodial-ysis	IV carnitine	Support-ive, alkali

Monitoring

Some clinicians recommend monitoring complete blood counts (including platelet counts) at baseline, then monthly for three months, and every three months thereafter. **However, currently routine monitoring of drug levels and hematological/biochemical parameters are not recommended.** In an event of features of an adverse effect, the following tests should be performed: complete blood count, liver function tests, serum electrolytes, plasma ammonia and serum valproic acid levels.

Contraindications are important and must be known to everyone and thought of by all who use valproic acid.

Contraindications to VPA include:

Known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase gamma (POLG; e.g., Alpers-Huttenlocher syndrome [AHS]) or children years of age suspected of having a POLG-related disorder.

Urea Cycle Defect

Hypersensitivity to valproic acid, divalproex, derivatives, or any component of the formulation

Hepatic disease or significant hepatic impairment

Special Considerations

Children up to 2

Neonates, infants, and children <2 years of age are at considerably increased risk for hepatotoxicity/hepatic failure, especially those on anticonvulsant polytherapy, with congenital metabolic disorders, with severe seizure disorders and mental retardation, or with organic brain disease. It is imperative to monitor these patients <2 years closely for appearance of malaise, loss of seizure control, weakness, facial edema, jaundice, and vomiting; to monitor liver enzymes prior to therapy and at 4-6 weeks intervals, especially during the first 6 carnitine is clearly indicated for the management of valproic acid overdose and hepatotoxicity, with the available evidence the routine prophylactic carnitine supplementation is not recommended.[30, 31] In this age group of less than years, a valproic acid-associated Reye's-like syndrome has also been reported.

Rare multiorgan hypersensitivity reactions have

been reported in paediatric patients in association with initiation of valproic acid. Patient may present with fever and rash in association with symptoms of organ system dysfunction [e.g., lymphadenopathy, hepatitis, abnormalities in liver function tests, hematologic abnormalities (eosinophilia, neutropenia, thrombocytopenia), pruritus, oliguria, nephritis, arthralgia, asthenia], drug related eosinophilia and systemic symptoms (DRESS); valproic acid and derivatives should be discontinued in patients suspected of having multiorgan hypersensitivity reactions.

Adolescent girls:

The adverse effects including hirsutism, weight gain and polycystic ovarian syndrome (risk x1.95 times) assumes greater significance among adolescent girls.[32] These should be balanced against the therapeutic benefits and discussed with the family before initiating VPA among adolescent girls.

Pregnancy and lactation:

VPA intake during pregnancy is contraindicated.[33,34] It has been associated with increased risk of neural tube defects, microcephaly, heart defects, and diaphragmatic hernia.[35] Also, it has been shown that low doses of VPA are secreted in breast milk. However, these VPA levels in breast milk are insignificant and do not impact infant's growth or development.[36] Nonetheless, it is recommended that infant's breast-feeding on mothers taking VPA should be monitored for jaundice and petechial rash. The intake of combination AEDs rather than VPA monotherapy among breast feeding mothers may be more hazardous. FDA has labeled VPA as category "2" for lactation (i.e., use with caution), while for pregnancy it has been provided with Category "D/X" label (i.e., should not be used in pregnancy).

Conclusion

VPA is a broad spectrum of AED with a beneficial effect in practically all known epilepsies. However, it is important to avoid its use in children with proven or suspected mitochondrial disorders. Also, its use should be cautious in children less than two years of age and among those on lamotrigine co-therapy.

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Table 1. Indications and dose of valproic acid

No.	Indication	Dose
1.	Seizures/ Epilepsy	Start: 10 mg/kg/day Increase by 10 mg/kg/day every 3 days Maintenance: 40 mg/kg/day In refractory seizures maintenance dose of 60 mg/kg/day can been administered Dose to be administered in two divided doses
2.	Status Epilepticus	Initial: 20-30 mg/kg IV infusion @ 6 mg/kg/min Additional 20 mg/kg can be administered after 15-20 minutes if required to a maximum of 40 mg/kg
3.	Migraine prophylaxis	Children ≥7years and adolescents ≤16 years: Initial: 10 to 15 mg/kg/day in 2 divided doses; maximum initial dose: 250 mg/dose. Titrate as needed over 4 to 6 weeks to 40 to 45 mg/kg/day in 2 divided doses; maximum daily dose: 1,000 mg/day Adolescents >16 years: Initial: 250 mg BD; titrate as needed to maximum of 1000 mg/day
4.	Bipolar Disorders	Initial: 10-15 mg/kg/day Titrate upwards to maximum of 60 mg/kg/day
• Dose escalation is at a rate of 5-10 mg/kg/day every 3-5 days • Monitor for side effects at doses >40 mg/kg/day		

Table 2. Guidelines for use of valproic acid in epilepsy

No.	Type of Seizure	ILAE (2013) recommendations (14)	NICE recommendations (15)
1.	GTCS	• VPA is possibly efficacious as monotherapy (Level C). • Others including CBZ, PB, PHT, and TPM are possibly (level C) and OXC is potentially (level D) efficacious/ effective for children with newly diagnosed or untreated generalized-onset tonic–clonic seizures.	• VPA as first line treatment
2.	Absence seizures	• VPA (and ETM) are efficacious as monotherapy as initial monotherapy for children with newly diagnosed or untreated absence seizures (Level A).	• VPA as the first line treatment
3.	Benign childhood epilepsy with centrotemporal spikes (BECTS)	• VPA (and CBZ) are efficacious as monotherapy (Level C). • GBP, LEV, OXC, and STM are potentially (level D) efficacious/effective as initial monotherapy for children with BECTS.	• VPA as the first line treatment (along with CBZ, LTG, OXC, LEV)
4.	Juvenile Myoclonic Epilepsy	• VPA (and TPM) are potentially efficacious/effective for patients with newly diagnosed JME (Level D).	• VPA as the first line treatment (along with LTG, LEV, TPM)
5.	Partial Seizures	• OXC is established (level A); CBZ, PB, PHT, TPM, VPA, and VGB are possibly (level C); and CLB, CZP, LTG, and ZNS are potentially (level D) 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
6.	Myoclonic	Not mentioned separately	- VPA as the first line drug
7.	Atonic seizures	Not mentioned separately	• - VPA as the first line drug

Levels of Evidence (For ILAE recommendations):
1. Class A: ≥1 Class I studies or meta-analysis meeting class I criteria sources OR ≥2 Class II studies
2. Class B: 1 Class II study or meta-analysis meeting class II criteria
3. Class C: ≥2 Class III double-blind or open-label studies
4. Class D: 1 Class III double-blind or open-label study OR ≥1 Class IV clinical studies OR Data from expert committee reports, opinions from experienced clinicians

Other seizures/epileptic encephalopathies where VPA has been found to be effective:
1. West syndrome (Class IV Evidence) (19)
2. Dravet syndrome (along with Stiripentol and CLB) (20)
3. Benign myoclonic epilepsy of infancy (20)
4. Lennox-Gastaut syndrome (22)
5. Myoclonic astatic epilepsy (22)
6. Continuous spike and wave during sleep (CSWS; First line- CLB, corticosteroids) (22)
7. Landau Klefner syndrome (First line-corticosteroids) (22)

Abbreviations: CBZ: Carbamazepine; CLB: Clobazam; CZP: Clonazepam; LEV: Levetiracetam; LTG: Lamotrigine; OXC: Oxcarbazepine; PB: Phenobarbitone; PHT: Phenytoin; TPM: Topiramate; VBG: Vigabatrin; VPA: Valproic Acid; ZNS: Zonisamide

Table 3. Ongoing clinical studies with valproic acid

Neurological Disorders
1. Spinal muscular atrophy type I 2. Autism 3. ADHD 4. Bipolar disorder 5. Cluster headache 6. Dementia 7. Depression 8. Mood disorder 9. Neuralgia 10. Schizophrenia 11. Amyotrophic lateral sclerosis
Malignancies
1. Autoimmune lymphoproliferative syndrome 2. CNS tumors 3. Breast cancer 4. CLL 5. HTLV-1 associated myelopathy 6. Nasopharyngeal carcinoma 7. Sarcoma
Dependences
1. Alcohol abuse or dependence 2. Cocaine dependence 3. Marijuana abuse
Others
1. Asthma 2. Hypersplenism 3. Insulin resistance

Table 4. Interaction of valproic acid 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

Table 5. Effect of other antiepileptics on valproic acid

Antiepileptic Drugs	Effect on Valproic Acid
Carbamazepine	Valproic acid levels decrease to 75% of pre-polytherapy level
Phenytoin	Valproic acid levels decrease to 75% of pre-polytherapy level
Phenobarbitone	Valproic acid levels decrease to 75% of pre-polytherapy level
Levetiracetam	Valproic acid levels unchanged
Ethosuximide	Valproic acid levels decrease to 28-37% of pre-polytherapy level

Table 6. Effects of Valproic acid on other antiepileptic drugs

Antiepileptic drug	Effect on its level on co-administration with valproic acid
Lamotrigine	Lamotrigine levels increase by 85%
Topiramate	Topiramate levels stay unchanged
Felbamate	Felbamate levels increase by 27%

Table 7. Adverse effects of valproic acid

Very common (10% or more)	Common (1% to 10%)	Uncommon (0.1% to 1%)	Rare (< 0.1%)	Frequency not reported
Gastro-Intestinal				
a. Abdominal pain b. Diarrhea c. Dyspepsia d. Gingival disorder e. Nausea f. Vomiting	a. Constipation b. Dry mouth c. Eructation d. Fecal incontinence e. Flatulence f. Gastroenteritis g. Glossitis h. Periodontal abscess i. Hematemesis j. Stomatitis	a. Pancreatitis (life-threatening)		
Hepatic				
	a. Increased liver enzymes (ALT and AST) particularly early in treatment			a. Severe liver damage (including hepatic failure sometimes resulting in death), increased serum bilirubin
Neurological				
a. Dizziness b. Headache c. Somnolence d. Tremor	a. Gait abnormality b. Amnesia c. Catatonic reaction d. Disturbance in attention e. Dysarthria f. Extrapyramidal disorder g. Hypertonia h. Hypokinesia i. Incoordination j. Increased reflexes k. Memory impairment l. Nystagmus m. Paresthesia n. Speech disorder o. Stupor p. Tardive dyskinesia q. Taste perversion	a. Ataxia b. Coma c. Encephalopathy d. Lethargy e. Reversible parkinsonism	a. Cognitive disorder b. Reversible dementia associated with reversible cerebral atrophy	a. Cerebral atrophy b. Dementia

Very common (10% or more)	Common (1% to 10%)	Uncommon (0.1% to 1%)	Rare (< 0.1%)	Frequency not reported
Dermatologic				
a. Alopecia	a. Discoid lupus erythematosus b. Dry skin c. Ecchymosis d. Furunculosis e. Maculopapular rash f. Petechiae g. Pruritus h. Rash i. Seborrhea	a. Abnormal hair texture b. Abnormal hair growth c. Hair color changes d. Sweating	a. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome b. Erythema multiforme c. Stevens-Johnson syndrome d. Toxic epidermal necrolysis	a. Acne b. Hirsutism c. Angioedema d. Generalized pruritus e. Photosensitivity
Endocrine				
		a. Hyperandrogenism b. Syndrome of inappropriate ADH secretion	a. Hypothyroidism	a. Abnormal thyroid function tests b. Elevated serum testosterone concentrations c. Parotid gland swelling
Genitourinary				
	a. Amenorrhea b. Cystitis c. Dysmenorrhea d. Dysuria e. Enuresis f. Metrorrhagia g. Urinary incontinence h. Urinary frequency i. Vaginal hemorrhage j. Vaginitis			a. Breast enlargement b. Galactorrhea c. Polycystic ovary disease
Hematologic				
a. Thrombocytopenia	a. Anemia b. Hemorrhage	a. Leucopenia b. Pancytopenia	a. Abnormal coagulation tests (e.g., prolonged PT, aPTT, INR) b. Agranulocytosis c. Decreased coagulation factors d. Pure red cell aplasia e. Macrocytosis	a. Aplastic anemia b. Bone marrow suppression c. Bruising d. Eosinophilia e. Frank hemorrhage f. Hypofibrinogenemia g. Anemia including macrocytic with or without folate deficiency h. Relative lymphocytosis

Very common (10% or more)	Common (1% to 10%)	Uncommon (0.1% to 1%)	Rare (< 0.1%)	Frequency not reported
Metabolic				
a. Weight gain	a. Increased appetite b. Hyponatremia		a. Hyperam-monemia	a. Acute intermittent porphyria b. Minor elevations of LDH (dose related) c. Decreased carnitine concentrations d. Hyperglycinemia
Psychiatric				
a. Nervousness	a. Abnormal dreams b. Agitation c. Anxiety d. Aggression e. Confusion f. Depression g. Emotional lability h. Hallucinations i. Insomnia		a. Abnormal behavior b. Learning disorder c. Psychomotor hyperactivity	a. Behavioral deterioration b. Psychosis

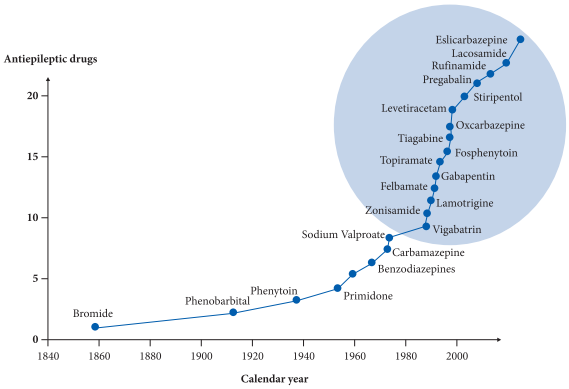

Figure 1. Chronological evolution of antiepileptic drugs (1)

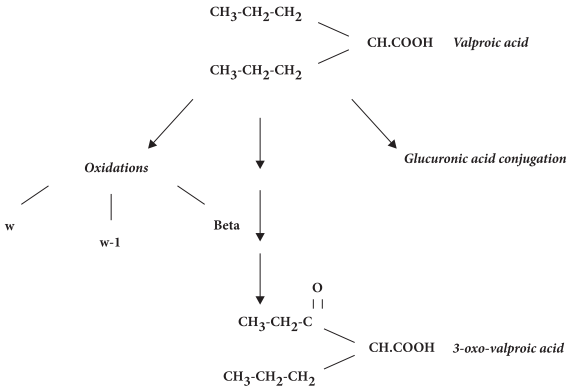

Figure 2. Major valproic acid metabolic pathways. The inactive forms are shown in lighter shade. (6)

Valproic Acid Use in Girls and Women with Epilepsy

Sanjeev V. Thomas

Introduction

It is estimated that there are about 1.2 million women with epilepsy in India who are in the reproductive age group. There is a complex interaction between the reproductive sex hormones, AEDs and epilepsy that makes women more prone to seizures during certain periods of their reproductive cycle or menstrual cycle. Several studies have shown that seizure freedom is the single most important predictor of good quality of life for people with epilepsy. Most women with active epilepsy would require continuation of treatment with antiepileptic drugs during pregnancy in order to remain seizure free. Antenatal exposure to anti-epileptic drugs can increase the risk of fetal malformations and long term neurocognitive developmental problems to the babies. Hence safety of the mother and baby is a major concern for women with epilepsy as they prepare for pregnancy. Considering the special situation of pregnancy, it is unlikely that prospective controlled clinical trials of antiepileptic drugs (Class I studies) would be undertaken. The pregnancy outcome of women with epilepsy had been under systematic studies for the past two decades. The prospective pregnancy registries had been set up in the UK (1996), North America (1997), Kerala (1998), Europe (1999) and Australia (2000) in order to address this research theme. The enrolment policies, methods and timing of ascertainment and definition of outcome measures vary between the registries to some extent. The neurocognitive outcome of the children born to women with epilepsy had been under scrutiny in the UK, North America (NEAD study) and Kerala (KREP). The observations from these registries and other studies have helped us to develop evidence based recommendations on management of epilepsy in pregnancy. This paper will be focussing on the safety of using valproic acid during pregnancy.

Indications for Valproic Acid

Valproic acid is a broad spectrum antiepileptic drug that is effective against a variety of seizure types and epilepsy syndromes starting in infancy to adulthood (Table 1). As a result it is not uncommon to find girls who are started on valproic acid continue it in to adolescence and womanhood, when the pregnancy related concerns commence.

Table 1: Epilepsy/Seizure Types
Absence seizures
Myoclonic seizures
Generalised tonic-clonic seizures
Epilepsy syndromes
Febrile seizures
Idiopathic Generalized Epilepsies
Childhood Absence Epilepsy
Juvenile Absence Epilepsy
Juvenile Myoclonic Epilepsy
Idiopathic Generalized Epilepsy
Localization related (Focal) Epilepsies
Benign childhood epilepsy with Centrotemporal Spikes
Other localization related epilepsies
Epileptic encephalopathies
West syndrome (infantile spasms)
Lennox-Gastaut Syndrome (LGS)
Landau-Kleffner syndrome (LKS)
Progressive myoclonic epilepsies

Adverse Effect Profile of Valproic Acid

Valproic acid can cause several adverse effects that can be particularly bothersome to women (Table 2).

Table 2. Adverse effects of valproic acid that can be of major concern to women with epilepsy
Hair loss
Tremor
Obesity
Menstrual irregularity
Polycystic ovarian syndrome
Infertility
Osteoporosis
Teratogenic effects and impaired cognitive development in prenatally exposed offspring

Fetal adverse effects of Valproic Acid

The potential risk of fetal malformations and late cognitive developmental problems of children are the most serious concern for girls and women with epilepsy.

Birth defects

Data from the retrospective population based studies in Norway[1] and Denmark[2] have shown that children of women with epilepsy who had used valproic acid carried increased risk of birth defects. The prospective cohort studies through the major pregnancy registries in UK[3], USA[4], Europe[5], India[6] and Australia[7] have confirmed the increased risk of neural tube defects and other major congenital malformations for children with antenatal exposure to valproic acid. The data from UK, EURAP and India have further shown that the risk of major malformations is proportionate to the dosage of valproic acid during pregnancy.[5]

Cognitive Adverse Effects

Recent studies from UK had for the first time pointed towards increased risk of educational backwardness for older children with antenatal exposure to valproic acid.[8] The data from the KREP had shown that children with antenatal exposure to AEDs performed significantly poorer than those without any exposure when examined at one year,[9] six years[10] and twelve years[11] of age. Those exposed to valproic acid had a trend towards poorer performance, when compared to those exposed to other AEDs in monotherapy. The data from the NEAD study had confirmed that antenatal exposure to valproic acid carried a dose dependent increased risk of lower IQ at three years[12] and six years of age.[13] The data from this registry had further confirmed the dose dependency of the cognitive developmental delay.

Importance of Seizure Control for Women with Epilepsy

The very objective of treatment of epilepsy is control of seizures, which is particularly relevant for women. The impact of social stigma is more for women than for men. Their social position, prospects of marriage, integration in the family and society at large depend on complete control of seizures. Occurrence of even breakthrough seizures in the middle of prolonged seizure freedom can jeopardize their functional status and add to their disability. Women with epilepsy who were married on the understanding that they are in remission may find their marriage at stake, if seizures recur during pregnancy or otherwise.

Women with idiopathic generalized epilepsy (generalized genetic epilepsy) are a subgroup that often achieve complete remission of seizures with medications and have normal cognitive functioning. Their prospects of education, employment and successful marriage are higher than others with frequent seizures or cognitive impairments. Those with juvenile myoclonic epilepsy are the typical prototypes of this subgroup.

Previous studies have shown that valproic acid is one AED that successfully controls seizures in JME and other types of IGEs.[14] It is a broad spectrum drug that is effective against myoclonus, generalized seizures and focal seizures with or without secondary generalization. It has no interaction with oral contraceptives.

The therapeutic efficacy of valproic acid vis-a-vis its adverse effects on the mother and the fetus has led to wide debate on its precise role in the treatment of epilepsy in girls and women. The various regulatory bodies and professional organizations have been attempting to bring in standardized guidelines on when and how to use valproic acid in women with epilepsy (See Table 3).

Indian Scenario

A modest estimate shows that there are at least 15 million women with epilepsy in the reproductive age group. The treatment gap of epilepsy ranges from 35 - 85% in certain areas of the country. Cost of the drugs, lack of continuous availability of AEDs in local dispensaries and hospitals, poor understanding of the illness and social stigma are important barriers to good compliance with treatment of epilepsy in India. This is further aggravated by the gender related restrictions for women to travel to hospitals for epilepsy care. The social stigma of epilepsy is often too restrictive for women to access health care for epilepsy. The lack of economic autonomy for women with epilepsy can limit the access to expensive investigations or therapy. A major proportion of pregnancies in India are unplanned as the proportion of women who access effective methods of contraception and plan pregnancy in India are less than the desired levels. These special situations need to be kept in mind while recommending treatment of epilepsy in women of reproductive age group.

Management of Epilepsy in Women who are Planning their Pregnancies

The clinicians need to initiate discussion on the impact of epilepsy and continuation of treatment with antiepileptic drugs for girls in their late teens as some of them may get married early. Since a large proportion of pregnancies in India are unplanned the clinician should take time to discuss with the woman and her relatives the possible adverse effects of antiepileptic drugs vis-a-vis the need for

Table 3: Summary of recommendations from major guideline organizations

Guideline	Year of updating	Main recommendation
ILAE Commission on European Affairs Recommendations[15]	July 2015	Valproic acid to be avoided in women with focal epilepsies. When used in women of child bearing potential, lowest effective dose of valproic acid should be used aiming at a dosage less than 600 mg per day. Women of childbearing potential who are not planning pregnancy and continue treatment with valproic acid should utilize effective contraception methods or otherwise ensure that unplanned pregnancies can be avoided.
NICE Guidelines[16]	Jan 2015	We are assessing the impact of this on the guideline. In the meantime, healthcare professionals are advised to use the guideline in conjunction with the latest MHRA advice.
European Union (EMA) recommendations[17]	Nov 2014	Doctors in the EU are now advised not to prescribe valproic acid for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproic acid is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.
US FDA recommendations[18]	June 2013	Valproic acid contraindicated for migraine prevention in pregnant women. It is a category X drug for migraine prevention. With regard to valproic acid use in pregnant women with epilepsy or bipolar disorder, valproic acid products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. Valproic acid products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder. With regard to women of childbearing age who are not pregnant, valproic acid should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproic acid products should use effective birth control.

continued medical treatment to maintain seizure freedom. It is important to carefully balance the efficacy of valproic acid in controlling epilepsy and maintaining seizure freedom with the potential adverse effects on the fetus including risk of birth defect and long term cognitive developmental issues. A shared decision making in which the clinician invites the patient and if possible the responsible family members to participate in the decision making with regard to the choice of antiepileptic drugs. It is important that the physician explains in simple terms the potential risk from breakthrough seizures as well as the adverse effects to the fetus and help the patients and their family members to make informed choices. The priorities of the patients with regard to need for seizure control, cost of treatment, access to medications and care, impact of relapse of seizure on social stigma, family relationships, driving, employment and adverse effects on fetus need to be given due considerations.

As general guidelines it can be stated that:

1. Valproic acid should preferably be avoided as the first line drug for treatment of epilepsy in girls and women of reproductive age.
2. Valproic acid may be avoided in obese women with history of menstrual irregularities or polycystic ovarian syndrome.
3. Whenever possible valproic acid dosage need to be maintained below 600 mg per day for adult women.
4. Valproic acid can be continued (preferably in low dose) in women in reproductive age group who are already in long term remission of epilepsy while on valproic acid.
5. Low dose valproic acid (<600 mg per day) may be considered under certain circumstances as one of the first line drugs for treating newly diagnosed generalized epilepsy in girls and women of reproductive age group after a full discussion on its risk to the patient.
6. Valproic acid can be used as a first line drug to treat age specific epilepsies of childhood such as absence or BECT that are known to resolve before puberty.
7. Valproic acid can be used in girls and women who are unlikely to become pregnant (girls with epileptic encephalopathies or significant co-morbidities and women who had undergone sterilization or have become menopausal).
8. All women and caregivers for girls should receive full information of the benefits and risks prior to treatment with valproic acid.
9. All women with childbearing potential need to be prescribed folic acid 5 mg daily.

Management of Pregnancy in Women who are on Valproic Acid

Once a woman is identified to be pregnant, there is little benefit from attempting to switch to other monotherapy/polytherapy. However, a dose reduction to less than 600 mg per day can be considered in early pregnancy in those who are in remission.

All Women with Epilepsy (WWE) need to continue folic acid 5 mg daily throughout pregnancy although its beneficial effects are not proven.

All pregnant women with epilepsy need to have a screening of serum alpha feto protein and a level III antenatal ultrasonography to carefully evaluate the fetal organs for any malformations.

Breastfeeding by Women who are Using Valproic Acid

The benefits of breast feeding outweigh the potential risk from the exposure to valproic acid through breast milk. There was no correlation between the child's IQ and exposure to antiepileptic drugs through breast milk.

Should a Woman Avoid Pregnancy if she is Using Valproic Acid as an Antiepileptic Drug?

The likelihood of achieving seizure remission and AED withdrawal within a reasonable period of time vis-a-vis the risk from AED exposure need to be taken considered carefully and weighed while reaching a decision regarding timing of pregnancy. The indefinite postponement of pregnancy anticipating AED withdrawal may not be wise as pregnancies beyond 30–35 years of age carry higher maternal and fetal adverse effects. The social commitments, other health conditions of the women are important aspects that can influence decisions regarding

planning of pregnancy. These factors have important bearing on the long term cognitive/behavioral outcomes of the children also. The woman and/or her caregiver should receive full information about the benefits and adverse effects of use of valproic acid during pregnancy so that they can participate in the shared decision making with the clinician.

These consensus statements on the use of valproic acid in girls and women would require further assessment after three years as considerable amount of new data are emerging from the various registries and cohort studies on the maternal and fetal adverse effects of use of valproic acid in the antenatal period.

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Valproic Acid in Epilepsy with Various Comorbidites and Systemic Disorders

Atma Ram Bansal and Neeraj N. Baheti

Epilepsy is a chronic disorder in majority. As with other chronic disorders, co-morbid conditions can frequently occur in epilepsy and may significantly affect epilepsy and its treatment. A person with epilepsy can have other systemic disorders requiring other medications. A detailed understanding of the interrelationships between comorbidities, systemic disorders and their treatments is optimal for effective management of patients. Valproic acid is a first line broad spectrum antiepileptic drug which is useful across all age groups and multiple seizure types. In this chapter we will review usefulness of valproic acid in persons with epilepsy and comorbidities and/or systemic disorders.

Valproic Acid in Epilepsy with Various Comorbidities

Mood disorders (see Table 1)

Depression is a very common undiagnosed and untreated comorbidity in patients with epilepsy especially refractory epilepsy with occurrence rate of 3 to 10 times more than general population.[1] The frequency of depression among medically refractory epilepsy populations can be as high as 50%, while in patients with controlled seizures the frequency is closer to 10%.[2] Depression in patients with epilepsy may relate to dysfunction in the prefrontal, inferior frontal, striatal, and mesial temporal regions.[3] Antiepileptic drugs (AEDs) are also known to exacerbate depression. Common such AEDs are phenobarbital, primidone, tiagabine, vigabatrin, and the benzodiazepines can exacerbate depression. Felbamate, levetiracetam, topiramate, and zonisamide have also been associated with depression.[4] Certain AEDs like carbamazepine, lamotrigine and valproic acid have mood stabilizing property. When assessing an epilepsy patient with depression, it is important to note whether AEDs with positive psychotropic properties (i.e., carbamazepine, lamotrigine, and valproic acid) have recently been discontinued, or whether AEDs with negative psychotropic properties (i.e., benzodiazepines, felbamate, levetiracetam, phenobarbital, primidone, tiagabine, topiramate, vigabatrin, and zonisamide) have been recently added or the dosage increased. Valproic acid increases extracellular serotonin[5] and also stimulates brain dopamine turnover thus making it an antiepileptic of choice in persons with concomitant mood disorders.[6] Following points need attention in a patient with epilepsy and mood disorders.

- During discontinuation of valproic acid, the person with epilepsy may show features of affective disorder like mania or depression and should be taken care of accordingly.
- Valproic acid can be a good choice in patient with affective disorder especially mania or bipolar disorder in view of its mood stabilizing property. It is particularly effective in bipolar affective disorder especially with rapid cycling and dysphoric mania.[7]
- Valproic acid is helpful in certain psychological symptoms like hostility, impulsivity, and aggression.

Migraine

Migraine and epilepsy are two neurological disorders with many similarities like episodic attacks, chronic disorders with associated autonomic and gastrointestinal symptoms. There are similarities in pathophysiology and treatment as well. Kindling, a pathological change characterized by lowering the threshold for subsequent attacks in epilepsy, has some similarities with sensitization of pain in migraine.[8] The people with epilepsy are more likely to have migraine and at the same time

epilepsy is more common in people with migraine than general population.[9, 10] In 1988, an open label study showed the effectiveness of valproic acid in migraine prevention.[11] Subsequently there have been double blind randomized studies on valproic acid monotherapy for migraine prophylaxis including extended release of valproic acid.[12,13]

Valproic acid mainly acts via GABA mediated transmission in epilepsy as well as in migraine. It inhibits GABA transaminase inhibitor and activates glutamic acid decarboxylase which leads to reduction in inflammation seen in migraine.[14]

As per AAN guidelines, valproic acid and divalproex sodium, both have level A recommendation (more than 2 class I trials) for use in migraine prophylaxis in adults.[15] In the recent Cochrane review, valproic acid is found to be effective in reducing headache frequency and is reasonably well tolerated in adult patients with episodic migraine.[16] Parentral valproic acid is also effective in aborting acute attack of headache in status migrainosus.[17] However, due to its potential teratogenic effects, it should be avoided in young women of 3 child bearing age group.

Systemic Disorders and Role of Valproic Acid

Thyroid disorders

There are conflicting reports of effects of valproic acid on thyroid functions. Majority of the reports mention minimal (subclinical) suppression of thyroid functions with valproic acid. But the changes are transient and reversible with withdrawal of medication.[18]

Obesity

Weight gain is a well-known adverse effect of VPA treatment, occurring in 40% of children and nearly 50% of women especially in younger age group. Pathophysiologically, an increase in serum insulin and insulin/glucose levels may cause weight gain, possibly by stimulating appetite. Although usually reversible, the weight gain can sometimes be progressive leading to hyperandrogenism and polycystic ovaries. Valproic acid should be used with caution in obese with an advice regarding dietary and life style modifications with frequent weight monitoring.

Polycystic ovarian syndrome

Increased rates of polycystic ovarian syndrome, decreased libido, infertility, and early menopause have been described in women with epilepsy. Polycystic ovarian syndrome has been more frequently reported in association with genetic (idiopathic) generalized than focal epilepsy syndromes, although more women with generalized epilepsy received valproic acid treatment. Randomised study has shown that polycystic ovarian syndrome features developed more frequently during valproic acid than lamotrigine treatment and these metabolic changes are partially reversible on discontinuing valproic acid.[19,20]

Renal Failure

More lipophylic high protein bound AEDs like carbamazepine, phenytoin, and valproic acid are little affected by renal disease. Hemodialysis has little impact on valproic acid levels as they are highly protein bound.[21] Although valproic acid is safe in mild-to-moderate renal failure, there are reports of acute tubular necrosis following valproic acid use and Fanconi's syndrome.[22]

Hepatic Failure

Valproic acid is a wide-spectrum isoenzyme inhibitor and increases its own serum level and that of other drugs sometimes causing toxicity thus dose reduction may be required in setting of hepatic dysfunction. Valproic acid can lead to hepatotoxicity and Rey's syndrome as idiosyncratic reaction.[23] Further details are given in the chapter of side effects.

Osteoporosis

Bone mineral density measurements reveal osteopenia or osteoporosis in 38% to 60% of people with epilepsy receiving AEDs in specialty clinics.[24] Both men and women with epilepsy have elevated rates of fractures (two-to six fold higher) compared to the general population. Evidence suggests that AEDs have negative effects on bone mineral density through a variety of mechanisms including induction of cytochrome P-450 system enzymes. Valproic acid although is an enzyme inhibitor but it has a strong association with osteoporosis. For a patient who needs to be started on AEDs preferably newer non-enzyme inducing AEDs may be a better choice. If such a person requires valproic acid or is already on the same, calcium and vitamin D supplementation

may be prescribed. In elderly population, a regular interval Dexa scan may help to detect bone loss at early stage.

HIV Infection/AIDS

The American Academy of Neurology in conjunction with ILAE published guidelines for AED use in HIV.[25] Although there is laboratory evidence that valproic acid may increase HIV replication *in vitro* and thus it might lead to accelerated destruction by HAART but these findings needs to be replicated.[26] Valproic acid has been associated with hepatic and multiorgan failure when used with antiretroviral drugs.[27] Valproic acid also increases the level of zidovudine. Hence taking all the things into consideration, valproic acid should be used with caution in the treatment of epilepsy in patients with HIV/AIDS.

Neuropathic pain syndromes

Valproic acid is of uncertain efficacy for treating neuropathic pain syndromes and in this situation sodium channel blockers should be used preferably.[28]

Stroke

The risk for development of epilepsy is 17-fold higher after stroke than in the age matched general population; it is estimated that 10-15% stroke patients develop epilepsy.[29] Phenytoin, phenobarbitone and benzodiazepines interfere with stroke recovery and hence are best avoided. Among the antiepileptics, valproic acid has less stroke risk than phenytoin.[30] There is an increased risk of insulin resistance and metabolic syndrome[31] and hence should be used with caution in such group of patients. If a patient is on long term anticoagulation, VPA may have significant interaction due to enzyme inhibition and hence should be avoided.

Malignancies and patients on chemotherapy

Valproic acid exerts an antiproliferative effect on cancer cells *in vitro* and vivo due to histone deacyetylase inhibition. There are preliminary reports of use of valproic acid in hematological and solid tumors including glioblastoma multiforme.[32,33] Valproic acid may aggravate hematologic and other toxicities of chemotherapeutic agents due to enzyme inhibition hence it should be best avoided.[34]

Hematological disorders

Thrombocytopenia, leukopenia, bone marrow suppression, lymphadenopathy and exacerbation of acute intermittent porphyria have been reported with valproic acid.[35] In the presence of underlying primary hematological disorders it is best to avoid valproic acid.

Cardiovascular disorders

Although safe in patients with cardiac comorbidities, valproic acid being highly protein bound can displace warfarin, digoxin, and amiodarone from its binding sites. It can lead to cardiac arrhythmias, increased anticoagulation. Hence close monitoring is needed in this situation.

Valproic Acid in ICU Care

Valproic acid is a well proven and effective drug in status epilepticus. Valproic acid is an alternative agent to phenytoin and can be used in status epilepticus even in cases where phenytoin has failed. The detail of VPA use in status is mentioned in detail in status epilepticus chapter. It is a preferred agent in cases of primary generalized epilepsy with status or patient with myclonic status (post-hypoxic state like Lance Adam Syndrome) and in patients with absence or non-convulsive state. There is no effect of VPA on QT interval and hence can be used in patients with cardiac arrhythmia. Valproic acid is quite safe in mild-to- moderate renal dysfunction. However, in cases of seizures/status epilepticus with preexisting significant hepatic dysfunction VPA is better avoided.

If any patient already on valproic acid is admitted in ICU for any systemic issues then monitoring of liver function tests and ammonia may be useful. There is a very significant drug interaction with carbapenem antibiotics. There are several case reports on carbapenem antibiotics, especially meropenem causing decrease in the plasma concentrations of valproic acid (VPA), thus decreasing its therapeutic activity.[36] The reported decrease in plasma level of VPA is more than 80% within 24 hours of starting meropenem. Hence, there is a high risk of withdrawal seizure in a patient who is well controlled on VPA after starting meropenem. It is advised that both the drugs should not be administered concomitantly.

CNS infections

CNS infections like tubercular meningitis commonly present with seizures especially in adults. For acute management of seizure in TBM, VPA can be used however for long term management it is not

a very good choice in view of risk of drug interaction (enzyme inhibition) and hepatotoxicity. It is better to avoid VPA and if given, liver functions should be monitored at regular intervals.[37] In bacterial meningitis VPA can be used for treating seizures but it should be better avoided if patient is on carbapenems especially meropenem.

Valproic acid can be used as an effective treatment option for symptomatic seizure or status epilepticus with herpes encephalitis. However, it should be avoided in malarial fever and suspected dengue encephalitis, in view of added risk of thrombocytopenia. If the patient is already on VPA, it is advisable to monitor platelet counts regularly. Though no studies have mentioned any safe platelet counts to continue VPA but any platelet count below 50,000/cu mm may warrant change of valproic acid.

Perioperative management

Valproic acid is well known to cause various hematological abnormalities most common being thrombocytopenia. The risk of thrombocytopenia caused by valproic acid is 5%, and the risk increases with the age of the patient and with the level of valproic acid in the blood.[38] Hematologic abnormalities can be recurrent, transient, or persistent and can be reversed with dosage reduction; drug discontinuation is rarely required.[39] There are conflicting reports about the bleeding risk during surgery.[40, 41] It is advisable to monitor routine coagulation parameters before any planned surgery. If the patient is on high doses of VPA or on multiple medications or history of easy bruising or bleeding and especially in cases with anticipated considerable blood loss then a detailed coagulation study including platelet count, bleeding time, prothrombine time, partial thromboplastin time, fibrinogen, von Willebrand factor level and/or a thromboelastogram should be done before surgery.[42] In emergent situations one can use DDAVP in perioperative period to increase von Willebrand factor levels and improve platelet function.

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Table 1

	Drugs adversely affecting mood disorders	Drugs with positive impact on mood disorders
1	Levetiracetam	Valproic Acid
2	Benzodiazepines	Carbamazepine
3	Phenobarbitone	Lamotrigine
4	Topiramate	Oxcarbazepine

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