Key Words: divalproex, valproic acid, valproate, divalproex sodium, partial epilepsies, partial seizures, mechanism of action, efficacy, adverse effects

The Efficacy of Divalproex for Partial Epilepsies

By Michael C. Smith, MD

ABSTRACT *~ Valproic acid has clear efficacy in the treatment of partial epilepsies. Its multiple mechanisms predicted its broad spectrum of efficacy and preclinical experimental data prompted its clinical use. Valproic acid's efficacy has been repeatedly demonstrated in clinical trials over the past 25 years. Its efficacy in the treatment of partial epilepsies is similar or better than both the traditional and new antiepileptic drugs. Its side effect profile is well known and manageable, especially with extended-release formulations.*
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INTRODUCTION

Valproic acid is a unique antiepileptic drug (AED). Its simple short-chained branched fatty acid chemical structure differs significantly from other cyclic-structured anticonvulsants such as phenytoin, carbamazepine, and phenobarbital. Its broad spectrum of activity is well documented in both experimental models of epilepsy and in over 25 years of worldwide use for multiple types of epilepsies.

Burton synthesized valproic acid in 1882, but it had no known clinical use until its anticonvulsant activity was fortuitously discovered by Meunier in 1963.[1] Working in Carraz's laboratory screening compounds for anticonvulsant activity, valproic acid had been used as a vehicle for dissolving the active ingredients of experimental compounds because of its superior solvent properties. As multiple compounds showed efficacy in this testing, Meunier tested the vehicle and found that valproic acid itself had anticonvulsant properties. This led to the confirmation of valproic acid's effectiveness in protecting against pentylenetetrazol (PTZ)-induced seizures. Carraz reported the first clinical trial of valproic acid in 1964 and the drug came on the market in France in 1967.[2] Its initial use was in adjunctive therapy in intractable epilepsies, but it was quickly found to have great value as the primary treatment in generalized epilepsies. Valproate's efficacy for the treatment of generalized seizures will be discussed separately in this issue. This review will concentrate on the utility of valproic acid in partial seizures. Preclinical experimental data predicted the usefulness of valproic acid in partial epilepsies and prompted its clinical use.[3]

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PRE-CLINICAL TESTING OF DIVALPROEX

Classic AED Testing Results

The initial testing of a putative antiepileptic drug allows a rapid, relatively inexpensive, but reliable method of screening compounds for anticonvulsant activity.[3] Thousands of compounds have been evaluated by the testing program established by the National Institutes of Health (NIH). The two major tests used are maximal electroshock (MES) and subcutaneous PTZ (PTZsc). The MES testing has been found to predict the clinical usefulness in generalized tonic-clonic seizures and partial seizures with secondary generalization.[3] The PTZsc testing predicts usefulness for absence seizures and myoclonic seizures.

The dose of an AED that blocks the seizures in 50% of the trials establishes the effective dose 50% (ED50).[3] Toxicity is evaluated in the righting response and Rotorod testing. The righting response tests an animal's alertness, while the Rotorod tests coordination. Doses that show toxicity in 50% of the animals, as judged by these tests, give the toxic dose 50% (TD50). The ratio of ED50/TD50 provides the therapeutic index (TI).[3] The higher the TI, the more effective a drug is predicted to be in clinical practice. Those compounds with a higher TI go on to the time-consuming and expensive clinical trials that allow for the Food and Drug Administration's (FDA's) approval, commercial production, and widespread clinical use. Valproic acid was shown by Swinyard and many other investigators to have good protection against MES and PTZsc testing, as well as a favorable TI.[3,4]

These results led to testing and demonstration of efficacy in other models of generalized seizures, including bicuculline, glutamic acid, and strychnine, as well as the feline model of absence seizure induced with penicillin.[3] Preclinical models for partial epilepsies also showed good efficacy and a favorable TI. Valproate, given by intermittent intraoperational injections, was found to be quite effective in suppressing the generalization of focal seizures induced by aluminum/cobalt focal lesions.[3] This suggests that valproate would be clinically effective in suppressing complex partial seizures and secondarily generalized tonic-clonic seizures, while having less effect on simple partial seizures arising from the cortical focus itself. However, continuous infusion of intravenous valproate resulting in serum levels greater than 100 mg/L suppressed the frequency, duration, and severity of seizures arising from alumina focus, suggesting that higher levels of valproate would suppress simple partial seizures.[5] The majority of these preclinical trials suggest that valproate at doses tested has superior ability to prevent the spread of epileptiform activity with less effect on the epileptic focus itself.[3] This testing led to clinical testing and to more specific testing to elucidate the exact

mechanisms of action responsible for the broad spectrum of clinical activity being demonstrated in clinical practice.

MECHANISM OF ACTION

Valproate has multiple mechanisms of action consistent with its broad-spectrum efficacy in all epilepsy types. Despite intensive investigation for over 30 years, an additional important mechanism has only recently been elucidated. Epilepsy is due to excessive excitability and synchronization of cortical neurons. Excessive excitability may be due to lack of normal inhibition or increased neuronal excitability. Valproate affects cortical hyperexcitability by both increasing inhibition through raising the levels of γ-aminobutyric acid (GABA), the inhibitory neurotransmitter, and decreasing neuronal excitability by lowering the concentration of glutamate, the major excitatory neurotransmitter.

Valproate has been shown to increase GABA levels by both increasing GABA production and by decreasing GABA breakdown.[3,6] This has been confirmed in the whole brain, synaptosomal preparation, and in cerebrospinal fluid (CSF) GABA levels.[6]

In addition to increasing cortical inhibition by increasing synaptic GABA, valproate has specific effects on neuronal channels and cortical circuits similar to most other AEDs that block the spread of epileptiform activity. Like other AEDs that block MES-induced seizures (phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide), valproate inhibits sustained repetitive firing of neurons.[7] However, unlike phenytoin and carbamazepine, it does not do this by directly interacting with the sodium channel. The inhibition on the abnormal sustained repetitive firing of neurons by valproate appears to be by activation of calcium-dependent potassium conductance.[3] Nevertheless, the blocking of sustained repetitive firing is the hallmark of all AEDs that are effective in the treatment of partial seizures. The other major effect of valproate on cortical circuits is its effect on cortical thalamic excitability.[8,9] The interaction with the transient calcium channel interferes with abnormal cortical-thalamic synchrony—the hallmark of absence epilepsy. This makes valproate very effective in absence and other primary generalized epilepsies.

Recently, there have been a number of reports on the effect of valproate on the excitatory glutamate system.[3,9] It had been hypothesized that valproate had an effect on this system. Valproate had clear effects on suppressing the electrical amygdale kindling and blunting epileptogenesis in the iron model of epilepsy (model of posttraumatic epilepsy).[3,10] However, valproate, in multiple studies, had no effect on glutamate/aspartate-binding or concentrations.[3,9] However, recently, it has been demonstrated and confirmed by a different investigator that valproate inhibits epileptogenesis by upregulating the glutamate-binding protein when excessive

glutamate release is seen in pathologic processes such as epilepsy.[10] This suggests that valproate has neuroprotective features that should decrease the excitototoxic neuronal injury seen in epilepsy, head trauma, and hypoxic-ischemic encephalopathy. Valproate's multiple mechanisms of action demonstrated in experimental models of both generalized and partial epilepsies correctly predicted its broad spectrum of efficacy in epilepsy.[3,9]

EFFICACY OF VALPROATE IN PARTIAL EPILEPSIES

After the establishment of the efficacy of valproate for generalized epilepsies, investigators began reporting the usefulness of valproate in the treatment of intractable partial seizures with secondary generalization. The numbers of patients in these early reports were small, but these reports were consistent with the preclinical studies suggesting that valproate was more effective in suppressing the spread of seizure activity (complex partial seizures with secondary generalization) than suppressing the focus of seizures (simple partial seizure). All the initial studies used valproate as adjunctive therapy in patients with intractable partial seizures. Covanis reported a good response in patients with complex partial seizures: five out of 11 patients became seizure-free when valproate was added to carbamazepine, while nine patients with simple partial seizures had a poor response.[11] In Henriksen's and Johannessen's study[12] of 100 children with uncontrolled partial epilepsy, only 9% of patients with simple partial seizures became seizure-free, and 63% responded favorably (greater than 50% reduction in seizure frequency). Complex partial seizures responded more favorably, with approximately 20% being seizure free and 80% responding favorably.[12]

Callaghan reported a large comparative monotherapy trial of valproate, carbamazepine, and phenytoin in newly diagnosed previously untreated patients. In 79 patients with only simple or complex partial seizures, the three drugs performed equally well in the reduction of the frequency of partial seizures and in the number of patients who became seizure-free.[13] Dean reported on 30 patients with partial epilepsy who switched to valproate because of intolerance to previous AEDs (carbamazepine, phenytoin): 12/30 became seizure-free and an additional 10/30 were responders (>50% seizure reduction).[14]

The most comprehensive study of valproate in partial seizures was the Department of Veterans Affairs Epilepsy Cooperative Trial II, carried out by Mattson and collaborators at multiple sites across the United States.[15] In this multicenter, double-blind study, 460 patients with complex partial or partial with secondary generalized tonic-clonic seizures were randomly assigned to either valproate or carbamazepine monotherapy. This study used target drug levels of valproate between 80-100 mg/L and

carbamazepine between 7-9 mg/L. Outcome measures included seizure count over 12 months; seizure rate per month; percentage of patients seizure-free; time to first seizure; and a seizure rating score (total number of generalized tonic–clonic, complex partial seizures, and simple partial seizures per month). These measures were determined at 12 and 24 months of treatment. Side effects, including systemic effects and neurotoxicity, were quantified. A combination of efficacy scores and side effect profile provided a combined score of clinical outcome. The conclusion was that there was no significant difference in the two medications for secondarily generalized tonic-clonic seizures. However, there was a significant difference in four of the five clinical outcome scores at 12 months in favor of carbamazepine. In addition, there was a significant difference in favor of carbamazepine in the composite rating score at 12 months; however, the composite ratings of the two drugs were equal at the time of the 24 month evaluation. This landmark study demonstrated that valproate was one of the drugs of choice for partial seizures with secondary generalization.[15]

A number of similar studies from Europe were reported in the mid-1990s. Richen reported a multicenter, randomized, comparison trial of valproate versus carbamazepine for primary generalized epilepsy and partial seizures with secondary generalization.[16] They found 70% of all patients were either seizure-free off medications or still on their randomized treatment with good control after a three-year trial. There was no difference in efficacy measures between patients on valproate or carbamazepine. Carbamazepine-treated patients had a higher early withdrawal rate primarily due to rash. There were two reported trials—one in children and the other in adults—that compared phenobarbital, phenytoin, carbamazepine, and valproate in patients with newly diagnosed epilepsy.[17,18] These patients had either generalized tonic-clonic seizures or partial seizures with or without secondary generalization. The results reported in children were that all drugs were equally effective.[17] Twenty percent of children were seizure-free and 73% had achieved a one-year remission by the third year of follow-up. Drop-out rate for phenobarbital was high, but acceptable for phenytoin (9%), carbamazepine (4%), and valproate (4%).[17] Similarly, in adults, efficacy for all the medications was equal, with 27% of patients remaining seizure-free and 75% experiencing one year of remission by the third year of follow-up.[18] Withdrawal rates due to side effects were greatest with phenobarbital (22%), followed by carbamazepine (11%), valproate (5%), and phenytoin (3%).[18]

These European randomized trials and other smaller studies suggest that all AEDs tested (valproate, diphenylhydantoin, carbemazepine, phenobarbitol) were equally effective for the treatment for partial

seizures, and all, except for phenobarbital, were well tolerated.[19,20] These trials differed from the Veterans Affairs cooperative trials in that only new-onset patients with epilepsy were entered, resulting in better patient outcome, and that no difference was found between carbamazepine and valproate in efficacy/side effects outcome measures. It also suggests that early aggressive treatment will put more patients into medical remission.

The efficacy and safety of adjunctive valproate therapy in the treatment of medically intractable partial epilepsy was reported in 1996.[21] This trial was a double-blind, placebo-controlled, parallel-group trial to meet the FDA guidelines on documenting efficacy and safety of AEDs. A similar trial design was used for FDA testing of the new AEDs during the mid to late 1990s. Patients on either phenytoin or carbamazepine monotherapy with inadequate seizure control were randomized to placebo or valproate treatment. Outcome measures were median reduction in seizure frequency and responder rate (percentage of patients who had 50% or greater reduction in seizure rate) during the treated period. Adjunctive valproate therapy significantly reduced the seizure frequency (7.9 versus 2.5 seizures/month) and produced a higher responder rate (38% versus 19%).[21]

More recently, valproate has been studied in comparison with the new generation of AEDs. Brodie reported on a comparison of valproate and vigabitrin in a double-blind substitution trial in carbamazepine-resistant partial epilepsy.[22] The two drugs were equally effective as judged by the percentage maintained on duo therapy or converted to monotherapy while maintaining seizure freedom.[22] In a comparison of lamotrigine and valproate in patients with newly diagnosed partial and generalized epilepsy, an equal percentage of patients (29% versus 26%) remained seizure-free.[23] Overall, adverse effects were equal for the two medications, except for weight gain that was higher in the valproate group.

A multicenter trial of add-on therapy to carbamazepine compared valproate and topiramate.[24] The trial's primary purpose was to evaluate cognitive changes associated with add-on therapy during the titration phase and steady-state. The efficacy of the two drugs was comparable with reduction in monthly seizure rates of 29.6% for topiramate and 22.1% for valproate. When comparing baseline to end-point, two of the measured cognitive tests showed statistical differences. In both, the patients receiving topiramate performed significantly worse on tests measuring short-term verbal memory than patients receiving valproate. The negative effect of topiramate was more pronounced in the titration phase.[24]

In a more recent trial, Beydoun et al reported on the safety and efficacy of valproate monotherapy in patients with poorly controlled partial epilepsy. This trial compared low-dose valproate (levels between

25-50 mg/L) and high dose valproate (levels between 80-150 mg/L).[25] The reduction in seizure frequency was significantly better for both complex partial seizures and secondarily generalized tonic–clonic seizures in the high-dose group when compared to the low-dose group in these patients with medically intractable partial epilepsy. However, side effects, especially tremor, were more pronounced in the high-dose group. This study documented that side effects, especially tremor, are associated with higher peak blood levels. However, as suggested from the preclinical studies, valproate's effectiveness for intractable partial seizures improves significantly with higher blood levels.

This trial confirms the preclinical studies that showed higher serum levels of valproate provide better efficacy in patients with intractable partial epilepsy. It also suggests that peak-level side effects may limit the clinical efficacy of valproate. Extended-release preparation of valproate should allow higher serum levels and improved efficacy without peak-level side effects. Early reported experience with extended release divalproex sodium supports this premise.[26] However, additional studies with larger number of patients are needed to confirm their findings.

ADVERSE EFFECTS

Valproic acid's adverse effects are well studied and reported in the literature with over 2000 peer-reviewed papers published since its release in France in the early 1970s.[26,27] The adverse effects range from relatively common, benign, and predictable to life-threatening, but rare. Over the past 30 years of valproate's use, three significant but rare adverse effects have caused concern among prescribing physicians. These are acute liver toxicity leading to liver failure, teratogenic effects, especially neural tube defects, and reproductive abnormalities and polycystic ovary disease in women.[27]

The clinical trials leading to FDA approval detected the common dose-dependent adverse effects that are seen early in treatment, especially while the AED is being titrated upward.[29] Many adverse effects are more prominent if there is a rapid titration schedule. Newer trials for psychiatric and migraine indications have reported the adverse effect profile in different clinical situations with the new extended-release preparation.[28] In general, there is a reduction of adverse effects with the extended-release formulation.[26] The trial of divalproex sodium as adjunctive therapy for complex partial seizures in patients uncontrolled with either phenytoin or carbamazepine monotherapy was reported in 1996.[29]

The adverse effects that occurred more frequently with divalproex sodium than placebo in more than 5% of the patients treated were nausea, asthenia, somnolence, vomiting, tremor, anorexia, and abdominal pain (Table 1).[29] A more meaningful study into the adverse effects of

divalproex sodium in patients with partial seizures was the trial evaluating divalproex sodium monotherapy with high doses versus low doses in patients with refractory partial epilepsy.[25] In the previous discussion about the efficacy of valproate in partial seizures, it is suggested that higher doses of valproate with higher blood levels result in improved efficacy in refractory partial epilepsy. The most common adverse effect in this trial

TABLE 1

ADVERSE EFFECTS REPORTED BY LESS THAN OR EQUAL TO 5% OF PATIENTS TREATED WITH DIVALPROEX SODIUM DURING PLACEBO-CONTROLLED TRIALS OF ADJUNCTIVE THERAPY FOR COMPLEX PARTIAL SEIZURES.*

BODY SYSTEM/EVENT	DIVALPROEX SODIUM (N=77)	PLACEBO (N=70)
Body as a whole		
Headache	31%	21%
Asthenia	27%	7%
Fever	6%	4%
Gastrointestinal system		
Nausea	48%	14%
Vomiting	27%	7%
Abdominal pain	23%	6%
Diarrhea	13%	6%
Anorexia	12%	0%
Dyspepsia	8%	4%
Constipation	5%	1%
Nervous system		
Somnolence	27%	11%
Tremor	25%	6%
Dizziness	25%	13%
Diplopia	16%	9%
Amblyopia/blurred vision	12%	9%
Ataxia	8%	1%
Nystagmus	8%	1%
Emotional lability	6%	4%
Mental slowing	6%	0%
Amnesia	5%	1%
Respiratory system		
Flu syndrome	12%	9%
Infection	12%	6%
Bronchitis	5%	1%
Rhinitis	5%	4%
Other		
Alopecia	6%	1%
Weight loss	6%	0%

*The dosage of divalproex sodium was increased gradually over eight weeks. At the maintenance period, the mean daily dose and serum valproic acid concentration were, respectively, 31.4mg/kd/day and 59.1 μg/mL. Modified from data from Abbott Labs.

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comparing high-dose (valproate level: mean 123 mg/L) and low-dose valproate (valproate level: mean 71 mg/L) also provided information about which adverse effects are truly dose-dependent and peak-level-dependent. This is important because an extended-release preparation should significantly decrease peak-level-dependent adverse effects. The most common adverse effects related to high-dose therapy were asthenia, nausea, diarrhea, vomiting, somnolence, alopecia, thrombocytopenia, and tremor. The only adverse effect that was more prevalent in the low-dose group was headache (Table 2).[25] Thrombocytopenia (less than 75,000/mm^3) was clearly dose-dependent with the probability of low platelet count increasing significantly at trough plasma valproate levels of greater than 110 mg/L in women and greater than 135 mg/L in men. The platelet count often normalized with treatment, and in those with continued thrombocytopenia no treatment was required.[25]

To put in perspective the frequency of adverse effects with valproate monotherapy compared to other AEDs, the frequency of drop-out rates in monotherapy trials comparing valproate with carbamazepine can be estimated.

In the largest of such trials, Richens reported a 10% withdrawal rate with valproate (5% first six months and 5% months 6-36) while

TABLE 2

ADVERSE EVENTS DURING DIVALPROEX SODIUM MONOTHERAPY IN PARTIAL EPILEPSIES, IN A TRIAL COMPARING HIGH- AND LOW-DOSE GROUPS

SIDE EFFECT	DIVALPROEX SODIUM, HIGH-DOSE 89-150 μG/ML (N=96)	DIVALPROEX SODIUM, LOW-DOSE, 25-50 μG/ML (N=47)
Tremor	61%	6%
Thrombocytopenia	31%	0%
Alopecia	28%	4%
Diarrhea	21%	4%
Asthenia	17%	0%
Vomiting	17%	0%
Headache	16%	32%
Weight gain	15%	4%
Anorexia	15%	0%
Exit rate from adverse effects	32%	2%

Modified and adapted from: Beydoun A, Sackellares JC, Shu V, and the Depakote Monotherapy for Partial Seizures Study Group. Safety and efficacy of divalproex sodium monotherpay in partial epilepsy: a double-blind, concentration-response designed clinical test. *Neurology.* 1997;48:182-188.

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carbamazepine had a total withdrawal rate of 20% (15% in first six months and 5% months 6-36). The difference in early side effects with carbamazepine was primarily due to skin rash. The cumulative incidence of any side effect at 36 months was 49.4% for valproate and 48.9% for carbamazepine. Other smaller monotherapy trials resulted in similar withdrawal rates and incidence of side effects for valproate, carbamazepine, and phenytoin for treatment of partial seizures.

ACUTE DOSE-RELATED ADVERSE EFFECTS

This is an important group of adverse effects because the preparation of valproate can dramatically affect the frequency and severity, and, therefore, can be ameliorated with the newer preparations. Gastrointenstinal distress and nausea with or without vomiting are the most common adverse effects with initiation of therapy with valproate. It has been significantly decreased with the enteric-coated, delayed-release, and extended-release preparations of divalproex sodium. Symptoms improve with time; continued and severe symtpomatology requires further investigation into metabolic, hepatic, and pancreatic dysfunction.[27,28,30]

Tremor is clearly a dose- and peak-related adverse effect. It is a low-amplitude, rapid tremor resembling an essential tremor.[27,28,31] Asterixis, which can be confused with tremor, suggests hepatic dysfunction.[27] Tremor responds to dosage resolution or change in preparation of the extended-release formulation.[26,31] Treatment of tremor with propranolol is at times necessary when dosage reduction results in breakthrough seizures. In patients on a combination of valproate and lamotrigine for their intractable partial epilepsies, the severity of tremor can limit the usefulness of this combination and cause significant difficulties with eating with utensils, drinking from a cup, and handwriting.

Acute encephalopathy has been reported with overdosages, with metabolic changes and in combination with other AEDs, especially phenobarbital.[27,28,32] Rarely, encephalopathy occurs without obvious metabolic derangement. Electroencephalography (EEG) shows typical slow wave abnormality. Clinical symptoms and EEG respond to discontinuation or reduction of valproate.[32]

CHRONIC ADVERSE EFFECTS WITH VALPROATE THERAPY

The chronic dose-related effects of valproate include weight gain and hair changes.[27,38,32] Weight gain is particularly troublesome in early adolescent females.[32,33,34] There is a report of increased appetite and food intake. The exact cause remains unknown, despite investigation.[33,34] Weight gain may be due to factors other than valproate use.[35] In a randomized study of children with new-onset epilepsy given carbamazepine or valproate, there were no significant differences in weight increase

in the two groups.[35] Baseline weight and routine monitoring of weight is important so that dietary input can be initiated. Recognition of significant weight gain and new menstrual irregularities may identify families at higher risk for reproductive abnormalities and polycystic ovary disease.[28]

IDIOSYNCRATIC/ALLERGIC ADVERSE EFFECTS

The idiosyncratic and allergic side effects are uncommon, but can be serious. Rash is less common with the initiation of valproate therapy than with phenytoin or carbamazepine.[28] Acute hepatotoxicity was the first major idiosyncratic reaction ascribed to valproate in the 1970s.[36] While minor elevation of liver transaminase is not uncommon, it is often seen with initiation of therapy and with dosage increases.[36] When these abnormalities remain within the range of two to three times normal without any abnormalities of liver synthetic function (albumin level, prothrombin time/partial thromboplastin time), valproate treatment may be continued.[36] The rare idiosyncratic severe hepatotoxicity occurs with an overall incidence of 1/10,000.[36] It typically occurs within the first six months of therapy and is thought to be limited to underlying metabolic abnormalities. Children under two years of age on multiple cytochrome P-450-inducing AEDs are at higher risk (1/500).[36] The incidences decrease with use and monotherapy. From 1987-1993, 1,000,000 patients were placed on valproate, with 29 cases of fatal hepatotoxicity.

Acute hemorrhagic pancreatitis has been reported with valproate therapy.[27,28,37] The incidence is estimated to be 1/40,000 patients treated. It is more common in younger patients (under 20 years) on multiple AEDs, and patients with chronic encephalopathy.[28,37] It typically occurs within the first year of therapy (70% of cases).[28,37] Abdominal pain, nausea, vomiting, and anorexia are presenting symptoms. Serum amylase and lipase are elevated and should be evaluated in the appropriate clinical setting.

Adverse effects of valproate in the reproductive system in women have been of intense interest and study, though much more needs to be done in this area.[38,39]

Teratogenicity associated with fetal exposure to valproate resulting in neural tube defects was first seen in France and reported in the early 1980s.[40] This early study led to additional retrospective studies and was confirmed by a prospective study.[41] The risk of neural tube defects with fetal exposure to valproate was estimated to be 1% to 2%. The risk appears to be dose- and peak-level-dependent.[28,41]

Planned pregnancy, folate supplementation, lowering of doses of valproate, and lowering peak levels by using extended-release formulations or multiple divided doses are suggested to decrease risk. Diagnostic ultrasound at 18-20 weeks is indicated and α-fetoprotein in serum or

amniotic fluid can be pursued. While folate supplementation has not been proven to reverse the risk of valproate-induced neural tube defects, it is prudent for all women of child-bearing potential on any AED to use folate supplementation.[42]

In the 1990s, a number of studies have described an increased incidence of polycystic ovaries and polycystic ovary syndrome in women with epilepsy, treated with valproate, carbamazepine, and other AEDs.[28,43] In one study, valproate appeared to be associated with an increased incidence of polycystic ovary syndrome;[43] in other studies, these findings were not replicated.[28,44,45] Reviews in this area documented that many factors were involved in this relatively common disorder.[45] In clinical practice, rapid weight gain on initiating valproate, carbamazepine ,or other AED therapy associated with menstrual irregularities should prompt further diagnostic testing (ultrasound, hormone levels) and change in AED therapy.

CONCLUSION

Valproate is an effective medication in partial epilepsies—equally effective compared to the traditional and newer AEDs. In medically intractable partial and complex partial epilepsy, higher serum levels improve clinical efficacy. Clinical side effects, especially peak dose side effects, commonly limit valproic acid's clinical effectiveness. New extended-release preparations of divalproex sodium offer improved clinical efficacy with tolerable side effects. Rare idiosyncratic side effects are well studied and may be recognized early, minimizing their morbidity. The new extended-release preparation of divalproex sodium favorably alters the efficacy/side effect equation. ⌘

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