SHOULD VALPROATE BE PRESCRIBED TO WOMEN OF CHILDBEARING AGE? (NO)

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Valproic acid was first synthesized in 1882 by B.S. Burton as an analogue of valeric acid, found naturally in valerian. For many decades its only use was in laboratories as a "metabolically inert" solvent for organic compounds. 1962, the French researcher Pierre Eymard serendipitously discovered the anticonvulsant properties of valproic acid while using it as a vehicle for a number of other compounds that were being screened for antiseizure activity. He found it prevented pentylenetetrazol-induced convulsions in laboratory rats. It was approved as an antiepileptic drug in 1967 in France and has become the most widely prescribed antiepileptic drug worldwide. VPA is an effective agent for the control of absence, myoclonic, tonic–clonic seizures and partial seizures. VPA has a wide spectrum of activity against both generalised and partial seizures in adults and children. Valproic acid has also been used for migraine prophylaxis and bipolar disorder.

VPA is a salt of dipropylacetic acid, which is conjugated in the liver and rapidly eliminated through urinary excretion

Common side effects are tremors, dyspepsia and/or weight gain. Less common are fatigue, peripheral edema, acne, dizziness, drowsiness, hair loss, headaches, nausea and sedation Valproic acid also causes hyperammonemia, an increase of ammonia levels in the blood, which can lead to vomiting and sluggishness, and ultimately to mental changes and brain damage. Valproate levels within the normal range are capable of causing hyperammonemia and ensuing encephalopathy. There have been reports of brain encephalopathy developing without hyperammonemia or elevated valproate levels. The foremost and most severe concern for anyone taking valproic acid is its potential for sudden and severe, possibly fatal, fulminating impairments in liver, hematopoietic and/or pancreatic function, especially in those just starting the medication. This particular warning is the first one listed on any drug adverse effect listing when one receives the drug at the pharmacy. VPA may have effects on serum androgen concentrations and it reduces serum follicle stimulating hormone levels in men with epilepsy. However, the clinical significance of the VPA related reproductive endocrine changes in men is unknown. On the other hand, in women the use of VPA is associated with a frequent occurrence of reproductive endocrine disorders characterized by polycystic changes in the ovaries, high serum testosterone concentrations (hyperandrogenism) and menstrual disorders. Young women with epilepsy seem to be especially vulnerable to the effects of VPA on serum androgen levels.

Women and Pubertal girls with epilepsy are at risk for hormonal or metabolic irregularities including obesity, amenorrhea, oligomenorrhea, anovulation, polycystic ovaries (PCO), polycystic ovary syndrome (PCOS), hyperandrogenism and dyslipidemia. Rates of menstrual disturbances are high in women with epilepsy and bipolar disorder and, in many cases, precede the diagnosis and treatment for the disorder. Treatment with valproate additionally contributes significantly to the development of menstrual abnormalities and an increase in testosterone levels over time.

VPA crosses the placenta and is present in a higher concentrationin the fetus than in the mother, although it remains unclear if the fetal serum concentration is higher during

embryogenesis. Exposure during pregnancy is associated with about three times as many major anomalies as usual, mainly spina bifida and, more rarely, with several other defects, possibly including a "valproate syndrome". Characteristics of this *valproate syndrome* include facial features that tend to evolve with age, including trigonocephaly, tall forehead with bifrontal narrowing, epicanthic folds, medial deficiency of eyebrows, flat nasal bridge, broad nasal root, anteverted nares, shallow philtrum, long upper lip and thin vermillion borders, thick lower lip and small downturned mouth. Prenatal exposure to VPA has additionally been linked to a variety of birth defects and deficiencies such as hypospadias,

omphalocele, inguinal hernia, duodenal atresia and scoliosis. Hyperbilirubinaemia, hepatotoxicity, transient hyperglycinaemia, afibrinogenaemia and fetal or neonatal distress may also be found.

Recently published studies demonstrated children of pregnant women taking valproate had an IQ nine points lower than a well-matched control group.

Currently there is an increase in the number of national and international pregnancy registries being formed in an effort to better identify the teratogenic effects of AEDs. These efforts hope to enhance our understanding of AEDs and their associated risks by addressing past study limitations.

In any case, the present data reinforce the recent recommendations of some authorities to avoid VPA in women of childbearing age whenever possible, and if VPA is needed to control convulsive seizures, to use the lowest effective dose regardless of underlying epilepsy syndrome