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# VALPROATE USED IN WOMEN OF CHILDBEARING AGE WITH EPILEPSY

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Valproate is one of the oldest known anti-epileptic drugs (AED) in practice which was discovered in 1881 and later in 1962 was approved for treating epilepsy. It is indicated in most of the seizure types including generalized onset (motor, non-motor and myoclonic), focal onset, unknown onset and unclassified. Valproate has other indications in migraine prophylaxis, and bipolar disorder.

The use of Valproate in women of childbearing age poses a serious issue due to its adverse pregnancy outcomes; foetal Valproate syndrome, and neurodevelopmental problems in future development<sup>1</sup>.

These major malformations include congenital heart defects, cleft lip, cleft palate, spina bifida and dysmorphic face and arms. Valproate's teratogenic potential can be quantified from the relative risk percentages it accounts to, risk of a major malformation in children varies from 7% in women taking valproate as compared to 2-3% in general population. This risk is found to be dose dependent with 10% in women on more than 1gm/day of valproate <sup>2</sup>.

In the NEAD study, children who were exposed to Valproate were prospectively followed at 3 years, 4.5 years, and 6 years. IQ scores were 6-9 points lower than in children whose mothers were on lamotrigine, phenytoin, or carbamazepine <sup>3,4,5</sup>.

The European medical association (EMA) in November 2014, advised against prescribing Valproate in women of childbearing ages, however in individual cases it might be the single best choice<sup>6,7</sup>.

Epilepsy Action in the UK reported that almost 1/5th of women taking sodium valproate for epilepsy were still not aware of risks in pregnancy<sup>8</sup>. The Medicines and Healthcare Products Regulatory Agency (MHRA) in its guidelines published in May 2018 have recommended pregnancy prevention measures for women of childbearing age on Valproate for any reason. The MHRA has further emphasized the need for yearly risk acknowledgments by the patients or their care givers <sup>9</sup>.

Clinicians are faced with a therapeutic challenge in choosing an effective AED in women of child-bearing age. There are different scenarios where Valproate can be the best choice.

For instance, in women with Epilepsy where seizures are only amenable to Valproate, attempting to switch to an alternative AED can result in life-threatening status epilepticus and may increase the risk of sudden death in epilepsy (SUDEP) There is also an increased risk of seizures while switching AEDs which could result in a driving restriction which may be unacceptable to some patients and could severely limit their lifestyle. In addition to this, it can prove difficult to find the correct dose for an alternative AED and patients may suffer significant side effects. Where Valproate is simply the most efficacious drug, attempts to switch AEDs may also result in multiple trials of medications which are ineffective and in cases of refractory epilepsy where other AEDs have failed.

There are grey areas that need to be explored further for a better understanding of the risks which epilepsy treatment poses. Most antiepileptics are teratogenic to some extent. The use of multiple antiepileptics can increase the risk of adverse pregnancy outcomes. Switching from Valproate does not necessarily mean that the alternative is completely safe. Pregnancy data is lacking for several of the newer AEDs. valproate at a smaller dose might have a better safety profile than these drugs valproate should be used considering fully these pros and cons and ensuring that patients are

fully aware of these. As a consensus Valproate is not recommended in women of childbearing age although there are exceptions when it can be the only effective option.

Consensus on use of Valproate in women of childbearing age:

Currently the consensus on use of Valproate in women of childbearing age converges upon the following:

- i. Valproate is considered the best Antiepileptic for their epilepsy types and other antiepileptics have failed to control seizures.
- ii. It should only be prescribed to fully informed women of childbearing age (or their fully informed parents / guardians / carers).
- iii. Adequate measures are taken for pregnancy prevention.
- iv. When, open communication, and appropriate and individualised discussion between clinician and woman with epilepsy and the potential side effects and teratogenesis of Valproate are fully considered and acknowledged.

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**Salman Mansoor;** Manuscript writing, literature search, case data collection, manuscript revision.

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