

## Management Issues in Pregnancy and Lactation:

# Recommendations and Conclusions<sup>1, 2, 3</sup>

### Level A recommendations (based on good and consistent scientific evidence):

- Maternal benzodiazepine use shortly before delivery is associated with floppy infant syndrome.
- Lithium exposure in pregnancy may be associated with a small increase in congenital cardiac malformations, with a risk ratio of 1.2 to 7.7
- Valproate exposure in pregnancy is associated with an increased risk of fetal anomalies, including neural tube defects, fetal valproate syndrome and long-term adverse neurocognitive effects. It should be avoided in pregnancy, especially during the first trimester.



**Note:** As of 2013, the FDA is advising health care professionals and women that the anti-seizure medication valproate sodium and related products (valproic acid and divalproex sodium) are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. Based on information from a recent study, there is evidence that these medications can cause decreased intelligence quotient (IQ) scores in children whose mothers took these medications while pregnant. Valproate's pregnancy category for migraine use was changed from "D" (potential benefit in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug). Valproate products remain pregnancy category "D" for treating epilepsy and manic episodes associated with bipolar disorder. (See additional FDA warnings and recommendations below).

- Carbamazepine exposure in pregnancy is associated with fetal carbamazepine syndrome. It should be avoided during pregnancy, if possible, especially during the first trimester.

### Additional FDA warnings and recommendations<sup>4</sup>:

- 2015** Pregnancy registry data show that maternal valproate use can cause neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias and limb malformations).
- 2015** Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following in utero exposure. Valproate is therefore contraindicated in pregnant women treated for prophylaxis of migraine. Valproate should only be used to treat pregnant women with epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable.

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**2013 (Birth Defects)** Valproate can cause fetal harm when administered to a pregnant woman. Pregnancy registry data show that maternal valproate use can cause neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations and malformations involving various body systems). The rate of congenital malformations among babies born to mothers using valproate is about four times higher than the rate among babies born to epileptic mothers using other anti-seizure monotherapies. Evidence suggests that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population.

**2013** Valproate can cause decreased IQ scores following in utero exposure. Published epidemiological studies have indicated that children exposed to valproate in utero have lower cognitive test scores than children exposed in utero to either another antiepileptic drug or to no antiepileptic drugs. The largest of these studies is a prospective cohort study conducted in the United States and United Kingdom that found children with prenatal exposure to valproate (n=62) had lower IQ scores at age 6 (97[95% C.I. 94-101]) than children with prenatal exposure to the other antiepileptic drug monotherapy treatments evaluated: lamotrigine (108 [95% C.I. 105-110]), carbamazepine (105 [95% C.I. 102-108]) and phenytoin (108 [95% C.I. 104-112]). It is not known when during pregnancy cognitive effects in valproate-exposed children occur. Because the women in this study were exposed to antiepileptic drugs throughout pregnancy, whether the risk for decreased IQ was related to a particular time period during pregnancy could not be assessed. Although all of the available studies have methodological limitations, the weight of the evidence supports the conclusion that valproate exposure in utero can cause decreased IQ in children. In animal studies, offspring with prenatal exposure to valproate had malformations similar to those seen in humans and demonstrated neurobehavioral deficits.

**2013 Fetal Risk Summary:** In animal studies, offspring with prenatal exposure to valproate had structural malformations similar to those seen in humans and demonstrated neurobehavioral deficits.

### FDA Clinical Considerations:

- Valproate can cause decreased IQ scores in children whose mothers were treated with valproate during pregnancy.
- Valproate should not be administered to a woman of childbearing potential because of the risks of decreased IQ, neural tube defects and other fetal adverse events that may occur very early in pregnancy.
- Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine).
- Valproate should not be used to treat women with epilepsy who are pregnant or who plan to become pregnant unless other treatments have failed to provide adequate symptom control or are otherwise unacceptable. In such women, the benefits of treatment with valproate during pregnancy may still outweigh the risks. When treating a pregnant woman or a woman of childbearing potential, carefully consider both the potential risks and benefits of treatment and provide appropriate counseling.

*This tool is provided as a resource and is not a substitute for the professional medical judgment of treating physicians or other health care practitioners. This guideline reflects the current state of knowledge at the time of development on effective and appropriate care. Proper use, adaptation, modifications or decisions to disregard in whole or in part are entirely the responsibility of the clinician who uses this guideline.*

### References

- <sup>1</sup>Adapted from A Summary for Monitoring Physical Health and Side-Effects of Psychiatric Medications in the Severely Mentally Ill Population (2014). The University of South Florida, Florida Medicaid Drug Therapy Management Program for Behavioral Health sponsored by the Florida Agency for Health Care Administration.
- <sup>2</sup>AGOG Practice Bulletin (2008). Clinical management guidelines for Obstetrician-Gynecologists: Use of psychiatric medications during pregnancy and lactation. *Obstetrics and Gynecology*, 111(1), 1001-1020.
- <sup>3</sup>National Guideline Clearinghouse (2013). Guideline summary – Use of psychiatric medications during pregnancy and lactation. Retrieved from <http://www.guideline.gov/content.aspx?id>
- <sup>4</sup>FDA (2015). Depakene (valproic acid), capsules and oral solution, Depakote (divalproex sodium) delayed release and Depakote sprinkle capsules (divalproex sodium coated particles in capsules), Depacon (valproate sodium) injection. Retrieved from <http://www.fda.gov/safety/medwatch/safetyinformation/ucm360487.htm>