# MedWatch Warns Of Fetal Risks in Valproate Products

BY ELIZABETH MECHCATIE

The high risk of neural tube defects and other major malformations in babies exposed to valproate sodium and the related products, valproic acid and divalproex sodium, during the first trimester is the focus of a Food and Drug Administration notice to health care professionals.

The FDA statement also emphasizes the need for health practitioners to counsel women of childbearing potential about these teratogenic risks, and to "consider alternative therapies, especially if using valproate to treat migraines or other conditions not usually considered life-threatening."

**The risk of a neural tube defect in a baby born to a mother who took valproate or one of the two related products during the first 12 weeks of pregnancy is 1 in 20.**

The statement was posted on the FDA's MedWatch site in December.

The risk of a neural tube defect in a baby born to a mother who took valproate or one of the two related products during the first 12 weeks of pregnancy is 1 in 20, compared with the background rate of 1 in 1,500 in the United States, according to the FDA.

The notice cites data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry, which indicate that the major malformation rate in babies born to women who have epilepsy and take valproate alone is nearly fourfold greater than among the babies born to women with epilepsy who take a different antiepileptic: 10.7%, compared with 2.9%.

The 16 major malformations among the babies in the registry who were exposed to valproate during the first trimester of pregnancy included neural tube defects, craniofacial defects, cardiovascular malformations, and malformations involving other body systems.

Included in the FDA statement were comments on the importance of taking folic acid supplements before and during the first trimester of pregnancy in order to reduce the risk of neural tube defects, and a recommendation that women who are treated with one of these drugs and who are not planning a pregnancy use an effective method of contraception.

Valproic acid, which is marketed as Depakene and as Stavzor, was approved in 1978 for the treatment of epilepsy. Valproate, marketed as Depacon, was approved more recently for the treatment of bipolar disorder and migraine headaches.

"As valproate's indications for use expand, it is critical that health care professionals caring for women of childbearing potential and taking valproate for any indication be informed that valproate causes an increased risk of major birth defects," the FDA statement said.

"Awareness of the therapeutic benefits and risks of valproate and alternative therapies, as well as the risks of untreated disease is critical for informed prescribing and counseling of all women taking valproate."

Divalproex sodium is marketed as Depakote, Depakote CP, and Depakote ER, and is approved for migraine prophylaxis, manic episodes associated with bipolar disorder, as well as epilepsy.

The FDA notice also includes an information section specific to patients.

The agency is working with the manufacturers of these products to make labeling changes that reflect the information regarding teratogenic risk. ■

*The notice can be found at: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm192788.htm. Pregnant women using valproate or other antiepileptic drugs should be encouraged to enroll in the NAAED Pregnancy Registry at 888-233-2334 or at www.aedpregnancyregistry.org. Adverse events associated with these drugs can be reported to MedWatch at: 800-332-1088 or www.fda.gov/medwatch/.*

## DRUGS, PREGNANCY, AND LACTATION

# PPD: Focus on Screening

Postpartum depression is a highly prevalent illness, with multiple studies consistently reporting rates of about 7%-10%, which include both minor and major depression. In some countries such as the United Kingdom, screening for postpartum depression (PPD) is part of standard health care. In the United States, screening is highly variable, although there has been increasing awareness of this illness and the potential value of screening.

Screening for PPD has been recommended as part of routine postpartum care by the American College of Obstetricians and Gynecologists (Obstet. Gynecol. 2010;115[pt. 1]:394-5). Several states, including New Jersey, have initiated mandated screening programs in a variety of settings to identify women suffering with PPD. In Maine, an interesting pilot project has been launched, supported by the state's psychiatric association, which entails screening women for PPD by a spectrum of clinicians including obstetricians and primary care physicians, with psychiatric backup by a group of psychiatrists with subspecialty expertise in the management of PPD.

BY LEE COHEN, M.D.

Few would argue about the theoretical value of screening for PPD, particularly when it leads to effective treatment, but very few studies have looked at whether screening is really cost effective. Specifically, it remains unclear whether screening for PPD leads to effective treatment of the illness (remission) and whether over time those treated do better clinically than those who are not identified or treated.

But a study conducted at the University of York (England), took a critical look at the extent to which screening for PPD in a primary care setting was cost effective when a standardized postnatal depression or generic depression screening tool was used. The analysis, using an economic model and a hypothetical population of women seen at 6 weeks post partum in a primary care setting, determined that screening for PPD was not cost effective and therefore, could not be supported by the National Health Service, based on screening criteria established by that organization (BMJ 2009;339:b5203). The authors determined that the main reason screening was not cost effective was the cost of care for women with false-positive screening results. They concluded that the results did not meet the criteria required for formally adopting such a screening program. The analysis did not factor in the associated costs of untreated PPD, including the effect on the family and the child, despite the extensive literature on the toll of untreated PPD, including the risk for chronic maternal depression, recurrent PPD, and adverse effects on infant and child development associated with untreated PPD.

This study was conducted in a country with a national health care system that cannot be entirely extrapolated to the United States. But cost-effectiveness and other issues surrounding the feasibility and overall value of screening for PPD are still relevant issues that need to be considered in this country, as screening increasingly becomes a part of routine postpartum care and as more of these programs are recommended by professional organizations, if not mandated by given states.

For those of us who treat this illness, the question is not whether we can effectively screen for PPD, because screening is a simple process that can be accomplished with well-validated and readily available instruments. And there are extremely effective modalities for getting patients well, including nonpharmacologic interventions, such as certain psychotherapies, and pharmacologic interventions, such as antidepressants. Therefore, the problem that looms largest with respect to instituting screening programs is not what is the most appropriate screen or how to identify women with the illness. Rather, the most challenging aspect of screening for PPD in the United States centers on what follows identification of illness. How do clinicians ensure that identified patients have access to treatment that restores euthymia?

In the United Kingdom, primary care physicians routinely manage PPD with regional backup from clinicians with expertise in reproductive psychiatry. In the United States, some primary care physicians treat PPD, but others may be reluctant to do so, which highlights the contention that until a system is in place that ensures treatment of the illness following screening, then it may not be advisable to rush to institute such a program.

A critical question also yet to be addressed is whether early identification of PPD translates into a positive long-term outcome. We need to collect data on what happens after women are diagnosed, whether they get treated, and if so, how they are treated—with psychotherapy or pharmacotherapy. Data are also needed on who provides treatment and what types of treatment appear to be most effective for which types of patients. And when patients do get well, we need to look at data on whether the improvement is sustained. The precise value of screening is impossible to determine until we have these data.

If there ever is a national mandate to screen for PPD, then it is critical to demonstrate that we have a treatment model in place that not only identifies patients who suffer from the illness, but that such a system includes delivery of effective treatment. While it currently may not be possible to quantify the benefits of a screening program for PPD, what *is* clear is that such a program might help to destigmatize mental illness and prompt patients to seek treatment from a variety of care providers. Perhaps with greater opportunities to receive effective treatment from a variety of clinicians, the morbidity of postpartum mood disturbance could be vastly limited.

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