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Should Women of Childbearing Potential Be Prescribed Valproate?

A Call to Action

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Prescribing medications during pregnancy can be complicated by a serious negative outcome—harm to the fetus. Probably the 2 best-known examples of medications that can cause severe teratogenicity are thalidomide and isotretinoin. Thalidomide, used for anxiety, insomnia, and tension, was associated with phocomelia (malformation of limbs that many children did not survive). Isotretinoin was reported to cause hydrocephaly, microcephaly, cleft palate, mental retardation, and heart problems. Generic brand names of both of these medications were withdrawn from the market. Thalidomide was later reintroduced to the market, and brand generic forms of isotretinoin are available; both drugs have restrictions associated with prescribing them to women of child-bearing age imposed by the US Food and Drug Administration (FDA). Prescribing thalidomide requires prescriber registration and special certification (one must fill out a Prescriber Enrollment Form); enrolling patients in a special program; providing contraception and emergency contraception counseling with each new prescription; scheduling pregnancy testing for females of reproductive potential and verifying negative pregnancy test prior to writing a new prescription and every subsequent one; reporting all pregnancies; completing a prescriber survey for every patient; and obtaining a unique prescription authorization number that has to be included on the prescription. Authorization numbers are valid for only 7 days from date of last pregnancy test for women of reproductive potential and 30 days for all others. Thalidomide can be prescribed for only 28 days, with no automatic refills or telephone prescription. Similarly, the iPLEDGE program for isotretinoin requires women of childbearing age to provide proof of a current, valid, negative pregnancy test in order to be entered into a special registry, and only patients in this registry are able to receive brand name isotretinoin (the registry includes patients, prescribers, pharmacies, and wholesalers). Physicians prescribing isotretinoin have to assume responsibilities for pregnancy counseling and entering negative pregnancy tests into the iPLEDGE system.

Valproate and its various formulations have been used in neurology and psychiatry for several decades—namely, for epilepsy, migraine prophylaxis, and bipolar disorder, either for acute mania or for prophylactic treatment, as a mood stabilizer. Valproate has been associated with various side effects and teratogenicity. Alsdorf and Wyszynski[1] pointed out that valproate is associated with 20-fold increases in neural tube defects, cleft lip and palate, limb defects, autism, cardiovascular abnormalities, genitourinary defects, developmental delay, and endocrinologic disorders. They[1] added that there is an established relationship between valproate dose and negative outcome—large doses potentially cause high peak fetal serum valproate levels resulting in more deleterious effects. Similarly, polytherapy with antiepileptic drugs increases the risk of teratogenicity. Ornoy,[2] in a detailed review of valproate use in pregnancy, describes a significant increase in the rate of developmental problems manifested by decreased verbal intelligence often with communication problems of the autism spectrum disorder in children with "valproate syndrome." In reviewing the neural tube defects associated with valproate, Ornoy[2] notes that valproate is associated mainly with lumbosacral meningomyelocele (spina bifida aperta) at 10 to 20 times the rate found in the general population.

Unfortunately, in spite of the high probability of teratogenic outcome with valproate, its use in pregnancy continues to be high. Although the majority of women treated for epilepsy during pregnancy are treated with monotherapy, a number of women continued to take valproate despite the longstanding evidence of valproate teratogenicity in a study by Kulaga and colleagues.[3] The level of informing patients about the teratogenic potential of valproate and other mood-stabilizing drugs seems to be low. In a study[4] of 138 women of childbearing age who were prescribed lithium, carbamazepine, and/or valproate, there was documented evidence that only 21% of these women were informed about teratogenicity and 24% had been advised about contraception. Some of the limiting factors in informing these women about teratogenicity were shared care (general practitioners and psychiatrists) and the possibility that in some of these women medication was started during an acute phase of illness when it can be difficult to discuss the adverse outcomes in full.[4]

Since most of the evidence of teratogenicity associated with valproate comes from data collected from women treated for epilepsy, some have questioned whether the maternal genetic background contributes to the negative outcome associated with valproate. Bromfield and colleagues[5] studied this issue, reviewing responses and medical records of enrollees in the North American Antiepileptic Drug Pregnancy Registry. They concluded that valproate and not the underlying genetic syndrome seemed to be associated with the elevated risk of malformation in the valproate-exposed fetus.

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Valproate teratogenicity, the continued prescribing of valproate during pregnancy, lack of clinicians' knowledge about valproate's unfavorable reproductive safety profile, and the low level of information provided to patients seem to be difficult to accept in reality. We all see women of childbearing age who are on valproate treatment while not using adequate birth control (ie, a condom plus another agent, or oral birth control and someone checking to make sure these pills are being administered in a timely manner), women whose partners have not been informed about the teratogenicity of this drug, and women who are not adherent to their outpatient medications. Frequently, we see inadequate justification of why pregnant women are not on treatment with medications with a more favorable reproductive safety profile, such as other mood stabilizers (eg, lithium after the first trimester—its teratogenicity may have been overestimated in the past[6]) and antipsychotics.

What should be done to decrease or eliminate the significant risk of adverse pregnancy outcome associated with valproate? Some advocate for careful planning of pregnancy and discussion of management options with all bipolar patients.[6] However, concerns about valproate prescribing pertain to girls and adolescents, as well as women of reproductive potential, regardless of whether they are planning pregnancy. A neurology expert panel[7] concluded that intrauterine first trimester exposure to valproate has higher risk of major congenital malformations compared to exposure to carbamazepine and possibly compared to exposure to phenytoin or lamotrigine. Thus, they recommended, "If possible, avoidance of valproate (VPA) and antiepileptic drug (AED) polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (Level B). If possible, avoidance of VPA and AED polytherapy throughout pregnancy should be considered to prevent reduced cognitive outcomes (Level B)."[7(p133)]

Since valproate interferes with folic acid metabolism, it has been recommended that women taking antipepileptic medications, namely valproate, be treated with 4 to 5 mg of folic acid per day at preconception and in the first 2 to 3 months of pregnancy to protect against neural tube defects.[2] However, reduction of neural tube defects by folic acid supplementation has not been demonstrated after exposure to valproate or other antiepileptics (though folic acid supplementation generally decreases neural tube defects in humans).[2] Interestingly, valproate is not contraindicated during pregnancy; there is only a strong warning against its use in pregnancy. One may recommend valproate to be contraindicated during pregnancy, but what about unrecognized pregnancy in acutely mentally ill female patients? It is important to realize that unplanned pregnancies are common in this population and it could be too late to just stop valproate use to avoid its adverse reproductive effects. Medications for acute psychiatric conditions, namely valproate, are often continued longer term for maintenance. Thus, initiation of valproate in the acute psychiatric setting for women of childbearing age is problematic—it could either preclude them from conceiving a baby or endanger an unplanned one. As mentioned, introducing counseling and requiring strict compliance with contraception is complicated and leaves a lot of problems. We may also adapt regulations similar to those used for prescribing thalidomide and isotretinoin. However, is it realistic that the FDA and drug manufacturers would be willing to introduce similar regulations and that psychiatrists would not complain that these regulations are too cumbersome, complicated, and intrusive?

None of the suggested precautions is fool-proof against the risk of delivering babies with neural tube defects, lower IQ, autism, and other complications. One may ask whether the use of valproate during pregnancy is really worth those risks. We have numerous safer medications that could be used in acute mania or in prophylaxis of bipolar disorder. The National Institute for Health Care and Excellence (NICE) in the United Kingdom recently released updated guidance on antenatal and postnatal mental health.[8] One of the NICE considerations for women of childbearing potential is a recommendation not to offer "valproate for acute or long treatment of a mental health problem in women of childbearing potential because of the increased risk of major congenital malformations (event rate 7%–10% relative to the baseline risk of about 3% in the general population) and adverse neurodevelopmental outcomes (average decrease in IQ of 9 points)."[(p1)] In view of the serious teratogenicity of valproate, possible holes in any other precautions or recommendations, and availability of other medications for bipolar disorder, this seems like the most reasonable conclusion. Thus, we join the NICE experts in their call for not offering valproate to women of childbearing age, and we actually recommend that the FDA and valproate manufacturers declare valproate contraindicated in women of childbearing age and issue guidelines for counseling women of childbearing potential with bipolar disorder.

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