On page 31 under the section "North American Antiepileptic Pregnancy Registry," the prevalence of major malformations in a total of 564 children exposed to lamotrigine monotherapy was incorrectly shown as "5 cases (2.7%)." The sentence has been corrected to read "15 cases (2.7%)."

Teratogenicity and Anticonvulsants: Lessons From Neurology to Psychiatry

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Anticonvulsants are considered first-line treatments for epilepsy, and some also exert useful effects as mood stabilizers for the treatment of bipolar (manic-depressive) disorder. Much of the research on anticonvulsant use during pregnancy has been done by neurologists studying women with epilepsy. Anticonvulsant use during pregnancy is associated with increased risk of fetal malformations, but withdrawing medication is highly risky for most women with epilepsy or bipolar disorder. Thus, careful clinical monitoring and coordinated care among patient, partner, obstetrician, and psychiatrist are necessary to limit both teratogenetic and neuropsychiatric risks. Several pregnancy registries have appeared. They include the International Registry of Antiepileptic Drugs and Pregnancy (EURAP), the North American Antiepileptic Pregnancy Registry, the International Lamotrigine Pregnancy Registry, the United Kingdom Epilepsy and Pregnancy Register, and the Australian Pregnancy Registry. Data from these registries are helping medical professionals in assessing risks associated with anticonvulsant use during pregnancy and communicating those risks to patients.

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OVERVIEW OF ANTICONVULSANT PRESCRIBING PATTERNS

Clinical parallels exist between issues facing pregnant women with epilepsy and those with bipolar disorder. In both disorders, uncontrolled maternal illness and exposure to drugs pose significant fetal risk.[1–5] Anticonvulsants or antiepileptic drugs (AEDs) are first-line treatments for epilepsy, and some are employed clinically as mood stabilizers for patients diagnosed with bipolar disorder. Psychiatrists and neurologists are by far the most frequent prescribers of these drugs.[2] Given the known teratogenetic effects of some AEDs and their potential endocrinological effects on women, there is good reason to consider avoiding such treatment in anticipation of and during pregnancy. Although medication would ideally be withdrawn prior to conception, this is a not a clinically plausible option for most women with bipolar disorder or epilepsy and necessitates challenging decisions.

Progress in understanding the use of AEDs across pregnancy planning, pregnancy, delivery, and breastfeeding has been relatively slow despite the high prevalence of both bipolar disorder and epilepsy among women of child-bearing potential. Neurology has led the way in developing and disseminating consumer information on clinical issues related to the use of AEDs by young women.[3,6,7] Indeed, much of what is known about AEDs in pregnancy is derived from data collected from studies of women with epilepsy. Psychiatry has relied on these data to inform patients with mood disorders about neuroendocrine consequences and potential teratogenic risks of these compounds.

There are extensive consensus guidelines for neurologists regarding the use of AEDs in women with epilepsy, but until recently, psychiatrists lacked such guidelines for managing pregnant women with bipolar disorder. Preliminary treatment guidelines based on limited data have been proposed for psychiatric use of AEDs.[4] However, many clinical management issues, such as understanding the pharmacokinetics of individual and potentially interacting AEDs, reproductive safety, neuroendocrine effects, and the value of monitoring blood levels of AEDs in pregnancy, are the same in women with bipolar disorder and epilepsy. Despite these similar issues, there appear to be great differences in clinical practice patterns between the specialties, as well as within each specialty among generalists and perinatal subspecialists.

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Table 1. Malformation Rates With Anticonvulsant Treatment: Pregnancy Registries

Registry	Patients (No.)	Type of AED Therapy	Malformation Rate (%)
International Registry of Antiepileptic Drugs and Pregnancy (EURAP)[10]	> 5000 enrolled pregnancies	Monotherapy Polytherapy	5.0 8.0
North American Antiepileptic Pregnancy Registry[11,15]	3633 women	Monotherapy: lamotrigine phenobarbital valproate	 2.7 6.5 10.7
International Lamotrigine Pregnancy Registry[18]	680 infants	Monotherapy: lamotrigine Polytherapy: lamotrigine + valproic acid	 2.8 10.5
United Kingdom Epilepsy and Pregnancy Register[9]	3607 cases	No AED exposure Monotherapy: carbamazepine valproate Polytherapy	3.5 2.2 6.2 6.0
Australian Pregnancy Registry[14]	≥ 450 women with 396 birth outcomes	No AED exposure Monotherapy: carbamazepine lamotrigine valproate	3.6 4.5 5.6 16.0

Abbreviation: AED = antiepileptic drug.

Viguera et al.[8] recently surveyed a random sample of Massachusetts psychiatrists and neurologists on their attitudes about practice patterns with prescribing anticonvulsants to women of childbearing age. They found that, overall, neurologists were more likely than psychiatrists to recommend continued use of AEDs by women planning pregnancy, already pregnant, or breastfeeding. Over 70% of neurologists indicated that they had positive or very positive attitudes about AED use in pregnancy and postpartum compared to 49% of psychiatrists. However, psychiatrists were more likely than neurologists to report that they routinely inform patients of potential long-term neurobehavioral risks associated with in utero exposure to AEDs and to switch a patient to an AED with less teratogenic potential in anticipation of pregnancy. No differences, however, were found between neurologists and psychiatrists in patterns of referring to a subspecialist for planning pregnancies when an AED would be used, informing patients of potential teratogenic risks of AEDs, attempting to discontinue AED treatment in patients who have been in sustained remission or recovery for at least 2 years, recommending folic acid before pregnancy to limit risks of spina bifida, or striving to avoid use of multiple AEDs in pregnancy.

The clear impression from these findings is that there are substantial differences between psychiatrists and neurologists regarding practices related to use of AEDs during pregnancy and lactation, as well as a lack of communication between these formerly close specialties. Effects of untreated epilepsy on maternal and fetal outcomes have been examined, but analogous research on potentially adverse effects of untreated bipolar disorder during pregnancy remains very limited.

ANTICONVULSANTS AND FETAL RISKS

When considering the use of medication during pregnancy, clinicians consider 3 types of risk to the developing fetus: (1) organ malformation or teratogenesis; (2) neonatal toxicity or withdrawal syndromes; and (3) potential long-term neurobehavioral sequelae. This article focuses on teratogenic and long-term neurobehavioral risks.

Teratogenic Risks

A *teratogen* is any agent that increases risk for fetal malformations, usually considered as pertaining to exposure within the first trimester. In general, the baseline risk for major malformations among live births to women not taking any medication or other exogenous, nonfood substances during pregnancy is in the range of 2% to 4%.[9] In order to evaluate whether a substance is a teratogen, one has to compare the risk for malformations associated with the putative teratogen against baseline risk in a comparison or control group ideally matched on as many other variables as possible.

Over the last decade, pregnancy registries have emerged as a useful method for collecting data on fetal risk in Europe, the United States, and Australia. These registries include the International Registry of Antiepileptic Drugs and Pregnancy (EURAP),[10] the North American Antiepileptic Pregnancy Registry,[11] the International Lamotrigine Pregnancy Registry,[12] the United Kingdom Epilepsy and Pregnancy Register,[13] and the Australian Pregnancy Registry[14] (Table 1). A main advantage of a pregnancy registry is the accumulation of enough data to support a robust interpretation. Methods among registries vary, but most are

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prospective in design and include both exposed and nonexposed pregnancies.

International Registry of Antiepileptic Drugs and Pregnancy. EURAP[10] is a Web-based epilepsy registry that collects data from 37 countries, based on enrollment of individual patients by their physicians. More than 5000 patients have been registered, and nearly 2000 mother-infant pair cases have been followed for at least 1 year. Physicians provide data on medication dosage, supplementation, and pregnancy outcomes. Although retrospective registration is permitted, data analysis includes only first trimester exposure before the pregnancy outcome is known. The malformation rate for fetuses exposed to a single AED is about 5% in this registry and is 8% with the use of 2 or more AEDs (polytherapy); however, information regarding specific anticonvulsants has not yet been released.

North American Antiepileptic Pregnancy Registry. The North American Antiepileptic Drug Pregnancy Registry[11] was established in 1997 and includes prospective data on anticonvulsant monotherapy only. Patients themselves must initiate contact with this registry. *Major malformations* are considered to be structural defects recognized within the first 5 days of neonatal life. Thus far, among AEDs, this Registry has published data on phenobarbital and valproic acid. The rate of major malformations for infants exposed to valproate was 10.7%, including spina bifida, heart defects, urogenital defects, and multiple anomalies.[15] The relative risk (RR) of malformation in infants exposed to valproate compared with an external control group of unexposed mother-infant pairs was high, at 7.3-fold.[15]

Data[16] on the reproductive safety of lamotrigine were recently released from the North American Antiepileptic Drug Registry and presented in an abstract at the annual meeting of the Teratology Society. The observed prevalence of major malformations[16] in a total of 564 children exposed to lamotrigine monotherapy was 15 cases (2.7%), including 5 cases of oral clefts, indicating an incidence of 8.9 per 1000 births. In a comparison group of 221,746 unexposed births, the incidence of oral clefts was 0.37 per 1000 births, indicating a 24-fold RR of oral cleft in infants exposed to lamotrigine. Since so few cases were involved in the North American Registry, this apparent RR should be viewed with caution. Moreover, other registries have not found such a great increase in risk for oral clefts. Among a total of 1623 lamotrigine-exposed infants surveyed in 5 other anticonvulsant registries, 4 infants with oral clefts were identified, indicating a frequency of 2.46 per 1000 births. If all available reported data are pooled, the risk of clefts with lamotrigine is 4.12 per 1000 (9/2184), or approximately 11-fold (RR = 4.12/0.37) above the base or control level of risk. An RR of that magnitude is of some concern.

Clearly, more data are essential to better evaluate the reproductive safety of lamotrigine. The available data just reviewed strongly suggest an increased risk of particular malformations in children exposed to lamotrigine, especially of midline palatal or other facial clefts. Nevertheless, it is important to put this risk into perspective. If we assume that the reported findings are true, the absolute risk of having a child with cleft lip or palate is about 4 in 1000, or 0.4%. Some women may elect to discontinue treatment with lamotrigine given such a risk. Many others with unstable bipolar illnesses, and particularly with prominent depression in the past, may be candidates for treatment with a mood stabilizer during pregnancy, especially owing to a very high risk of depressive recurrences in the first trimester.[17] However, some plausible alternatives to lamotrigine also carry some teratogenic risk. Thus, some women may elect to continue treatment with lamotrigine, acknowledging that, while there may be risks associated with this exposure, other treatment options are not risk-free.

The International Lamotrigine Pregnancy Registry. Data[18] from the International Lamotrigine Pregnancy Registry recently presented at the meeting of the American Academy of Neurology did not indicate an elevated risk of fetal malformations associated with lamotrigine exposure. In a total of 680 first-trimester exposures to lamotrigine monotherapy, the frequency of major congenital malformations was 2.8% (19/271). These findings are consistent with previous reports,[19] which observed rates of malformation in lamotrigine-exposed infants similar to those observed in the general population.[12,19] This registry also includes data[18] on AED polytherapy: when lamotrigine was combined with valproic acid, the risk for malformations increased to 10.5%. No specific patterns of birth defects and, specifically, midline facial clefts, were noted in these findings.

The United Kingdom Epilepsy and Pregnancy Register. The United Kingdom Epilepsy and Pregnancy Register[13] is a physician-directed registry wherein infants are followed for up to 3 months after birth. A recent data analysis[9] found that the rate of congenital malformation for pregnancies involving AED exposure was 6.2% for valproate compared with 2.2% for carbamazepine, a significant difference ($p < .001$). The major malformation rate was even higher with fetal exposure to AED polytherapy (6.0%, $p = .010$). When combination therapy included valproate, the risk was several-fold greater than with other AEDs. Moreover, the rate of major malformations was greater with higher doses of AEDs.

The Australian Pregnancy Registry. To date, the Australian Pregnancy Registry,[14] a prospective, observational cohort program, has enrolled more than 450 women with 396 birth outcomes. Participants include pregnant women taking AEDs for epilepsy or other indications and women with epilepsy not taking AEDs. The risk of fetal malformations for valproate, similar to the findings in other registries, was higher (16%) than with carbamazepine (4.5%), lamotrigine monotherapy (5.6%), or no AED exposure

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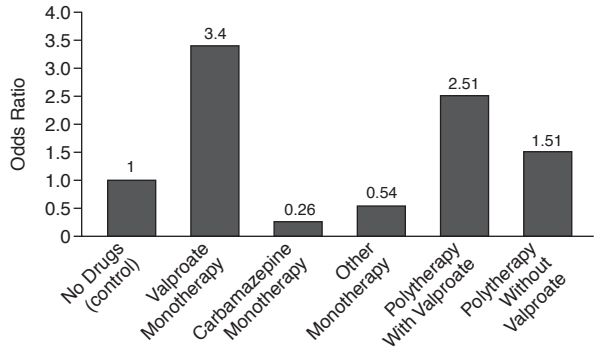
Figure 1. Rates of Special Education Among Children Born to Mothers Receiving Anticonvulsant Treatment During Pregnancy[a]



[a]Data from Adab et al.[20]

(3.6%). There was also evidence of a dose-risk relationship, especially with valproic acid at total daily doses above 1 gram.

Neurobehavioral Effects

Adverse neurobehavioral outcomes are additional, potentially important risks to consider when prescribing AEDs during pregnancy. At present, this risk is only partially quantified.

What can we learn from the epilepsy literature about neurodevelopment of children exposed to AEDs? Recent findings[20] indicate a relationship between IQ scores and the risk for long-term neurobehavioral effects on children of mothers who took AEDs during pregnancy. Researchers in the United Kingdom surveyed 721 women in a regional epilepsy clinic about the schooling of their children (Figure 1). Use of special education support was correlated with the mother's use of specific AEDs during pregnancy. Children exposed to valproic acid in utero had a 3 times greater risk of developmental difficulties requiring special educational interventions than children without such drug exposure. Children exposed in utero to carbamazepine or other AEDs given in monotherapy had no greater risk of developmental difficulties than children not exposed to any drug treatment.

A subsequent study[21] of 249 children born to mothers with epilepsy found a high proportion of verbal IQ scores less than 69 (impaired). The proportion of children with such low IQ scores was greatest following in utero exposure to valproic acid (22.0%), intermediate with multiple AEDs (8.2%), lowest with carbamazepine (7.7%), and 7.5% with no AED exposure.

Gailey and colleagues[22] conducted a well-controlled study comparing IQ scores in children aged 2 to 10 years born to mothers with epilepsy with those from a similar-sized group of normal controls. Findings were controlled for maternal age and education level and whether mothers had received AEDs as monotherapy or polytherapy. The mean verbal IQ score of children whose mothers had used valproate monotherapy during pregnancy was 84, and lower than among either children whose mothers had taken carbamazepine or healthy controls.

The ongoing Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study[23] is prospective and supported by the National Institute of Mental Health. It considers neurodevelopmental outcomes following in utero exposure to several AEDs, including carbamazepine, lamotrigine, phenytoin, and valproic acid, each in monotherapy. This study involves over 25 sites in the United States and the United Kingdom, and has enrolled 361 mother-child pairs to date. The available data from this study suggest that children exposed to valproic acid were at increased risk for developmental delays compared with children exposed to phenytoin, lamotrigine, or carbamazepine monotherapy. In addition, there was suggestive evidence of an association between risk for developmental delay and anticonvulsant dose.

RECOMMENDATIONS

New findings from pregnancy registries have begun to characterize potential teratogenic risks for valproic acid and lamotrigine, with some comparisons to older AEDs including barbiturates, carbamazepine, and phenytoin, as well as considering associations between in utero exposure to AEDs and later neurobehavioral development. Treating bipolar disorder in pregnancy is a dynamic process. Treatment options evolve on the basis of the patient's observed course of illness before and during pregnancy.

Safe treatment of women diagnosed with bipolar disorder during pregnancy, similar to safe treatment of epilepsy, is greatly enhanced with proper prepregnancy treatment planning and close clinical monitoring during pregnancy. The goal of clinicians caring for women with bipolar disorder who are either planning to conceive or are pregnant should be to provide the most up-to-date information regarding the spectrum of risks associated with either pursuing or deferring treatment with psychotropic medicines.

Conceptualizing pregnancies among women with bipolar disorder as *high-risk* pregnancies emphasizes the importance of sustained clinical monitoring and coordinated care among patient, partner, obstetrician, and psychiatrist. Pending controlled prospective studies of both the risk for potentially severe illness recurrence in pregnancy and further delineation of risks of medications on fetal and postnatal development, clinicians must continue to care for pregnant women with bipolar disorder while recognizing the limitations of the current knowledge base and weighing partially calculated risks.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), lamotrigine (Lamictal and others), phenytoin (Dilantin, Phenytek, and others), valproic acid (Depakene, Myproic Acid, and others).

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Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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