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# Teratogenic medications and concurrent contraceptive use in women of childbearing ability with epilepsy

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ABSTRACT

*Background:* Many antiepileptic drugs (AEDs) have the potential to cause teratogenicity. We evaluated eight antiepileptic drugs (AEDs) classified as Federal Drug Administration (FDA) pregnancy category D, X, or N designations and having documented teratogenic effects. These include carbamazepine, ethosuximide, fosphenytoin, phenobarbital, phenytoin, primidone, topiramate, and valproate. Women with epilepsy (WWE) may need one or more of these AEDs for seizure control but may be unaware of the potential teratogenicity associated with their use. In utero exposure to AEDs increases the risks for both congenital malformations and other teratogenic defects. Given that approximately 50% of pregnancies are unintended, it is likely that women with epilepsy taking these medications could unknowingly put a growing fetus at risk. For women using contraception while taking these medications, many choose combined hormonal contraceptives (CHCs). Drug–drug interactions exist between AEDs and CHCs that may decrease contraceptive efficacy. The aim of this study was to evaluate prescribing patterns for potentially teratogenic AEDs and contraceptive use in WWE of childbearing ability, including those with potential drug–drug interactions. This study also determined the number of WWE of childbearing ability prescribed potentially teratogenic AEDs and documentation of a pregnancy or contraception plan.
*Methods:* This was a retrospective, observational study of WWE age 15–44 years, of childbearing ability, prescribed an AED from July 1, 2011 to June 30, 2012, and who had an appointment at the University of Colorado Hospital Outpatient Neurology Clinic (Anschutz Medical Campus).
*Results:* One hundred fifteen women with an average age of 30.7 years and various types of seizures were evaluated. The majority of patients were prescribed topiramate (34/115, 30%) or carbamazepine (27/115, 23%). Of the women, 30/115 (26%) had a documented contraception method when taking a potentially teratogenic AED. Of these women prescribed contraception, most (18/30, 60%) used an oral combined hormonal contraceptive or progestin-only pill, a majority of which had a potential for a drug–drug interaction with their AEDs (16/18, 89%). Less than 7% of women received counseling on a contraception plan, and 18% of subjects received counseling on a pregnancy plan.
*Conclusions:* Most WWE of childbearing ability taking potentially teratogenic AEDs were not using contraception. Those using contraception frequently had a method that has a significant drug–drug interaction which reduces the effectiveness of contraception. Women with epilepsy of childbearing ability prescribed an AED should be using effective contraception or participating in active discussions about pregnancy planning to avoid unplanned pregnancies and possible teratogenic effects of these AEDs. Documentation about pregnancy planning or contraceptive use in WWE of childbearing ability is minimal and should be discussed at least annually. It is critical for providers to discuss with WWE of childbearing ability the benefits and risks of various AED treatments; the need to select appropriate, effective contraception when pregnancy is not desired; and the importance of counseling regarding contraceptive or pregnancy planning.



## 1. Introduction

There are an estimated one-half million women of childbearing age with epilepsy in the United States [1]. The traditional antiepileptic drugs (AEDs) have been known to increase the risk of major congenital malformations and IQ deficits in the developing fetus. At the time this study was initiated, there were eight antiepileptic drugs (AEDs) that were documented to have teratogenic effects with FDA labels of category D, X, or N (not classified): carbamazepine, ethosuximide, fosphenytoin, phenobarbital, phenytoin, primidone, topiramate, and valproate [2–9]. See Table 1 [10–32]. The FDA defined a category D medication as having positive evidence of human fetal risk, and a category X medication as having demonstrated fetal abnormalities and/or positive

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**Table 1**
Antiepileptic drug (AED) pregnancy category and risks.

| AED & pregnancy category | Risk |
|---|---|
| Carbamazepine (D) | Use during early pregnancy has been associated with an increased risk of neural tube defects. Craniofacial abnormalities and developmental delay have been associated [10,11]. |
| Ethosuximide (N) (Australia — D) | Interferes with embryo development in experimental animals. Reported human experience with this medication during pregnancy is too limited to contribute to an estimate of birth defect risk [12]. |
| Fosphenytoin (D) | Animal teratogen. Congenital anomaly, abnormal birth weight, and mental deficiency have been associated [13]. |
| Phenobarbital (D) | Animal teratogen. Congenital anomaly, abnormal birth weight, and mental deficiency have been associated [14–16]. |
| Phenytoin (D) | The spectrum of malformations is similar with many anticonvulsant drugs including facial clefts and aspects of fetal hydantoin syndrome [16–18]. |
| Primidone (D) | Use of agent during pregnancy has been associated with an increase in birth defects [19–22]. |
| Topiramate (D) | Produces abnormal pregnancy outcomes in experimental animals. Human case reports and registry data have identified both normal and abnormal pregnancy outcome after topiramate exposure [23–27]. |
| Valproate (X — migraine) (D — other indications) | Known teratogen to humans. Facial dysmorphology, congenital heart defects, spina bifida, cleft lip and palate, and developmental delays are some of the teratogenic effects seen [28–32]. |

evidence of human fetal risk in animals or humans. Women may need one or more of these medications to control seizure activity, yet may not be aware of the potential adverse effects for a fetus. In utero exposure to AEDs increases the risks for both congenital malformations and other teratogenic defects. The prevalence of major congenital malformations in offspring of women with epilepsy is estimated at 4% to 10%, which represents a 2- to 4-fold increase compared with the general population [33–36]. A recent study using the North American AED Pregnancy Registry provided estimates of the risk of major malformations among infants exposed to specific AEDs as monotherapy during the first trimester of pregnancy. The reported risk of malformation was 9.3% for valproate, 5.5% for phenobarbital, 4.2% for topiramate, 3.0% for carbamazepine, and 2.9% for phenytoin [25]. Polytherapy with AEDs is associated with a higher malformation rate than monotherapy [1]. The most common malformations seen with AEDs are cardiac defects, facial clefts, hypospadias, and neural tube defects. Furthermore, studies suggest that children exposed to valproate have significantly lower IQs than children exposed to other AEDs [37–42]. Given that approximately 50% of pregnancies are unintended, it is likely that women with epilepsy taking these medications could put a growing fetus at risk unknowingly [43].

For those women that do use contraception while taking these medications, many choose combined hormonal contraceptives (CHCs). They are prescribed for 17% of fertile women with epilepsy, which is as frequent as all women age 15–44 years [44,45]. Many women are unaware of drug interactions between CHCs and AEDs that may decrease contraceptive efficacy [46]. Estrogens and progestogens are metabolized by cytochrome P450 3A4. Several AEDs, including phenytoin, phenobarbital, carbamazepine, felbamate, topiramate, oxcarbazepine and primidone, induce cytochrome P450 3A4, leading to enhanced metabolism of either or both the estrogenic and progestogenic component of CHCs, thereby reducing their efficacy in preventing pregnancy. Alternatively, CHCs can also decrease the concentrations of AEDs such as lamotrigine and, thereby, increase the risk of seizures [47]. In one study, 65% of women prescribed a cytochrome p450-inducing AED were unaware of decreased oral contraceptive efficacy. Forty percent of those prescribed category D AEDs were unaware of potential teratogenic effects [48]. Women simultaneously using hormonal contraception and AEDs must be aware of the potential drug interactions as well as potential teratogenic effects.

A surprising number of physicians also do not have adequate knowledge about these potential interactions. A questionnaire revealed that nearly 30% of primary care physicians were unaware that there was an interaction between CHCs and AEDs [49]. In addition, approximately 50% of women with epilepsy taking CHCs indicate that they have never been given information about this specific issue by their prescribing physicians [48,49]. In addition, a study was done to assess pharmacists' knowledge of women's issues in epilepsy using the Knowledge of Women's Issues and Epilepsy II questionnaire. It revealed that 75% of pharmacists knew the drug interaction between enzyme-inducing AEDs and contraceptives; however, 69.1% stated that they did not know why there was a drug interaction between hormones and seizure control [49]. Thus, there are still significant gaps in knowledge for patients and health-care providers regarding this issue. Specifically, most of the studies evaluating potentially teratogenic drug use are observational database studies without individual patient level data. Additionally, health-care provider and patient knowledge is largely performed through surveys.

Education and awareness of these issues are critical as the American Academy of Neurology has included "counseling for women of childbearing potential with epilepsy" in its quality measurement set [50]. Specifically, this quality measure aims to measure and track "all female patients of childbearing potential (12–44 years old) diagnosed with epilepsy who were counseled or referred for counseling for how epilepsy and its treatment may affect contraception or pregnancy at least once a year". Furthermore, counseling should include a discussion about folic acid supplementation, contraception, potential antiseizure medication effect(s) on pregnancy, safe pregnancies, and breastfeeding.

This retrospective analysis aimed to address these issues by providing objective information about prescribing patterns for potentially teratogenic AEDs and contraceptive use. In addition, this study estimated the number of women with epilepsy (WWE) of childbearing ability prescribed potentially teratogenic AEDs with a concurrent contraceptive, and documentation of a pregnancy or contraception plan. For those WWE using AEDs and contraception, the prevalence of potential drug interactions was also determined.

## 2. Materials and methods

This study was a retrospective observational study whose subjects were selected at the University of Colorado Hospital Outpatient Neurology Clinics (Anschutz Medical Campus) in Aurora, CO. Patients that met our inclusion criteria were identified using ICD-9-CM codes in the EPIC (TM) and Epilepsy (TM) electronic health record (EHR) databases. This study was approved by the Colorado Institutional Review Board.

### 2.1. Study population

Subjects were eligible for inclusion if they were reproductive-aged women aged 15 to 44 years; diagnosed with epilepsy; and given a prescription for an AED with teratogenic potential (category D, X, or N) from July 1, 2011 to June 30, 2012 at the University of Colorado Hospital Neurology Clinics (Anschutz Medical Campus). The eight AEDs with a category D, X, or N are: phenobarbital, primidone, phenytoin, fosphenytoin, ethosuximide, carbamazepine, valproate, and topiramate. Exclusion criteria included women less than 15 years and over 44 years, women that had surgical sterilization, women that had early menopause, and women who had a hysterectomy.

### 2.2. Data collection and analysis

For eligible patients, the EHR was scanned systematically for AEDs prescribed and a documented pregnancy or contraceptive plan. Data were collected into a Microsoft Access database and included patient demographics: prescribed AEDs, duration of treatment and dose, concomitant medications (including contraception), documentation of a