

Antiepileptic drugs: Are women aware of interactions with oral contraceptives and potential teratogenicity?

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ABSTRACT

Women with epilepsy (WWE)'s knowledge of the interaction between antiepileptic drugs (AEDs) and oral contraceptives (OCs) and the potential teratogenicity of AEDs has received limited study. We conducted a cross-sectional questionnaire study (English or Spanish) among young WWE (18–44 years) to assess demographic characteristics, current AED use, and knowledge of AED interactions with OCs and teratogenicity. We used the Food and Drug Administration's classification system to categorize each AED's teratogenic potential. Participants ($n = 148$) had a mean age of 32 years (SD 8); 32% spoke Spanish and described themselves as Hispanic. Among women prescribed a cytochrome p450-inducing AED, 65% were unaware of decreased OC efficacy. Forty percent of those prescribed Category D AEDs were unaware of potential teratogenic effects. WWE have limited knowledge of the potential interaction between AEDs and OCs and the teratogenic effects of AEDs. Educational efforts should highlight the reproductive health effects of AEDs in WWE.

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1. Introduction

Approximately 1,000,000 women in the United States have epilepsy. Health care for reproductive-age women with epilepsy (WWE) must include consideration of contraception. When pregnancies are planned, health care providers can optimize medication management for seizure control and minimize the risk of teratogenesis. Unfortunately, contraception is a challenge for women in the United States; approximately 50% of their pregnancies are unplanned [1]. Pregnancy planning is especially complex for young WWE who are treated with antiepileptic drugs (AEDs). Providers and women need to be aware of drug interactions potentially decreasing the effectiveness of hormonal contraception, as well as AED-related teratogenicity.

Practice guidelines emphasize use of effective contraception and discussion of the increased risk of teratogenesis for WWE [2]; published research, however, documents barriers to implementation of these guidelines. Some health care providers (both obstetrician/gynecologists and neurologists) misunderstand AED interactions with hormonal contraception and potential teratogenicity [3–5]. Additionally, providers' counseling may be inadequate

or ineffective [6]. A British survey study reported that 51% of WWE claimed to have never received advice on contraception [7].

We found only one Norwegian study that examined knowledge of the reproductive health effects of AEDs among WWE themselves [5]. We conducted a pilot questionnaire study to explore knowledge among U.S. WWE of the impact of AEDs on oral contraceptive (OC) effectiveness and the potential teratogenicity of AEDs.

2. Methods

We conducted a cross-sectional questionnaire study in a convenience sample of women with epilepsy presenting for routine outpatient care. The study was approved by the institutional review board of the Columbia University Medical Center. Participants were recruited from three practice locations within the Columbia Comprehensive Epilepsy Center between July 2005 and February 2006.

All women presenting for routine visits were approached by a research assistant before they met with their treating physician to ascertain knowledge prior to physician counseling. Eligible participants included adult WWE between the ages of 18 and 44. We excluded women over the age of 44 because we wanted to examine knowledge among women of reproductive age. We excluded women with cognitive impairment who were unable to understand the questionnaire.

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We developed our questionnaire in English and Spanish. Participants were allowed to select the version in the language they preferred. Participants signed an informed consent, and the questionnaire was administered by a research assistant in a private room. The questionnaire assessed demographic characteristics, reproductive history, sexual orientation and behavior, contraception, and pharmacotherapy. Collected demographic information included age, ethnicity, insurance payor, spoken language, and level of educational attainment. We asked participants if they describe themselves as Hispanic to explore possible disparities in reproductive health outcomes by ethnicity. Results regarding reproductive history, use of contraception, and sexual behavior have been published elsewhere [8].

Participants were asked to list all their current medications. We did not review medical records to assess whether the medications participants listed agreed with what had been prescribed. A few participants reported using benzodiazepines; we did not categorize benzodiazepines as AEDs for this analysis because they were typically used intermittently. Short- and long-acting carbamazepine preparations were both categorized as carbamazepine. Short- and long-acting valproate preparations were treated similarly. Questions regarding the effects of medications were asked in an open-ended format. If there was no response, the research assistant prompted the participant with the response categories.

Multiple forms of hormonal contraception are available in the United States (patch, ring, implant, and injectable). We chose to question women solely about OCs and AEDs, because OCs remain the most commonly used form of hormonal contraception [9] and very few pharmacokinetic studies have examined the effects of other hormonal forms of contraception and AEDs. To assess awareness of AED–OC interactions, women were asked “Do you know if [this AED] changes how birth control pills work?” Participant responses were coded by the research assistant as: (1) decreases effectiveness, (2) causes no change in effectiveness, or (3) doesn’t know. All participants were asked this question, regardless of their current contraceptive method, if any.

To assess awareness of potential teratogenicity, participants were asked “Do you know if [this AED] affects the development of a baby during pregnancy?” Responses were coded by the research assistant as: (1) bad effect, (2) good effect, (3) no effect, or (4) doesn’t know. After administering the first few question-

naires, we added the additional response category “unknown effect” after some participants volunteered that response.

We chose to use the FDA categorization system—A, B, C, D, or X—to assign a fetal risk level for exposure to each AED in pregnancy [10]. The FDA categorizes all AEDs as either C (animal studies demonstrate adverse effects without controlled studies in women) or D (positive evidence of human fetal risk). Gabapentin, oxcarbazepine, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide are Category C drugs. Carbamazepine, phenobarbital, phenytoin, primidone, and valproate are Category D drugs.

We classified phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and topiramate as cytochrome p450 isoenzyme inducers that accelerate metabolism of sex steroids, thereby potentially increasing the risk of hormonal contraceptive failure [11]. We classified gabapentin, pregabalin, lamotrigine, valproate, and zonisamide as noninducers that do not increase the risk of hormonal contraceptive failure [11].

Data were entered into an SPSS database (SPSS Version 13.0). Statistics were exploratory and descriptive as no specific hypothesis was tested. No a priori power analysis was performed.

3. Results

The flow of participants through the study is illustrated in Fig. 1, as previously published [8]. We stopped enrollment after 148 women completed questionnaires because increasing numbers of women we approached participated previously.

Demographic characteristics of the participants are summarized in Table 1. Our sample was diverse in ethnicity, language, educational attainment, socioeconomic status, and type of payor for medical services. The mean age was 31.7 years (SD 7.8), with 26% aged 18 to 25, 36.4% aged 26 to 35, and 37% aged 36 to 44.

Overall, the 148 women who completed questionnaires reported taking 154 Category C AEDs and 50 Category D AEDs. Six women (4%) reported no current AED therapy (two of these were pregnant), 89 (60%) reported taking one AED, 44 (30%) reported taking two AEDs, and 9 (6%) reported taking three AEDs.

Overall, the most common response was that women did not know if their AED affected fetal development (Table 2). Results were similar for Category C AEDs (45% did not know) and Category D AEDs (40% did not know). Of concern, some women indicated that there was “no effect” of a Category D AED or even a “good effect” on a developing fetus. Ten (6%) women reported their AED had an unknown effect on fetal development; seven of these women were taking lamotrigine. No woman reported the effects of any Category D AED as unknown.

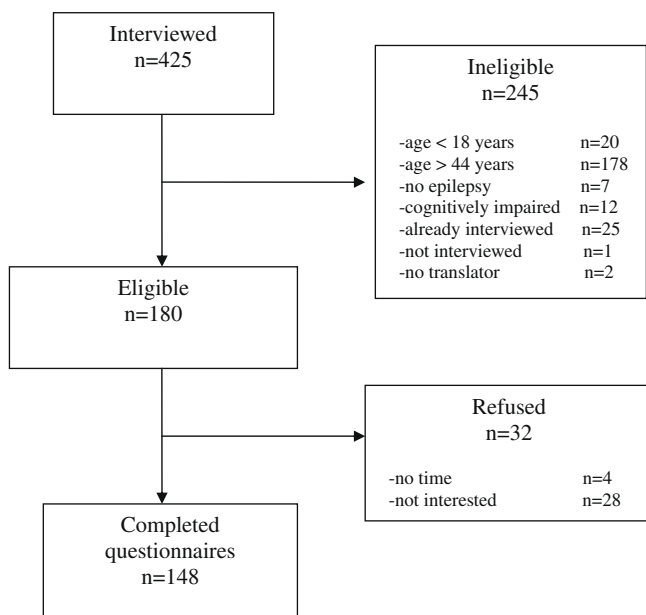


Fig. 1. Flow of participants.

Table 1
Description of participants (n = 148).

Characteristic	n (%)
Spoken language	
English	100 (68)
Spanish	12 (8)
English and Spanish	36 (24)
Ethnicity	
Hispanic	47 (32)
Non-Hispanic	101 (68)
Education	
<High school	31 (21)
Completed high school	20 (14)
Some college or degree	60 (41)
Postgraduate education	37 (25)
Health insurance	
Medicaid	57 (39)
Medicare	3 (2)
Commercial payer	82 (55)
Self-pay	6 (4)

Table 2
Women's responses to "Does this AED affect fetal development?"^a

Number of women taking AED	Patient response, N (%)			
	Bad effect on fetal development	Good effect on fetal development	No effect on fetal development	Doesn't know effect on fetal development
AED Category C				
GBP ^b 8	2 (25)	0	2 (25)	3 (38)
OXC 13	6 (46)	0	0	6 (46)
LEV ^b 37	13 (35)	0	2 (5)	20 (54)
LTG 69	15 (22)	2 (3)	19 (28)	26 (38)
PGB 2	0	0	0	2 (100)
TPM 15	5 (33)	1 (7)	1 (7)	8 (53)
ZNS 10	4 (40)	0	0	5 (50)
Total 154 ^c	25 (29)	3 (2)	24 (16)	70 (45)
AED Category D				
CBZ ^b 26	8 (31)	2 (8)	2 (8)	12 (46)
PB 2	0	0	1 (50)	1 (50)
PHT 9	6 (67)	0	0	3 (33)
PRM 1	0	0	0	1 (100)
VPA 12	8 (67)	1 (8)	0	3 (25)
Total 50	22 (44)	3 (6)	3 (6)	20 (40)

^a Patients' responses on potential teratogenicity or effects of AED on the development of the baby for each individual AED prescribed. *N* = number of women using AED as either mono- or polytherapy. GBP, gabapentin; OXC, oxcarbazepine; LTG, lamotrigine; LEV, levetiracetam; PGB, pregabalin; TPM, topiramate; ZNS, zonisamide; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; VPA, valproate.

^b Each of these prescribed AED groups had missing responses (GBP = 1, LEV = 1, CBZ = 2).

^c For Category C AEDs, the total response categories do not add to the total number of AEDs rated because 10 women reported that their AED had an unknown effect on fetal development.

Table 3
Women's responses to "Does this AED change how birth control pills work?"^a

No. of women taking AED	Patient response, N (%)		
	AED decreases effectiveness of OC	AED decreases effectiveness of OC	Doesn't know if AED changes effectiveness of OC
p450 inducers			
CBZ 26	8 (31)	1 (4)	17 (65)
OXC 13	5 (38)	0	8 (62)
PB 2	1 (50)	0	1 (50)
PHT 9	1 (11)	1 (11)	7 (78)
PRM 1	0	0	1 (100)
TPM 15	6 (40)	0	9 (60)
Total 66	21 (32)	2 (3)	43 (65)
Non-p450 inducers			
GBP 8	2 (25)	5 (63)	1 (13)
LTG 69	19 (28)	21 (30)	29 (42)
LEV 37	7 (19)	6 (16)	22 (59)
PGB 2	0	0	2 (100)
VPA 12	5 (42)	2 (17)	5 (42)
ZNS 10	3 (30)	1 (10)	6 (60)
Total 138	36 (26)	35 (25)	65 (47)

^a Patients' responses on interaction between OCs and AEDs. *N* = number of women using AED as either mono- or polytherapy. GBP, gabapentin; OXC, oxcarbazepine; LTG, lamotrigine; LEV, levetiracetam; PGB, pregabalin; TPM, topiramate; ZNS, zonisamide; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; VPA, valproate.

Table 3 summarizes the results regarding knowledge about drug interactions for each AED. The 148 participants reported taking 66 AEDs categorized as p450 inducers and 138 AEDs categorized as noninducers. Most women using enzyme-inducing AEDs did not know if their current AED decreased the effectiveness of OCs. Results were similar for individual enzyme-inducing AEDs.

We also examined what proportion of WWE had correct knowledge about AED–OC interactions. WWE were classified as correct if they knew all their AEDs did or did not decrease OC effectiveness. They were classified as incorrect if they (1) did not know the AED's effect on OCs, or (2) believed there was an effect when there was none, or (3) believed there was no effect when there was an effect. Overall, of the 142 women taking at least one AED, only 19.7% (*n* = 29) were correct: 28.1% (*n* = 42) of those taking one AED were correct, 6.8% (*n* = 10) of those taking two AEDs were correct, and none of the nine women taking three drugs were correct.

Correct knowledge about drug interactions is most relevant for women currently using hormonal contraception. In our sample, 16

women currently used OCs; of those, 8 were incorrect. Of the 3 using the contraceptive patch, 2 were incorrect, and the one woman using the injectable (depo medroxyprogesterone acetate) was also incorrect.

Contraceptive knowledge is also relevant for women who have a history of pregnancy or are currently at risk for getting pregnant. Those who reported current sexual intercourse were slightly more likely to be correct about their current AED–OC interactions than those who were not sexually active (Fisher's exact test, *P* = 0.04). Those reporting current use of any contraception (*P* = 0.57), a history of pregnancy (*P* = 0.34), a birth (*P* = 0.34), or a voluntary abortion (*P* = 0.41) were no more likely to be correct than those who were not using contraception, had never been pregnant, had never given birth, or had never had an abortion, respectively.

Finally, we investigated if socioeconomic characteristics were associated with awareness of the effects of AEDs on OCs. Type of payor was associated with knowledge; 9% of those with Medicaid or Medicare were correct versus 27% of those with commercial

insurance or who paid out-of-pocket ($P = 0.004$). With respect to ethnicity, 7% of those who self-identified as Hispanic or Latina were correct versus 26% of those identifying as non-Hispanic ($P = 0.004$). For language, 11% of Spanish speakers were correct versus 24% of English speakers ($P = 0.06$). Finally, 6% of those with a high school degree or less education were correct versus 27% of those with more education ($P = 0.003$). We did not include race in this analysis because women were unable to self-identify with simple categorizations of race (especially choosing between white and black).

4. Discussion

The WWE presenting for treatment at our academic medical center had very limited knowledge of the reproductive health effects of their current AEDs. Forty-five percent of those prescribed Category C AEDs and 40% prescribed Category D AEDs were unaware of potential teratogenic effects. Among those prescribed a cytochrome p450 enzyme-inducing AED, 65% were unaware of a decrease in OC efficacy. This limited knowledge may result in preventable morbidity: unplanned pregnancy, fetal exposure to teratogenic AEDs, and maternal stress. Women in our sample reported that 50% of their pregnancies were unplanned. We did not assess if these unplanned pregnancies occurred in the context of a drug interaction, whether fetal AED exposure occurred, or whether AED exposure contributed to the decision to have an abortion [8].

Overall, WWE in our sample were unclear about the safety of AEDs during fetal development. Women seemed most knowledgeable about valproate and phenytoin, which they identified as the least safe (67% of responses indicated a “bad effect”), but few women reported using these AEDs. Women were less knowledgeable about the most commonly prescribed AEDs, lamotrigine and levetiracetam. Confusion among WWE in our sample may reflect inadequate counseling, especially for women speaking exclusively Spanish. Alternatively, confusion may be secondary to an evolving understanding of AED teratogenesis. For example, recent data suggest that carbamazepine, a Category D AED, may have minimal teratogenic effects when prescribed as monotherapy [12]. Moreover, the concept of Category C merely reflects a lack of information and, therefore, may be confusing to both practitioner and WWE alike.

Women in this sample were also unclear about the effects of enzyme-inducing AEDs on OCs. Most of those prescribed enzyme inducers were unaware of potential decreased OC efficacy, and some of those prescribed noninducers mistakenly believed those AEDs decrease OC efficacy. Knowledge was especially low among those WWE who had Medicaid, self-identified as Hispanic, were less educated, and spoke Spanish. These women were also more likely to have unplanned pregnancies [8]. One explanation for low knowledge might be that such information is not personally relevant to some WWE; that is, they may not be sexually active or have experienced pregnancy. Our data do not support this explanation; low knowledge was common regardless of sexual behavior or reproductive history. Of interest, women seemed most knowledgeable about gabapentin, 63% correctly responded that there was no effect on OCs, but only eight women used this AED.

Poor understanding of hormonal interactions with AEDs increases the risk of unplanned pregnancy in two ways. Some women prescribed inducers will become pregnant due to an unrecognized drug interaction and some women will become pregnant as a result of choosing less effective barrier methods such as male condoms if they mistakenly believe hormonal methods are ineffective. Incorrect knowledge about AED–OC interactions among health care providers no doubt contributes to women’s confusion.

An important strength of our study is that we obtained knowledge directly from women themselves. Other studies have assessed counseling; however, the occurrence of counseling does not guarantee understanding or behavior. A Norwegian study examined medical records to assess if WWE were counseled about contraception and pregnancy-related issues [5]. In addition, 112 of 157 WWE completed a questionnaire. Most medical records (67%) did not document counseling; however, 71% of WWE prescribed enzyme-inducing AEDs who completed the questionnaire knew their AED could increase the risk of OC failure. Knowledge among these Norwegian WWE was better than in our sample; however, women with correct knowledge may have been more likely to complete questionnaires.

Inadequate contraceptive counseling and low uptake of highly effective contraception during use of potentially teratogenic medication are not unique to WWE. Schwarz examined pharmacy and medical records of 488,175 women aged 15 to 44 and found that one of every six women studied were prescribed a Category D or X medication [13]. These women were no more likely to have received contraceptive counseling, filled a contraceptive prescription, or been sterilized than women not prescribed teratogenic medications. Unfortunately, our study found similar results using information from women themselves. A poor understanding of teratogenic medication effects may undermine use of effective contraceptive methods; women probably are less likely to risk pregnancy if they understand their medication negatively affects fetal development.

Our study has limitations. Our results reflect a particular prescribing pattern and counseling style for this medical center that may not be generalizable to other settings. We planned to assess knowledge about drug interactions among women currently using a hormonal method and enzyme-inducing AED. However, we were not able to examine this issue with precision because too few WWE in our sample were sexually active and currently using hormonal methods. This question could be addressed by a larger study. Not only do AEDs affect the efficacy of OCs, but concomitant administration of OCs and lamotrigine decrease the available concentration of lamotrigine. As we did not ask about this specifically, the lack of data regarding WWE’s knowledge about this interaction is also a limitation. Our results about knowledge are preliminary. We cannot determine if low knowledge reflects inadequate counseling or current limited understanding of the teratogenic effects of AEDs, or both. Because of this uncertainty, we did not investigate specific demographic variables associated with teratogenic knowledge of AEDs. Finally, we did not assess knowledge of the teratogenic effects of polytherapy, which is a known risk factor for increased rates of major congenital malformations.

In conclusion, we found that WWE had limited knowledge about (1) potential teratogenic effects of AEDs and (2) interactions between AEDs and OCs. Further research should determine if our findings are generalizable to other populations of WWE. Educational interventions, both for providers and for WWE, are needed to improve reproductive health for this population. Poor, Hispanic women may derive more benefit from such interventions.

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