



Review

Differential impact of antiepileptic drugs on the effects of contraceptive methods on seizures: Interim findings of the epilepsy birth control registry



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ABSTRACT

Purpose: To present the interim findings of the Epilepsy Birth Control Registry (EBCR) regarding the impact of various contraceptive methods on seizures, stratified by antiepileptic drug (AED) type.

Methods: This is an observational study that reports interim findings on the first 750 subjects.

Results: There are significantly greater relative risks (RR) for both seizure increase and decrease with hormonal contraception (HC) than with non-hormonal contraception (NHC). The rates of HC experiences associated with seizure increase (21.0%) are greater than with NHC (3.9%) (RR = 5.39 [95% CI = 3.77–7.73, $p < 0.0001$]). The rates of HC experiences associated with seizure decrease (10.3%) are greater than with NHC (5.6%) (RR = 1.85 [95% CI = 1.30–2.62, $p = 0.0006$]). While differences can reflect biological effects or reporting bias, the finding of a greater RR for seizure increase with hormonal patch than with combined oral contraceptive, perhaps related to the delivery of substantially higher concentrations of hormones, and a greater RR for seizure decrease with depomedroxyprogesterone, known to reduce seizure frequency when used in dosages which produce amenorrhea, support biological effects. All AED categories showed significantly higher frequencies of reports of seizure increase when combined with HC than with NHC. RR for seizure increase with HC was higher with valproate than with any other AED category. There were no significant differences among AEDs for seizure decrease with HC at this juncture of the study. Overall, NEIAEDs had the most favorable profile with regard to reports of seizure increase and decrease when used with HC.

Conclusions: Interim EBCR findings suggest that contraception category and interactions between contraception category and AED category are predictive factors for changes in seizure frequency in WWE.

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1. Introduction

Family planning and contraception are important considerations for women of reproductive age. They present particularly important challenges for women with epilepsy (WWE) and their clinicians because reproductive steroids have neuroactive properties that have the potential to impact seizures [1] and there are reciprocal interactions between hormones and some antiepileptic drugs (AEDs) that may impact both seizures and contraception

[2–4]. There is also the potential for hormonal contraception to affect epilepsy co-morbidities such as depression and headache which are overrepresented in WWE [5,6]. Despite the importance of these issues, there has been little formal study of contraception in WWE in the community and hence, a lack of evidence-based guidelines for the selection of optimal contraceptive methods for this special population.

2. Epilepsy Birth Control Registry

The Epilepsy Birth Control Registry (EBCR) is a collaborative effort among medical, epidemiological/biostatistical and bioinformational technology specialists to develop a web-based survey methodology to conduct long-term, prospective, observational studies that will characterize the contraceptive practices of WWE in the community, the decision making process involved in the selection of a contraceptive method and the contraception

Abbreviations: WWE, women with epilepsy; RR, relative risk; HC, hormonal contraception; NHC, non-hormonal contraception; AED, antiepileptic drug; EBCR, Epilepsy Birth Control Registry; EIAED, enzyme inducing AED; GluAED, glucuronidated AEDs; NEIAED, non enzyme inducing AED; InhAED, enzyme inhibiting AED.

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concerns of this special population. The subjects were of reproductive age and age of consent between 18 and 47 years. The study aims to generate hypotheses that will be tested in order to assess and compare the safety and efficacy of various forms of contraception used by this special population. “Safety” refers to the incidence of seizure exacerbation, as well as other specific adverse neurological, neuropsychiatric and reproductive events that may be associated with the use of various types of contraception. “Efficacy” refers to the incidence of unplanned pregnancies associated with the use of various contraceptive methods. The ultimate goal of the project is to develop evidence-based guidelines for safe and effective contraceptive practices for WWE, identify disparities in the availability and use of optimal contraceptive methods related to demographic factors, and develop educational interventions based on information derived from the Registry.

The specific aims of the EBCR project are the following:

1. To characterize the contraceptive practices of WWE.
2. To characterize the decision making process.
3. To determine the impact of various contraceptive methods on seizures, stratified by AED type.
4. To determine reasons for discontinuation of various contraceptive methods.
5. To estimate rates of fertility, unintended pregnancy, and pregnancy outcomes.
6. To determine rates of folic acid use and factors that determine its use.

This report presents the interim results of the 3rd specific aim, i.e., the impact of various contraceptive methods on seizures, stratified by AED type.

3. Demographic characteristics of the EBCR population

The first 750 WWE who completed the EBCR survey, 18–47 years of age, provided the data for this interim analysis. Ninety five percent of surveys were completed by participants located in the USA. The average age \pm standard deviation of the subjects was 28.3 ± 6.9 years; 53.3% in the 18–27 year old cohort, 35.9% in the 28–37 year old cohort and 10.8% in the 38–47 year old cohort. Using 2010 USA census figures [7], racial minorities, including Hispanic ethnicity, were underrepresented, i.e., 8.8% of the EBCR population versus 25.2% of the general population. Subjects had higher education levels as compared to the general population; 83.4% had taken college courses or had college degrees versus 59.2% in the general population. Average household income was less than that of the general population, i.e., 40.1% had less than 25,000 USD income as compared to 20.5% in the general population. In summary, on average, the subjects were younger and better educated but with lower household income than the general population. One can speculate that younger women may be more inclined to utilize web based information and inquire about contraception and that younger age and the morbidity of epilepsy may be factors in the lower income. Minorities were underrepresented despite the great majority of participants, i.e., 77.6%, reporting that they learned about the Project on line through Facebook, epilepsy.com and the Epilepsy Foundation that have wide outreach.

4. Epilepsy and antiepileptic drug characteristics

Four hundred thirty four (57.9%) of the 750 WWE reported currently having generalized convulsive seizures, 304 (40.5%), complex partial and 198 (26.4%), simple partial seizures. One hundred sixty four (21.9%) reported complex partial seizures as their most severe seizure type and 76 (10.1%) reported simple partial seizures as their most severe seizure type. Seventy six (10.1%) of the WWE were free of seizures.

The numbers and frequencies of AEDs used alone or in combination are listed in Table 1a. 56.3% were using polytherapy, 36.6%, monotherapy and 6.0% were on no AED. The most frequent combinations, i.e., those comprising $\geq 3.5\%$ of all combinations, are listed in Table 1b. To provide a meaningful power for statistical comparisons at this stage of enrolment in the Project, AEDs were grouped into six categories based on their effects on enzymatic metabolism: (1) No AED, (2) enzyme inducing AEDs (EIAEDs) which included phenobarbital, phenytoin, carbamazepine, oxcarbazepine and topiramate in dosages above 200 mg daily, (3) glucuronidated AEDs (GluAEDs) which included only lamotrigine, (4) non-enzyme inducing AEDs (NEIAEDs) which included levetiracetam, zonisamide, gabapentin, topiramate in dosages up to 200 mg daily, lacosamide, clobazam, pregabalin and tiagabine, (5) enzyme inhibiting AEDs (InhAEDs) which included only valproate, and (6) mixed categories. Note, valproate was listed in the enzyme inhibiting category although it is also partially glucuronidated. When there was a combination of a category that affected enzymes and a NEIAED, the combination was listed by the AED category that affected enzymes. If the combination was comprised of two or more AEDs with different enzyme categories, they were listed under the mixed category. The frequencies of use of the AED categories are presented in Table 1c.

5. Contraceptive practices of women with epilepsy in the community

The categories and subcategories of contraception that were in use by the EBCR population are as follows: (1) none, (2) withdrawal, (3) barrier (condom, diaphragm), (4) systemic

Table 1a
AEDs used alone or in combination.

AED	N = 1128
Lamotrigine	268 (23.8%)
Levetiracetam	217 (19.2%)
Topiramate	119 (10.5%)
Carbamazepine	75 (6.6%)
Valproate	69 (6.1%)
Zonisamide	67 (5.9%)
Oxcarbazepine	56 (5.0%)
None	45 (4.0%)
Phenytoin	39 (3.5%)
Clonazepam	33 (2.9%)
Other	33 (2.9%)
Lacosamide	30 (2.7%)
Pregabalin	24 (2.1%)
Gabapentin	16 (1.4%)
Phenobarbital	11 (1.0%)
Clobazam	10 (0.9%)
Tiagabine	8 (0.7%)
Primidone	8 (0.7%)

Table 1b
AED combinations.

AED	N = 283 ($\geq 3.5\%$)
Lamotrigine + Levetiracetam	51 (18.0%)
Lamotrigine + Topiramate	22 (7.8%)
Levetiracetam + Topiramate	14 (4.9%)
Lamotrigine + Valproate	11 (3.9%)
Lamotrigine + Carbamazepine	10 (3.5%)
Lamotrigine + Zonisamide	10 (3.5%)
Levetiracetam + Carbamazepine	10 (3.5%)
Levetiracetam + Oxcarbazepine	10 (3.5%)
Levetiracetam + Zonisamide	10 (3.5%)

AED combinations constituting $\geq 3.5\%$ of the 283 combinations are presented.

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