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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.


## 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 ± 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 ≥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 (>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 ≥3.5% of the 283 combinations are presented.

**Table 1c**
AEDs by categories.

| AED | N = 750 |
|---|---|
| None | 45 (6.0%) |
| EIAED | 198 (26.4%) |
| GluAED | 221 (29.5%) |
| NEIAED | 207 (27.6%) |
| InhAED | 44 (6.9%) |
| Mixed | 35 (4.7%) |

EIAED, enzyme inducing AEDs; GluAED, glucuronidated AEDs (lamotrigine only); NEIAED, non enzyme inducing AEDs; InhAED, enzyme inhibiting AEDs (valproate only); Mixed, mixed categories.

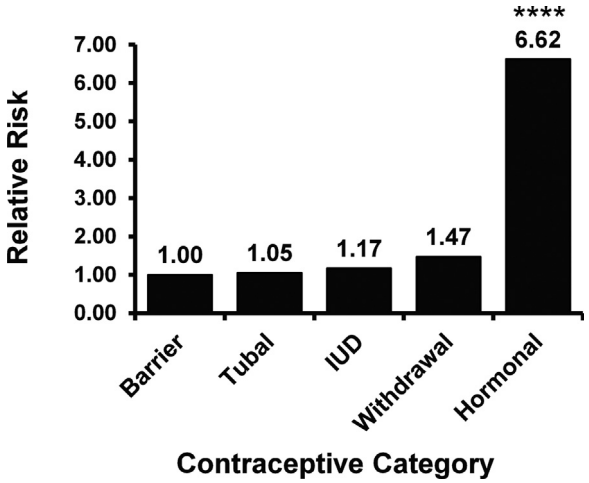


**Fig. 1.** Relative risks for seizure increase on various categories of contraception in comparison to barrier category which had the lowest rate at 3.2%. Hormonal contraception was the only category that showed a significantly greater risk (****$p < 0.0001$). Hormonal category also had a significantly greater risk for seizure increase than tubal ($p < 0.05$), IUD ($p < 0.0001$) and withdrawal ($p < 0.0001$).

hormonal (combination – oral contraceptive pills, hormonal patch, vaginal ring; progestin only – progestin pills, implanted progestin, depomedroxyprogesterone), (5) intrauterine device (IUD – progestin coated, copper), (6) tubal ligation, and (7) partner with vasectomy. The 750 women reported 1581 contraceptive experiences: 237 (15.0%) withdrawal, 474 (30.0%) barrier, 706 (44.6%) systemic hormonal, 134 (8.5%) IUD and 30 (1.9%) tubal ligation. When used in combination, the category is listed under the generally more effective method.

## 6. Differential effects of the various contraceptive categories and methods on seizure frequency

For each of the 1581 contraceptive experiences, the women were asked the question "Do you think that this method of birth control changed how often you had seizures?" Response choices were "no change," "increase," or "decrease." Although the majority of responses were "no change" a substantial number of experiences were reported to have been associated with a change in seizures, whether increase or decrease. The numbers and frequencies are tabulated by contraceptive category in Table 2a. The lowest rate of seizure increase was reported with barrier methods (3.2%) whereas the highest occurred with systemic hormonal methods (21.0%). The relative risks of seizure increase with each category of contraception relative to barrier, the one with the lowest rate, are presented in Fig. 1. The relative risk of seizure increase was significantly and substantially greater with hormonal contraception (HC) than with each of the categories of non-hormonal contraception (NHC). Overall, in comparison to non-hormonal methods, hormonal contraception had a significantly greater relative risk of both seizure increase HC: 148/706 experiences (21.0%) vs. NHC: 34/875 (3.9%); RR = 5.39 [95% CI = 3.77–7.73, $p < 0.0001$] and seizure decrease HC: 73/706 (10.3%) vs. NHC: 49/875 (5.6%); RR = 1.85 [95% CI = 1.30–2.62, $p = 0.0006$], with seizure increase being substantially higher (RR = 5.39 vs. 1.85). Significant differences between hormonal and non-hormonal categories may reflect a biological effect, reporting bias or both. In support of biological factors are some significant differences among the methods listed in the hormonal category. Specifically, hormonal patch, which is the only combined contraception method that is known to produce substantially higher, i.e., by 60%, serum estrogen levels than the 35 microgram containing ethinyl estradiol pill [8,9], was associated with a significantly greater relative risk for seizure increase than the oral contraceptive method (RR = 1.81, 95% CI = 1.13–2.90), the most frequently used and lowest seizure risk hormonal contraceptive method in the EBCR population (Table 2b). In contrast, depomedroxyprogesterone which is known to reduce seizure frequency when used in dosages which produce amenorrhea [10], was associated with a significantly greater relative risk for seizure decrease than the oral contraceptive method (RR = 1.81, 95% CI = 1.10–2.98; Table 2b). Both of these significant differences in the EBCR population are consistent with plausible biological mechanisms of action. For example, the association of higher rates of reports of seizure increase with hormonal patch may reflect the delivery of higher concentrations of estrogen since estrogen may have a proconvulsant effect [1]. The higher rates of reports of seizure decrease with depomedroxyprogesterone may reflect the suppression of estrogen production by the ovary in the setting of amenorrhea. This does not exclude other plausible operant mechanisms. We previously reviewed some of the neuroactive properties of progesterone and estradiol [1]. Of note, however, there is very little basic science and experimental animal evidence regarding the neuroactive properties of the most common

**Table 2a**
Frequencies of seizure changes with various categories of contraception.

| | N = 1581 | Sz increase (%) | Sz decrease (%) |
|---|---|---|---|
| Withdrawal | 237 | 11 (4.6%) | 6 (2.5%) |
| Barrier | 474 | 15 (3.2%) | 19 (4.0%) |
| Hormonal | 706 | 148 (21.0%) | 73 (10.3%) |
| IUD | 134 | 5 (3.7%) | 19 (14.2%) |
| Tubal ligation | 30 | 1 (3.3%) | 5 (16.7%) |

**Table 2b**
Comparisons of subcategories of hormonal contraception on reports of seizure change.

| | N | Sz increase (%) | Sz decrease (%) |
|---|---|---|---|
| Combined | | | |
| Oral | | | |
| Combined OCP | 435 | 80 (18.4%) | 40 (9.2%) |
| Non-oral | | | |
| Vaginal ring | 63 | 16 (25.4%) | 5 (7.9%) |
| Hormone patch | 42 | 14 (33.3%) | 3 (7.1%) |
| Progestin only | | | |
| Oral | | | |
| Progestin OCP | 30 | 8 (26.7%) | 4 (13.3%) |
| Non-oral | | | |
| Progestin implant | 16 | 5 (31.3%) | 1 (6.3%) |
| DMPA | 120 | 25 (20.8%) | 20 (16.7%) |

IUD, intrauterine device, Sz, seizure frequency; OCP, oral contraceptive pills; DMPA, depomedroxyprogesterone.

synthetic steroid constituents of hormonal contraception such as ethinyl estradiol, norethindrone, norgestrel and drospirenone as they may pertain to brain substrates with epileptic discharges and seizures. One study that examined the effects of certain estrogens and progestins on electroshock seizure thresholds in female rats found that, although synthetic progestins did not have a significant effect, co-administration with ethinyl estradiol or mestranol, another synthetic estrogen, significantly lowered the seizure threshold [11]. An abstract of another study reports an increase in seizure severity with ethinyl estradiol treatment in the baboon [12]. Nevertheless, the evidence regarding the neuroactive properties of contraceptive hormones is strikingly scant, given the widespread clinical use of hormonal contraception.

## 7. Differential effects of antiepileptic drug categories on changes in seizure frequency with hormonal contraception

The 750 subjects used a total of 1128 AEDs alone or in combination. The frequencies of use alone, in combination and by categories are presented in Tables 1a–1c. The frequencies of reports of seizure increase on HC and NHC, stratified by AED monotherapy category is presented in Fig. 2. All of the AED categories showed significantly and substantially higher frequencies of reports of seizure increase when combined with HC as compared to NHC.

Binary logistic regression showed an interaction between contraception category and AED category as a predictive factor for seizure increase ($p < 0.001$). Odds ratios were significant for interactions between AED categories and hormonal but not non-hormonal categories of contraception. In comparison to the Barrier and No AED combination, odds ratios were as follows: Hormonal and InhAED (valproate), OR = 6.220 (3.025–12.791), $p = 0.0005$; Hormonal and GluAED (lamotrigine), OR = 2.773 (1.535–5.009), $p = 0.001$; Hormonal and EIAEDs, OR = 2.258 (1.257–4.057), $p = 0.006$; Hormonal and NEIAED, OR = 2.014 (1.026–3.955), $p = 0.042$. The relative risks for seizure increase on HC, stratified by AED monotherapy category is presented in Fig. 3. The enzyme inhibiting category, valproate, showed a trend for or significantly greater risk for seizure increase as compared to each of the other AED categories. Of note, in 40 experiences on valproate + HC use, seizure increase was reported in 15 (37.5%) whereas there were no reports (0.0%) of seizure increase in 43 experiences on valproate + NHC (Fisher's exact test for seizure increase: $p < 0.0001$). In contrast, seizure decrease reports with valproate were very similar for the HC and NHC groups: 2/40 (5.6%) on valproate + HC versus 2/43 (4.7%) on valproate + NHC (Fisher's exact test for seizure decrease: $p$ = NS) (Table 3).

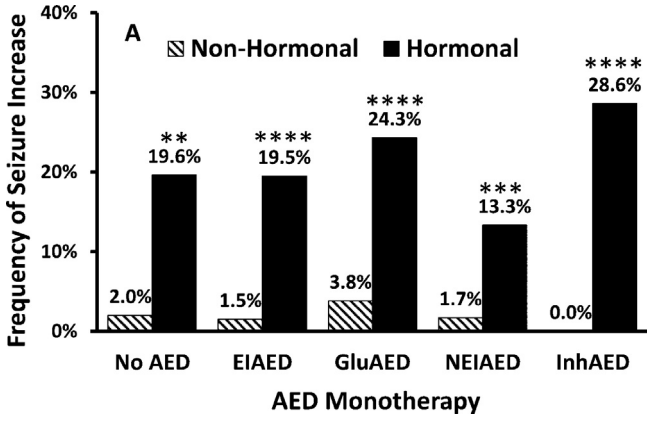


**Fig. 2.** Seizure frequencies are greater on hormonal contraception (HC) than on non-hormonal (NHC) contraception for each AED monotherapy category: $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$, $^{****}p \leq 0.0001$.

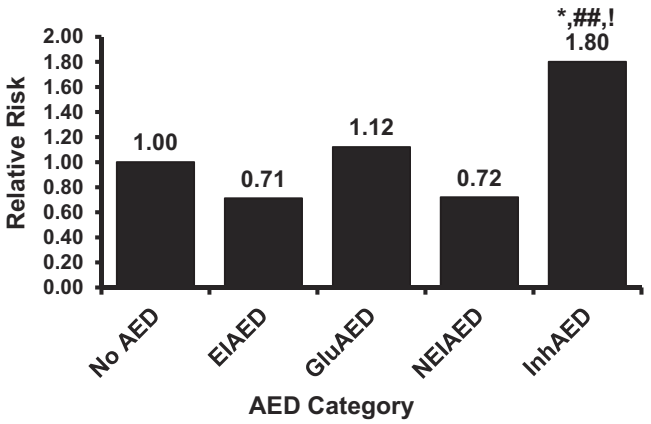


**Fig. 3.** Relative risk for seizure increase is presented relative to No AED rate of 20.7%. The relative risk is greater for the enzyme inhibitory category (valproate) than for each of the other AED categories: $^{*}p \leq 0.05$ in comparison to No AED, $^{\#\#}p \leq 0.01$ in comparison to EIAED and NEIAED, $^{!}p \leq 0.10$ in comparison to GluAED.

Binary logistic regression also showed an interaction between contraception category and AED category as a predictive factor for seizure decrease ($p = 0.006$). Odds ratios again were significant for interactions between AED categories and hormonal but not non-hormonal categories of contraception. Odds ratios for interaction between hormonal contraception and AED category relative to the Barrier and No AED category were as follows: Hormonal and NEIAED, OR = 3.896 (1.762–8.618), $p = 0.001$; Hormonal and EIAED, OR = 2.950 (1.384–6.286), $p = 0.005$; Hormonal and GluAED (lamotrigine), OR = 2.271 (0.994–5.191), $p = 0.052$; Hormonal and InhAED (valproate), OR = 1.039 (0.225–4.790), $p = 0.961$. A comparison of the relative risks for seizure decrease on hormonal contraception for each of the 4 categories of AED monotherapy versus no AED category showed no significant difference at this juncture in the study. Relative to No AED which was associated with reports of seizure decrease in 8.5% of the HC experiences, the RR for EIAED was 0.7360 (95%CI: 0.4229–1.2808), for GluAED (lamotrigine) was 0.6794 (0.3638–1.2688), for NEIAED was 1.1846 (0.4622–3.0358) and for InhAED (valproate) was 0.5857 (0.1274–2.6924). Of note, the RR for seizure decrease was two times greater on NEIAEDs (1.1846) which had the highest RR as compared to valproate (0.5857) which had the lowest RR.

## 8. Hormonal contraception, AEDs and seizures in women with epilepsy

As part of family planning, it is important for women with epilepsy to know what constitutes safe and effective contraception. A relatively recent authoritative review [13] states that "there is no evidence that oral contraceptives increase seizure activity." This view is generally consistent with prior authoritative reviews

**Table 3**
Frequencies of changes in seizure frequency on valproate monotherapy stratified by contraception type.

| | *N* | Sz increase (%) | Sz decrease (%) |
|---|---|---|---|
| Valproate | | | |
| Hormonal contraception | 40 | 15 (37.5%) | 2 (5.6%) |
| Non-hormonal contraception | 43 | 0 (0.0%) | 2 (4.7%) |

Sz, seizure frequency.
Fisher's exact test for seizure increase: $p < 0.0001$.
Fisher's exact test for seizure decrease: $p$ = NS.

[14] but large-scale, community-based, epidemiological studies are lacking.

The EBCR Project utilizes a web-based survey to access a large representative sample of women with epilepsy in the community. The large sample size is required to control for the many demographic, epilepsy, AED and contraceptive variables in the analysis. The EBCR preliminary findings are, by patient reports, that HC is associated with a broader dynamic range of seizure responses manifested by a significantly greater risk for both seizure increase and decrease than NHC but with the relative risk for seizure increase predominating. Seizure increase is significantly more likely to occur with all AED categories in combination with HC than with NHC. The odds ratio for seizure increase with HC appears to be greater for the enzyme inhibiting category, specifically valproate, than for any other AED category in relation to the reference combination of Barrier and No AED. With HC, valproate showed a greater relative risk for seizure increase as compared to any other AED category. The occurrence of a greater increase in seizures with valproate as compared to other AEDs is now raised as a potential issue but remains to be verified in the full study. A pathophysiological mechanism remains to be demonstrated. HC lowers glucuronidated AED serum levels. This has been demonstrated for valproate as well as lamotrigine. The lowering of AED levels, however, would not be an entirely adequate explanation since lamotrigine levels are found to drop more than valproate with HC [15], yet the rates of reports of seizure increase with HC are greater when combined with valproate (37.5%) than with lamotrigine which had a rate very similar to No AED (23.3% vs. 20.0%) in the EBCR population. Another consideration is that these AEDs may have differential effects on contraceptive hormone levels. Whereas lamotrigine has an insignificant lowering effect on ethinyl estradiol levels [16], might the enzyme inhibiting valproate possibly raise ethinyl estradiol levels in women? Higher serum estradiol levels on valproate treatment have been reported to occur in men with epilepsy as compared to healthy controls ($0.25 \pm 0.10$ on a mean daily dose of $986 \pm 285$ mg vs. $0.15 \pm 0.08$ nmol/L; $p < 0.01$) [17]. There is as yet no conclusive evidence in this regard for ethinyl estradiol in women with epilepsy. One study of ethinyl estradiol levels before and after introduction of valproate therapy reported no significant difference [18]. The study of only six women, however, lacked power to detect a moderate valproate effect and did find an 11% higher, albeit statistically insignificant, increase in the area under the curve for ethinyl estradiol as compared to a 0.3% increase for levonorgestrel, even on a clinically low dose of valproate 200 mg bid. Of course, the impact of valproate may relate to changes in the concentrations of other neuroactive steroids not under consideration here. Among the AED categories, NEIAEDs had the most favorable profile with regard to reports of seizure increase and decrease when used in combination with HC.

The EBCR is currently still gathering retrospective data and is addressing the limitations of the retrospective survey by conducting a pilot to determine whether the methodology may be effective in retaining a representative population for the conduct of a long-term, prospective, serial survey study. A validation study is also required. Given the importance of family planning and the large volume of hormonal contraception use by women with epilepsy, further basic science studies are also important to establish the neuroactive properties of contraceptive hormones as they pertain to seizures and the effects of valproate on ethinyl estradiol levels.

## Conflict of interest

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