



## Folic acid use by women with epilepsy: Findings of the Epilepsy Birth Control Registry



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### ABSTRACT

**Purpose:** To determine the prevalence and predictors of folic acid (FA) use by women with epilepsy (WWE) at risk of unintended pregnancy.

**Methods:** These retrospective data come from the Epilepsy Birth Control Registry (EBCR) web-based survey of 1144 WWE in the community, 18–47 years, who provided demographic, epilepsy, AED, contraception, pregnancy, healthcare visits and FA data. We report prevalence and predictors of FA use in relation to risk of pregnancy (not at risk, at risk, seeking pregnancy, pregnant), demographics, seizure types and AED and contraception categories.

**Results:** 368 (47.6%) of the 773 WWE at risk of unintended pregnancy in the EBCR took FA supplement. Being at risk was a significant predictor in comparison to WWE not at risk (OR = 1.464 [1.103–1.944],  $p = 0.008$ ). In comparison to WWE at risk, FA use trended greater for WWE actively seeking pregnancy (29/47, 61.7% v 368/773, 47.6%;  $p = 0.0605$ ) and was greater for pregnant WWE (17/19, 89.5% v 368/773, 47.6%;  $p = 0.0007$ ). Demographic predictors for WWE at risk were race ( $p = 0.003$ ), education ( $p = 0.012$ ) and income (0.043) with significantly greater FA use by Caucasians than minorities and direct correlations between FA use and levels of education and household income. Seizure type, AED use, category and dosage, polytherapy and contraceptive category were not predictors. A healthcare provider visit during the year prior to the survey was not a predictor. Prevalence of FA use was similar following visits with gynecologists – 51.7%, neurologists – 48.7% and primary care – 48.6%. FA supplementation by prescription was greater for WWE at risk on AED versus no AED (190/355, 53.5% v 3/13, 23.1%;  $p = 0.045$ ).

**Conclusion:** Low prevalence of preconception FA use may reflect a need for more education. In addition, further research is needed to provide definitive evidence that FA reduces congenital malformations in the offspring of WWE.

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### 1. Introduction

Folic acid (FA) deficiency during early pregnancy is associated with greater risks of major congenital malformations (MCMs) in the general population [1]. FA supplementation as a preconception intervention lessens MCMs, especially neural tube defects, as evidenced by randomized controlled trials, systematic reviews and meta-analysis findings [2]. It has been the longstanding recommendation of the Centers for Disease Control (CDC) that women of childbearing age “consume 0.4 mg of FA acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other neural tube defects (NTDs)” [3]. In a

national survey in 2007, however, the CDC found that only 40% of all women of reproductive age reported taking a FA supplement [4].

Women with epilepsy (WWE) are at increased risk for having offspring with MCMs [5–8]. The risk relates largely to the teratogenic effects of antiepileptic drugs (AEDs) [5–8], especially in susceptible individuals [6]. Pooled data from 26 studies reveal a MCM rate of 6.1% in offspring of WWE who were treated with AEDs, 2.8% among children of women with untreated epilepsy and 2.2% in the healthy control group [6]. The risk varies by AED type and dosage [6]. AED monotherapy doubles the risk and polytherapy triples the risk [6–8]. Extensive details quantifying the risks of specific AEDs are available in the publications of the European (EURAP) and North American (NAAED) pregnancy registries [6,7]. Although exact percentages vary among studies, there does appear to be wide consensus that valproate has the highest risk in a range of 6.3%–10.7% whereas lamotrigine (2.0–2.9%) and levetiracetam (0.7–2.0%) have the lowest risks [5–10]. Barbiturates, carbamazepine,

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phenytoin and valproate are all classified as category D drugs [5]. The first 3 are enzyme inducing AEDs which lower serum levels of FA; valproate acts as a FA antagonist [5–8]. A significantly increased risk is not evident in WWE who do not take AEDs [7].

FA supplementation reduces substantially the risks for the most common MCMs in the general population (conotruncal cardiac malformations, neural tube defects, orofacial clefts), especially neural tube malformations which are decreased by 60–70% [2]. The reduction of MCMs in the offspring of WWE who take FA supplement has not been demonstrated conclusively and has been questioned by the findings of the UK Epilepsy and Pregnancy Register [9,11]. Based on the strength of the evidence in the general population and the absence of known adverse effects of commonly prescribed dosages of FA supplement, the American Academy of Neurology and American Epilepsy Society continue to recommend preconception FA supplementation for WWE [12].

The Epilepsy Birth Control Registry (EBCR) is a web-based survey and educational site that gathers demographic, epilepsy, AED, contraceptive, reproductive and FA data from WWE in the community. In this analysis, we examine the prevalence and predictors of FA use by WWE at risk of unintended pregnancy.

## 2. Methods

### 2.1. Subjects

The participants were 1144 WWE, 18–47 years old, who completed the EBCR survey between 2010 and 2014. WWE who were interested in contraception were directed to the survey from various referral sources such as epilepsy organization websites, social media, internet searches and study brochures posted in clinics.

### 2.2. Data collection and definitions

We used an online survey methodology located at [epilepsybirthcontrolregistry.com](http://epilepsybirthcontrolregistry.com) to gather data regarding the prevalence of current use of FA supplement by WWE and the predictors of FA use in relation to the risk of unintended pregnancy, demographics, seizure type, AED use, AED categories and visits to healthcare providers. We defined “at risk” as sexually active WWE who denied a personal history of infertility, hysterectomy, tubal ligation or male partners with vasectomy. It does not include WWE who are not using contraception because they are actively seeking pregnancy or are pregnant. The detailed methodology, criteria for categorization of AEDs and contraceptive methods, demographics of participants and contraceptive practices of participants were reported previously [13].

Demographic characteristics included age, race, ethnicity, education, household income, health insurance and geographic location.

Participants classified their seizures as generalized convulsive, complex partial and simple partial on the basis of descriptions of each category provided in the survey question. The participants provided the names and daily dosages of current AEDs. We categorized AED treatment as none, monotherapy or polytherapy. We grouped AEDs into 6 categories based on their effects on enzymatic metabolism: 1) No AED, 2) enzyme inducing AEDs (EIAEDs) which included phenobarbital, phenytoin, carbamazepine, oxcarbazepine and topiramate >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 ≤200 mg daily, lacosamide, clobazam, pregabalin and tiagabine, 5) enzyme inhibiting AEDs (InhAEDs) which included only valproate, and 6) mixed categories. Although oxcarbazepine is a weak enzyme inducer of cytochrome P450 and its neuroactive monohydroxylated derivative is principally glucuronidated, oxcarbazepine is a relatively potent inducer of the CYP3A isoform of cytochrome P450 which is responsible for the metabolism of contraceptive ethinyl estradiol and levonorgestrel and has

been shown to reduce their levels very substantially [14]. Therefore, we included oxcarbazepine in the enzyme inducing category. Note, valproate was listed in the InhAED category although it is also partially glucuronidated. When there was a combination of an AED that affected enzymes and a NEIAED, we listed the combination by the category that affected enzymes. If the combination was comprised of two or more categories that affect enzymes, they were listed as mixed category.

We categorized contraception into two broad classes: hormonal (HC) and non-HC (NHC). The classes were further parceled into categories and subcategories of contraception as follows: 1) none, 2) withdrawal, 3) barrier (condom, diaphragm), 4) systemic hormonal (oral contraceptive pill [OCP] - combination [COCP] or progestin-only [POCP], transdermal hormonal patch, vaginal ring, progestin implant, depomedroxyprogesterone), 5) intrauterine device (IUD - progestin or copper), 6) tubal ligation and 7) partner with vasectomy. Withdrawal, barrier, hormonal and IUD are considered as reversible forms of contraception. Combinations are either specified as such or are listed by the category that is considered more effective in the general population.

### 2.3. Outcomes

1. Prevalence of folic acid use.
2. Predictors of folic acid use by the following variables: 1) risk status for unintended pregnancy, 2) demographics, 3) seizure type, 4) AED use, 5) AED categories, 6) categories of reversible contraception, 7) seeing a healthcare provider during the preceding year.
3. Frequencies and predictors of the various forms of folic acid supplementation.

### 2.4. Statistical analysis

We report FA use prevalence as proportions and percentages. We compared proportions by  $\chi^2$  analysis. We carried out binary logistic regression to explore the following potential predictors of FA use: demographic (age, race/ethnicity, education, household income), most severe seizure type (generalized convulsive, partial), use of AED (yes, no), AED category (None, EIAED, GluAED, NEIAED, InhAED), pregnancy risk status (yes, no), reversible categories of contraception (withdrawal, barrier, hormonal, IUD) and visits to primary care, neurology and gynecology healthcare providers during the year prior to taking the survey (yes, no). We used Spearman correlational analysis to relate the levels of education and household income to the percentage of WWE at risk who take FA supplement.

This study was approved by the Western Institutional Review Board as well as the Columbia University Medical Center Institutional Review Board. Online consent was obtained from all participants. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

## 3. Results

### 3.1. Survey participants and prevalence of folic acid use

1108 (96.9%) of the 1144 survey participants responded to the question regarding the use of a FA supplement. 773 (69.8%) of the 1108 WWE were at risk of unintended pregnancy, 269 (24.3%) were not at risk, 47 (4.2%) were seeking pregnancy and 19 (1.7%) were pregnant. 517 (46.7%) of the 1108 WWE took a FA supplement.

### 3.2. Predictors of folic acid use

Being at risk of unintended pregnancy was a significant predictor of FA use in comparison to WWE not at risk (368/773, 47.6% v 103/269, 38.3%; OR = 1.464 [1.103–1.944],  $p = 0.008$ ) (Table 1). In comparison

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