Hyperandrogenism, Ovulatory Dysfunction, and Polycystic Ovary Syndrome with Valproate versus Lamotrigine

Martha J. Morrell, MD,[1] Frances J. Hayes, MD,[2] Patrick M. Sluss, MD,[2] Judith M. Adams, MD,[2] Mohit Bhatt, MD,[3] Cigdem Ozkara, MD,[4] Clay R. Warnock, M.S.[5] and Jouko Isojärvi, MD[6,7]

Objective: To evaluate development of components of polycystic ovary syndrome (PCOS) and PCOS in women with epilepsy initiating valproate or lamotrigine therapy.

Methods: Female individuals with epilepsy and regular menstrual cycles were eligible for this prospective study. Participants were randomized to 12 months of valproate (n = 225) or lamotrigine (n = 222) therapy. Serum androgen levels were measured every 3 months. Urinary pregnanediol glucuronide levels were measured weekly for two 3-month periods. The primary end point was development of PCOS components (ie, hyperandrogenism or ovulatory dysfunction). A post hoc analysis was conducted in women more than 2 years after menarche (177 lamotrigine, (HA) 186 valproate) to exclude OD the confounding effect of puberty.

Results: More women in the valproate group than the lamotrigine group developed (OD) in the prospective (54% valproate, 38% lamotrigine; $p = 0.010$) and the post hoc (HA) analyses (36% valproate, 23% lamotrigine; $p = 0.007$). More women in the valproate group than the lamotrigine group developed PCOS (9 vs 2%; $p = 0.007$). Development of HA was more frequent with OD valproate than lamotrigine among those initiating treatment at age younger than 26 years (44% valproate, 23% lamotrigine; $p = 0.002$) but was similar if treatment was started at age 26 years or older (24% valproate, 22% lamotrigine).

Interpretation: Development of HA occurred more frequently with valproate than lamotrigine, especially if medication was started at age younger than 26 years.

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Women with epilepsy have a greater risk for reproductive health disorders, including infertility and polycystic ovary syndrome (PCOS), than women without epilepsy.[1–7] PCOS is an endocrine disorder characterized by oligoovulation or anovulation and phenotypic or serological evidence of hyperandrogenism. PCOS is associated with infertility and important long-term health consequences such as metabolic disorders (obesity, glucose intolerance, hyperinsulinemia, dyslipidemia) and endometrial carcinoma.[8]

In cross-sectional studies, women with epilepsy receiving valproate are more likely to display signs typical of PCOS than are women with epilepsy receiving other antiepileptic drugs.[4,5,9–15] In contrast, lamotrigine has not been associated with an increased prevalence of PCOS,[12,15] and substituting lamotrigine for valproate was associated with reduction in body weight and normalization of serum hormone and lipid levels in a study of women with epilepsy.[16] To date, the impact of antiepileptic drugs on menstrual cyclicity and serum androgen levels in women with epilepsy has not been examined in prospective studies. The aim of this study was to define the relative contributions of epilepsy per se and the antiepileptic drugs valproate and lamotrigine to the development of a PCOS phenotype including ovulatory dysfunction, increased androgen levels, and polycystic ovarian morphology. In this multisite, international, open-label study, women with newly diagnosed or inadequately controlled epilepsy were randomized to therapy with either lamotrigine or valproate and were followed prospectively for up to 1 year to assess for the development of ovulatory dysfunction and/or hyperandrogenism.

From [1]Stanford University, Stanford and Neuropace, Mountain View, CA; [2]Massachusetts General Hospital, Boston, MA; [3]Jaslok Hospital and Kokilaben Dhirubhai Ambani Hospital, Mumbai, India; [4]Istanbul University, Istanbul, Turkey; [5]GlaxoSmithKline, Research Triangle Park, NC; [6]University of Oulu, Oulu, Finland; and [7]UCB Group, Research Triangle Park, NC.

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Address correspondence to Dr Morrell, Neuropace, 1375 Shorebird Way, Mountain View, CA 94043.
E-mail: mmorrell@neuropace.com

Subjects and Methods

This international, multicenter study (Protocol LAM30007) was administered by the sponsor GlaxoSmithKline and conducted at 76 sites in 16 countries in North America, Europe, South America, and Asia. The study protocol was approved by institutional review boards for the study sites.

Subjects

All subjects provided written, informed consent before participation in the study. Subjects were female individuals between the ages of 13 and 40 years with a confident diagnosis of epilepsy and seizures that could be recognized by the subject or a caregiver. Seizures were classified based on clinical history and/or electroencephalographic data using the International Classification of Epileptic Seizures. All subjects had either newly diagnosed/untreated epilepsy (ie, fewer than 2 weeks of prior antiepileptic drug treatment) or inadequately controlled epilepsy despite treatment with a single antiepileptic drug for at least 3 months. Subjects treated for uncomplicated febrile seizures before age 7 were eligible to participate.

All subjects reported a history of regular menstrual cycles (defined as cycle length $\geq$25 days and $\leq$35 days with a variation in cycle length of $\leq$4 days from one cycle to the next) with at least two regular menstrual cycles immediately before the screening visit. A negative urine pregnancy test was required at the screening visit. Women of childbearing potential agreed to use adequate nonhormonal contraception throughout the study and/or to practice sexual abstinence. Folic acid supplementation at a dose left to the investigator's discretion was recommended for all subjects.

Women were excluded if pregnant, less than 6 months postpartum, breast-feeding, or planning a pregnancy during the course of the study or within 3 weeks after the last dose of study drug. Other exclusion criteria included body mass index (BMI) more than 35kg/m^2, increased androgen level (total testosterone $>$ 150ng/dl [5.2nmol/L] or dehydroepiandrosterone sulfate (DHEA-S) $>$ 800μg/dl [21.7μmol/L]), or signs of decreased ovarian reserve (follicle-stimulating hormone [FSH] $>$ 16IU/L on days 1–6 of the menstrual cycle or FSH $>$ 22IU/L on any other day of the menstrual cycle]). Women with hyperandrogenism were randomized but were not included in the primary analysis population. Women currently or previously treated with lamotrigine, valproate, or felbamate were excluded, as were women chronically treated with any other medication (other than one chronic antiepileptic drug) known to influence seizure control. For newly diagnosed/untreated subjects, treatment for up to 2 weeks with an antiepileptic drug other than lamotrigine, valproate, or felbamate was allowed before enrollment in the study; however, the antiepileptic drug was to be discontinued within 2 weeks after the initiation of study medication.

Women taking hormonal medication were excluded from the trial. Women were also excluded for medical conditions or past surgeries that could affect hormone levels or menstrual function (eg, oophorectomy, adrenal dysfunction, Cushing's syndrome, diabetes, thyroid dysfunction). Additional grounds for exclusion were a serious or unstable medical or psychological condition, a current history of alcohol or drug abuse, clinically significant impairment of renal or hepatic function, or use of any investigational drug within the 30 days before study enrollment.

Treatment

A central randomization scheme was used to assign eligible subjects on a random, equal basis to receive either lamotrigine or valproate. Newly diagnosed subjects received lamotrigine or valproate as monotherapy; subjects entering the study with inadequately controlled epilepsy received lamotrigine or valproate in addition to a single background antiepileptic drug. The target maintenance dose for lamotrigine monotherapy was 100 to 200mg/day with the dose not to exceed 500mg/day. The target doses for lamotrigine added to enzyme-inducing antiepileptic drugs and nonenzyme-inducing antiepileptic drugs were 200 to 400mg/day and 100 to 200mg/day, respectively. The target maintenance dose for valproate was 1,000mg/day. The investigator could escalate the doses at a rate slower than the recommended dosing schedule. For subjects with inadequately controlled epilepsy receiving lamotrigine or valproate as adjunctive therapy, the dose of the concurrent antiepileptic drug was kept as constant as possible except for any necessary adjustments in concomitant antiepileptic drugs because of drug interactions.

Clinic Visits

The screening visit included a medical and neurological history, physical examination, and ovarian ultrasound. Each subject was given a diary card to record information about her menstrual cycles, and seizure type and frequency. Serum was obtained for routine chemistry and hematology, and a detailed reproductive hormone evaluation. If the screening visit did not occur during the first 6 days of the participant's menstrual cycle but all eligibility criteria were met, then she initiated treatment and was instructed to return during days 1 to 6 of her next menstrual cycle for a baseline hormone sample.

After determination of eligibility at a screening visit, clinic visits were scheduled every three menstrual cycles (months 3, 6, 9, and 12) for 1 year. Participants were seen on one morning during the first 6 days of their menstrual cycle after a 12-hour fast. If a participant became amenorrheic or oligomenorrheic (defined as more than 6 weeks without a menstrual bleed), the visit was based on a calculated 28-day cycle counted forward from the start of the last true menstrual cycle.

At the clinic visits, data were collected for height and weight, seizure frequency, and concomitant medications. Diaries were reviewed together with menstrual cycle information and the total number of seizures, by type, since the last visit. Investigators assessed participants for and queried parents or caregivers about adverse events, defined as any untoward medical occurrence regardless of its suspected cause. Blood samples were obtained for hormone evaluation. New diary cards and ovulation kits were distributed.

The 12-month visit also included confirmation of epilepsy classification, a neurological examination, and an ovarian ultrasound. A urine pregnancy test was provided for the participant to complete 3 weeks after the last dose of study drug. Results of the pregnancy test were mailed to the investigator.

Ovulation Testing

Ovulation testing was based on the ratio of urine pregnanediol glucuronide to creatinine ratio. Ratios exceeding 1,500 were interpreted as indicating ovulation. Weekly morning urine samples for ovulation testing were collected by participants at home during months 4 to 6 and 10 to 12, and stored frozen until transfer to the study site and subsequent shipment to the central laboratory (Reproductive Endocrine Unit Reference Laboratory of the Massachusetts General Hospital). Pregnanediol glucuronide and creatinine were measured by microtiter plate enzyme-linked immunosorbent assay.[17,18]

Endocrine Assessments

Hormones measured at every visit included total testosterone, androstenedione, DHEA-S, sex hormone–binding globulin (SHBG), luteinizing hormone (LH), and FSH. Free testosterone levels were calculated from total testosterone and SHBG.

Blood samples for hormone measurements were collected into no-additive clot tubes. Serum or plasma was harvested by centrifugation, frozen, and shipped to the central laboratory on dry ice for analysis. Endocrine measurements were performed on serum specimens. FSH and LH were measured on an automated immunoassay system (AxSYM; Abbott Diagnostics, Abbott Park, IL) using microparticle enzyme immunoassay methods. SHBG and DHEA-S were measured by chemiluminescence immunoassays using an automated immunoanalyzer (Immulite; Diagnostic Products Corporation, Los Angeles, CA). Androstenedione was measured using a plate enzyme-linked immunosorbent assay (Diagnostic System Laboratories, Webster, TX). Total testosterone was measured using a solid-phase radioimmunoassay (Coat-a-Count; Diagnostic Products Corporation, Los Angeles, CA). Values for lower and upper limits of normal, respectively, were 5 and 63ng/dl for testosterone, 0.10 and 3.35ng/ml for androstenedione, 50 and 344μg/dL for DHEA-S, 21 and 139 nmol/L for SHBG, 1.0 and 8.2 IU/L for LH, and 2.8 and 8.9 IU/L for FSH.

All hormone analyses were conducted at a central laboratory (Reproductive Endocrine Unit Laboratory of the Massachusetts General Hospital). All assays were performed according to manufacturer's specifications, which were verified by the central laboratory. Assays were monitored using commercial quality-control materials and materials received for proficiency testing from the College of American Pathologists.

Ovarian Ultrasonography

A transvaginal ultrasound was obtained during days 1 to 7 of the menstrual cycle to assess for polycystic ovaries at screening and the 12-month clinic visit. Sites were encouraged to have the same ultrasonographer perform all studies and to obtain three longitudinal sections and one transverse section for each ovary, two endometrial images, and measurements of the endometrium, as well as the diameter of all large cysts ($\geq$10mm). The sonographic images and a report with the resulting measurements were sent to a blinded central reader (J.M.A.). Where transvaginal ultrasound was not practical, transabdominal ultrasound was obtained. Participants were considered to have new-onset polycystic ovaries if there was sonographic evidence of 10 or more peripherally oriented 2 to 8mm cysts surrounding an increased stroma in at least 1 ovary.[19]

Seizures

Seizure history was collected at the screen visit and included the number of seizures, by type, experienced in the prior 2 years. At each visit, the total number of seizures, by type, since the last visit, was recorded as per the usual practice at the site. Monthly seizure frequency was calculated based on these data.

Measures and Statistics

PLANNED ANALYSES. The intent-to-treat population, comprising all randomized subjects who took at least one dose of study medication and who did not have hyperandrogenism at screening, was considered the primary population for reproductive endocrine end points. The primary end point was the proportion of subjects who developed components of PCOS at any point during the study. Subjects were considered to have reached this end point if they developed either ovulatory dysfunction, which was defined as the presence of two or more anovulatory cycles as measured by urinary pregnanediol glucuronide assays during two 3-month periods of the study, or hyperandrogenism, which was defined as a serum total or free testosterone or DHEA-S level more than 95th percentile of regularly ovulating women in the early follicular phase (days 1–6) of the menstrual cycle. The definition of PCOS remains controversial. At the time this study began, the most commonly accepted definition was that of the National Institute of Health/National Institute of Child Health and Human Development consensus panel: the presence of hyperandrogenism and/or hyperandrogenemia, oligoovulation, and the exclusion of other known endocrine disorders (eg, Cushing's syndrome).[20] Inclusion of polycystic ovaries in the definition is particularly controversial and for that reason was not included. To minimize cultural impact on evaluation of the primary end point and the potential for bias in an open-label, multinational study, we used the objective measure of blood androgen levels rather than clinical presentation (eg, hirsutism, acne) as the marker of androgen excess.

Treatment groups were compared on the primary end point using a Cochran–Mantel–Haenszel χ^2 test adjusted for grouped center and epilepsy at enrollment (ie, newly diagnosed/untreated or inadequately controlled). To account for possible differential withdrawal rates between treatment groups, we also analyzed the primary end point using a life table Mantel–Haenszel test.

It was assumed that 25% of subjects randomized to valproate and 10% of subjects randomized to lamotrigine would develop components of PCOS during the study. A total of 226 subjects (113 per treatment arm) were required to detect this difference with 80% power at the two-sided 5% level of significance. Enrollment of 190 subjects per treatment arm was planned to incorporate a 20% allowance for randomized subjects who had components of PCOS at screen, and a 25% allowance for participants who met the

criteria and subsequently withdrew during the course of the study.

Key secondary end points included development of PCOS (defined as both hyperandrogenism and ovulatory dysfunction); development of polycystic ovaries via sonography; and changes from screening in androgens, other hormones, seizure frequency, and body weight/BMI. The end points of PCOS and polycystic ovaries via sonography were analyzed in the same manner as the primary end point. Estimates of treatment effect were provided using odds ratios and 95% confidence intervals (CIs). Changes from screening were analyzed using analysis of covariance with screening values as a covariate. CIs (95%) were constructed around treatment differences. If underlying assumptions did not hold, then the appropriate nonparametric tests (ie, nonparametric analysis of covariance) were used. All tests were two-sided with an overall α level of 0.05. No adjustments were made for multiplicity.

The safety population, comprising all randomized subjects who took at least one dose of study medication, was used for all tolerability analyses. Tolerability measures included the percentages of participants with adverse events (regardless of suspected cause), with serious adverse events, and with adverse events that led to premature withdrawal from the study. Adverse-event data were summarized using descriptive statistics.

Post Hoc Analyses

At the time the study was designed, the possibility of a differential reproductive impact based on age within the study population had not been considered. In preparation for review of the data, a consortium of advisors proposed consideration of a subpopulation based on age of onset of menses to make the study population as representative of the current published literature as possible. Therefore, post hoc analyses of the primary and key secondary end points listed earlier were conducted for the post hoc intent-to-treat population, which was defined as participants in the original intent-to-treat population who had at least one postbaseline reproductive endocrine assessment and who were at least 2 years past menarche. The criterion of having at least one postbaseline reproductive endocrine assessment was included in an attempt to reduce the influence on study results of a high number of "unknown" responses arising from the sensitivity of the combination end points to missing data in the intent-to-treat population. The criterion of being at least 2 years past menarche was included in an attempt to minimize the impact on study results of significant peripubertal fluctuations in serum reproductive hormones.[21] The primary and key secondary end points were analyzed for the post hoc intent-to-treat population in the same manner as described earlier for the intent-to-treat population. The primary end point and key secondary end points were also analyzed in the post hoc intent-to-treat population by age group ($<$26 years, $\geq$26 years) and by seizure type (partial seizures only, generalized seizures only) using a two-sided Fisher's exact test.

Results

Results of Prospective Analyses

DISPOSITION. A total of 447 subjects were randomized to treatment (222 lamotrigine, 225 valproate). Of the 447 randomized subjects, 107 (23% of the lamotrigine group and 24% of the valproate group) withdrew prematurely from the study (Fig 1). The most common reasons for premature withdrawal were withdrawal of consent (5% lamotrigine, 7% valproate) and lost to follow-up (4% lamotrigine, 6% valproate). The proportion of participants completing the study was 77% in the lamotrigine group and 76% in the valproate group (see Fig 1).

The number of subjects in the intent-to-treat population, comprising all randomized subjects who took at least one dose of study medication and who did not have components of PCOS at screening, was 412 (201 in the lamotrigine group and 211 in the valproate group). The number of subjects in the safety population, comprising all randomized subjects who took at least one dose of study medication, was 441 (219 in the lamotrigine group and 222 in the valproate group).

Treatment groups were comparable with respect to age, race, BMI, epilepsy, and antiepileptic medication history at enrollment (Table 1). Most participants had idiopathic, newly diagnosed epilepsy, and the majority had generalized seizures only. Forty-three subjects (20%) in the lamotrigine group and 33 subjects (15%) in the valproate group had inadequately controlled epilepsy before entering the study and were taking a single concurrent antiepileptic drug. Thirty-three subjects in the lamotrigine group and 29 in the valproate group were taking an enzyme-inducing antiepileptic drug.

EXPOSURE TO STUDY MEDICATION. The mean (standard deviation [SD]) duration of exposure was 47.2 weeks (17.3) (n = 219) for lamotrigine and 47.5 ±

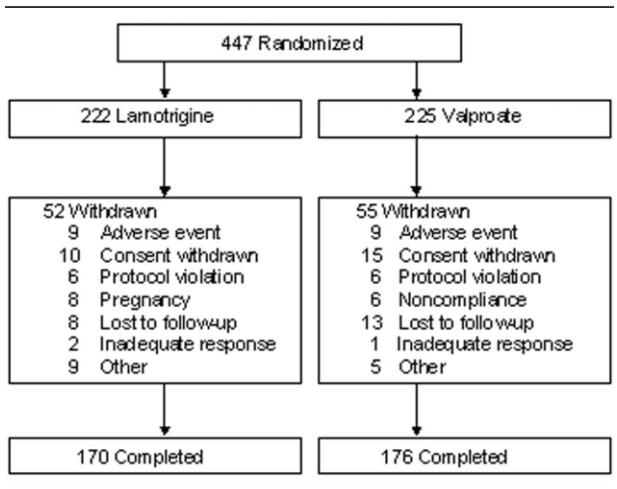

Fig 1. Disposition.

Table 1. **Subject Characteristics (Safety Population)**

Characteristics	Lamotrigine Group (N = 219)	Valproate Group (N = 222)
Demographics and baseline characteristics		
Mean (SD) age, yr	21.8 (6.3)	22.9 (7.3)
Race, n (%)		
White	121 (55)	113 (51)
Indian	81 (37)	81 (36)
American Hispanic	11 (5)	17 (8)
Black	6 (3)	8 (4)
Other	0 (0)	3 (1)
Mean (SD) height, cm	170 (8.2)	159 (9.2)
Mean (SD) weight, kg	55.4 (11.0)	56.0 (11.6)
Mean (SD) body mass index, kg/m^2	21.6 (3.5)	22.0 (4.1)
Epilepsy history		
Epilepsy at enrollment, n (%)		
Newly diagnosed/untreated	176 (80)	189 (85)
Inadequately controlled	43 (20)	33 (15)
Mean age at first seizure, yr (SD)	18.3 (7.4)	19.1 (8.2)
Mean duration of epilepsy, years (SD)	3.4 (5.3)	3.8 (5.7)
Causative factor, n (%)		
Idiopathic	150 (68)	167 (75)
Symptomatic	33 (15)	20 (9)
Cryptogenic	36 (16)	35 (16)
Presenting seizure type		
Partial only	84 (38)	86 (39)
Generalized only	129 (59)	139 (59)
Both partial and generalized	6 (3)	4 (2)
Concurrent AED		
Any AED	43 (20)	33 (15)
Carbamazepine	17 (8)	12 (5)
Phenobarbital	8 (4)	10 (4)
Phenytoin	8 (4)	7 (3)
Other AED	10 (5)	4 (2)
Serum hormone and SHBG concentrations at baseline		
Total testosterone, ng/dl	33.2 ± 15.9 (n = 196)	31.2 ± 14.2 (n = 194)
Free testosterone, ng/dl	0.024 ± 0.020 (n = 196)	0.020 ± 0.014 (n = 194)
SHBG, nmol/L	61.9 ± 33.9 (n = 196)	72.0 ± 45.0 (n = 193)
DHEA-S, μg/dl	176.8 ± 98.0 (n = 183)	145.6 ± 84.8 (n = 180)
Androstenedione, ng/ml	2.6 ±.6 (n = 175)	2.6 ± 1.6 (n = 183)

SD = standard deviation; AED = antiepileptic drug; SHBG = sex hormone–binding globulin; DHEA-S = dehydroepiandrosterone sulfate.

16.5 weeks for valproate (n = 222), and was similar between the monotherapy and adjunctive therapy subgroups. Mean average total (SD) daily dose of study medication was 152mg (78.4) in the lamotrigine group and 862mg (28.3) in the valproate group. The corresponding values for newly diagnosed subjects taking monotherapy were 152mg (78.9) for lamotrigine (n = 177) and 884mg (284.3) for valproate (n = 189). The corresponding values for subjects entering the study with inadequately controlled epilepsy taking adjunctive therapy were 150mg (76.9) for lamotrigine (n = 42) and 737mg (268.9) for valproate (n = 33).

PRIMARY AND SECONDARY END POINTS: COMPONENTS OF POLYCYSTIC OVARY SYNDROME. In the intent-to-treat population, fewer participants in the lamotrigine group developed hyperandrogenism or ovulatory dysfunction (38%) than the valproate group (54%) (odds ratio, 0.516; 95% CI, 0.311–0.856; $p = 0.010$ by Cochran–Mantel–Haenszel χ^2 test; $p = 0.003$ by life table Mantel–Haenszel test) (Table 2). Likewise, a significantly lower incidence of the individual components of ovulatory dysfunction and hyperandrogenism was observed in the lamotrigine group. In addition, fewer subjects developed PCOS using a combined measure of ovulatory dysfunction and hyperandrogenism in the lamotrigine group (2%) than the valproate group (9%) ($p = 0.007$ by Cochran–Mantel–Haenszel χ^2 test). When analyzed separately, no difference was noted between participants with newly diagnosed epilepsy versus inadequately controlled epilepsy (data not shown).

OTHER ENDOCRINE RESULTS. Significant differences between treatment groups were observed for change-from-screen values for total testosterone, DHEA-S, and SHBG (Table 3). The difference between treatment groups for total testosterone was driven by the increased levels in the valproate-treated subjects. Valproate and lamotrigine appeared to have opposite effects on DHEA-S and SHBG. DHEA-S decreased and SHBG increased with valproate treatment, whereas SHBG decreased and DHEA-S increased with lamotrigine treatment. Changes were not significant for free testosterone, androstenedione, LH, or FSH.

MENSTRUAL FUNCTION AND POLYCYSTIC OVARY MORPHOLOGY. Treatment groups did not differ about subject-reported menstrual cycle frequency, length, or regularity. Polycystic ovaries were present at screen in 40% of subjects. Of the subjects without polycystic ovaries at entry and with evaluable sonographic data (n = 67 in lamotrigine group; n = 70 in valproate group), 40% in each treatment group developed polycystic ovaries during the study. Baseline androgen and polycystic ovarian status will be the subject of a separate publication.

BODY WEIGHT/BODY MASS INDEX. In the intent-to-treat population, a greater increase in mean body weight was observed during the first year of valproate therapy (2.97kg; SD, 4.2) than in the first year of lamotrigine therapy (0.36kg; SD, 3.6) ($p < 0.001$). Similar changes were observed for BMI (valproate: 1.06; SD, 1.7; lamotrigine: 0.07; SD, 1.5) ($p < 0.001$). However, differences between lamotrigine and valproate in the incidence of hyperandrogenism and ovulatory dysfunction remained statistically significant after adjusting for changes in BMI (≤2 or >2): 9% for the valproate group versus 2% for the lamotrigine group (odds ratio, 0.185; 95% CI, 0.049–0.703; $p = 0.007$).

Table 2. **Incidence of Polycystic Ovary Syndrome Components (Intent-to-Treat Population)**

Outcome	Lamotrigine Group (N = 201)	Valproate Group (N = 211)	*p*
Either ovary syndrome components, n	120	145	
n (%)	45 (38)	78 (54)	0.010[a], 0.003[b]
Ovulatory dysfunction, n	145	154	
n (%)	29 (20)	48 (31)	0.028[a]
Hyperandrogenism, n	120	143	
n (%)	19 (16)	44 (31)	0.004[a]
Increased total testosterone level	10 (8)	37 (26)	
Increased free testosterone level	0 (0)	5 (4)	
Increased DHEA-S concentration	11 (9)	8 (6)	

[a] Analysis of covariance model adjusted for grouped center and screening value.
[b] Life table Mantel–Haenszel test adjusted for grouped center and epilepsy at enrollment.
DHEA-S = dehydroepiandrosterone sulfate.

Table 3. **Change from Screen in Endocrine Parameters**

Parameters	Lamotrigine Group (n = 201)	Valproate Group (n = 211)	p[a]
Total testosterone, ng/dl	0.9 ± 12.9 (n = 161)	8.8 ± 16.0 (n = 167)	<0.001
Free testosterone, ng/dl	0.003 ± 0.012 (n = 161)	0.004 ± 0.012 (n = 167)	0.57
DHEA-S, μg/dl	16.6 ± 57.6 (n = 148)	−10.0 ± 54.2 (n = 150)	<0.001
Androstenedione, ng/dl	0.29 ± 1.8 (n = 158)	0.3 ± 2.3 (n = 167)	0.84
SHBG, nmol/L	−7.6 ± 32.3 (n = 161)	6.5 ± 41.7 (n = 166)	<0.001
LH, IU/L	−0.59 ± 6.6 (n = 161)	0.39 ± 5.0 (n = 167)	0.47
FSH, IU/L	0.39 ± 7.3 (n = 161)	−0.07 ± 2.6 (n = 167)	0.35

[a] Analysis of covariance model adjusted for grouped center and screening value.
DHEA-S = dehydroepiandrosterone sulfate; SHBG = sex hormone–binding globulin; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

SEIZURES. Seizure frequency was reduced in both treatment groups. Seizure frequency at screen in this primarily newly diagnosed population was 1 per month in the lamotrigine group and 0.5 per month in the valproate group. Forty-six percent of subjects in the valproate group became seizure free compared with 37% in the lamotrigine group ($p = 0.092$).

ADVERSE EVENTS. In the safety population (n = 219 lamotrigine; n = 222 valproate), the proportion of participants with at least one adverse event was 56% in the lamotrigine group and 55% in the valproate group. Table 4 shows the adverse events reported in 5% or more of subjects in either treatment group. Headache was the most frequently reported adverse event in each group. Tremor, vomiting, nausea, alopecia, and weight increase were reported more frequent in the valproate group. The occurrence of rash (including rash, erythema multiforme, rash morbilliform, angioneurotic edema, rash macular, rash papular, and urticaria) was similar between groups (5% for lamotrigine, 4% for valproate). The number of subjects who withdrew from the study because of rash was 5 in the lamotrigine group and 0 in the valproate group. No cases of serious rash were reported in either group. The proportion of participants who discontinued because of an adverse event was similar between treatment groups (4%). The occurrence of serious adverse events was slightly greater in the valproate group (4%) than the lamotrigine group (2%).

Results of Post Hoc Analyses (Subjects Who Had at Least One Postbaseline Reproductive Endocrine Assessment and Were More Than 2 Years Past Menarche)

DISPOSITION. The number of subjects in the post hoc intent-to-treat population, which included subjects who were in the original intent-to-treat population, who had at least one postbaseline reproductive endocrine assessment, and who were more than 2 years past menarche, was 363 (177 lamotrigine, 186 valproate). Demographics of the post hoc intent-to-treat population were comparable between treatment groups and similar to those of the full intent-to-treat population. The mean age of menarche was 13.0 ± 1.3 years in the lamotrigine group and 12.9 ± 1.3 in the valproate group.

DEVELOPMENT OF COMPONENTS OF POLYCYSTIC OVARY SYNDROME AND POLYCYSTIC OVARY MORPHOLOGY. Women receiving valproate were more likely to develop components of PCOS (ovulatory dysfunction and/or hyperandrogenism) than were women receiving

Table 4. **Most Common Adverse Events (≥5%) of Lamotrigine and Valproate Treatments**

Events	Lamotrigine Group (N = 219), n (%)	Valproate Group (n = 222), n (%)
Any event	123 (56)	122 (55)
Headache	29 (13)	39 (18)
Pyrexia	15 (7)	13 (6)
Nasopharyngitis	12 (5)	11 (5)
Dizziness	11 (5)	10 (5)
Rash	10 (5)	9 (4)
Vomiting	6 (3)	16 (7)
Alopecia	3 (1)	25 (11)
Nausea	3 (1)	16 (7)
Tremor	2 (<1)	18 (8)
Weight increase	0	11 (5)

lamotrigine (Fig 2). More than one third (36%) of women receiving valproate had a component of PCOS compared with 23% of women receiving lamotrigine ($p = 0.007$). Incidence of both ovulatory dysfunction (25% valproate, 14% lamotrigine; $p = 0.021$) and hyperandrogenism (22% valproate, 12% lamotrigine; $p = 0.017$) was more common with valproate than lamotrigine during the first year of treatment (see Fig 2). Also, the incidence of PCOS defined as both ovulatory dysfunction and hyperandrogenism was more common with valproate than lamotrigine (7 vs 1%; $p = 0.011$) (see Fig 2). These results were consistent in magnitude and significance with those from the predefined intent-to-treat population.

In the analysis by age group, the difference between lamotrigine and valproate in the incidence of components of PCOS was evident in the women aged younger than 26 years. In this younger group, 44% (45/103) receiving valproate developed a component of PCOS compared with 23% (24/105) of women receiving lamotrigine ($p = 0.002$). If medication was started at the age of 26 years or older, no measurable difference was observed in the incidence of components of PCOS between women receiving valproate (15/63, 24%) and those receiving lamotrigine (11/49, 22%).

In the analysis by seizure type, the incidence of components of PCOS was greater among women treated with valproate with partial seizures only (valproate 26/61, 43%; lamotrigine 9/55, 16%; $p = 0.005$) than among women with generalized seizures only (valproate 33/102, 32%; lamotrigine 23/95, 24%; p value was not significant).

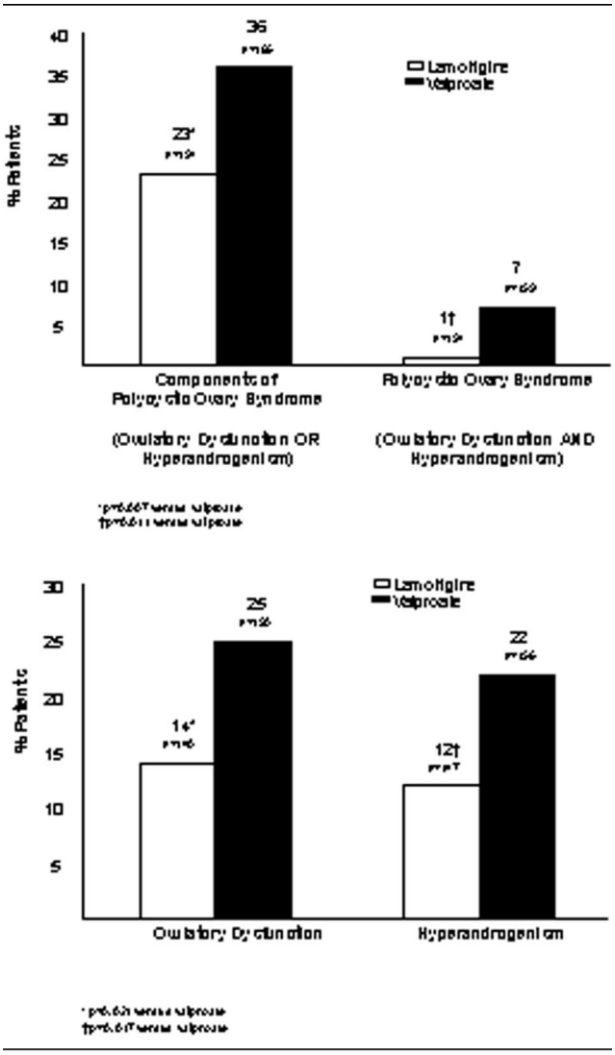

Fig 2. Incidence of polycystic ovary syndrome and its components at 1 year (post hoc intent-to-treat population). White bars *represent lamotrigine treatment;* black bars *represent valproate treatment.*

HORMONE AND SEX HORMONE–BINDING GLOBULIN CONCENTRATIONS. One year of treatment with valproate compared with lamotrigine was associated with statistically significant increases in serum total testosterone (median percentage change 42.2% with valproate, 0.9% with lamotrigine; $p < 0.001$) and SHBG (median percentage change 5.2% with valproate, −10.5% with lamotrigine; $p = 0.005$) and decreases in DHEA-S (median percentage change −11.9% with valproate, 1.7% with lamotrigine; $p = 0.004$) in the post hoc intent-to-treat population (Fig 3). The increase in serum total testosterone levels was most prominent in valproate-treated women younger than 26 years and was particularly marked in participants younger than 17 years (Fig 4). Median change from screening in serum total testosterone in subjects younger than 26 years was −0.4% in the lamotrigine group (n = 100) and 30.1% in the valproate group (n = 96). The corresponding values for subjects 26 years or older were 8.0% in the lamotrigine group (n = 47) and 14.7% in the valproate group (n = 60). Serum androstenedione, free testosterone, and gonadotropin levels did not change significantly during treatment with either valproate or lamotrigine (data not shown).

Discussion

Approximately 4 to 7% of women in the general population and 15 to 25% of women with epilepsy experience symptoms consistent with the definition of PCOS used in this study.[2,22–26] A syndrome resembling PCOS appears to be more commonly observed in women with epilepsy who are receiving valproate.[2,4,9–13,26] Features of PCOS in this population include menstrual cycle abnormalities, anovulatory cycles, increased androgen levels, carbohydrate intolerance with obesity, and polycystic-appearing ovaries. Because these observations have been primarily derived from cross-sectional studies, it has been difficult to determine the relative contributions of epilepsy and anti-

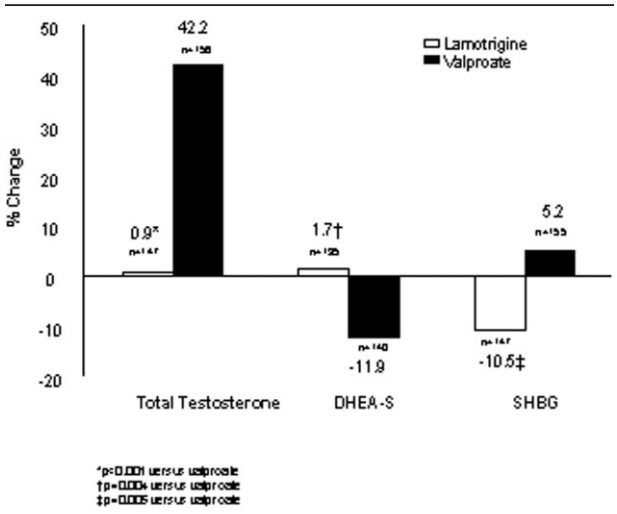

Fig 3. Median percentage change from screening in serum sex hormones during valproate (black bars) *or lamotrigine treatment* (white bars) *(post hoc intent-to-treat population). DHEA-S = dehydroepiandrosterone sulfate; SHBG = sex hormone–binding globulin.*

epileptic drugs to development of components of PCOS. This investigation is the first prospective, randomized, longitudinal study to address the impact of antiepileptic drugs on the emergence of components of PCOS in a large, multinational, multiethnic population of women with epilepsy. This study was conducted to better define the relative contributions of epilepsy, valproate, and lamotrigine to the development of components of PCOS during the first year of treatment with these antiepileptic drugs. Subjects initiating valproate monotherapy or adjunctive therapy were more likely to develop treatment-emergent components of PCOS than were women initiating lamotrigine monotherapy or adjunctive therapy. The results suggest that women with epilepsy receiving valproate are at increased risk for development of ovulatory dysfunction, hyperandrogenism, and increased body mass; that onset of these endocrine and metabolic changes can occur within several months of initiation of treatment with valproate; and that these effects are most prominent in younger women. Although not addressed in this study, other data suggest that valproate-associated changes are reversible if the drug is discontinued.[14,16]

The study findings are consistent with a possible role of valproate in the development of ovulatory dysfunction and hyperandrogenism in women with epilepsy. A number of studies suggest that valproate predisposes to ovulatory dysfunction in women.[5,9,10] In one study, women with primary (idiopathic) generalized epilepsy (n = 35) were more likely to have anovulatory cycles than those with localization-related epilepsy (n = 59).[5] Treatment with valproate was an independent variable associated with more frequent anovulatory cycles.[5] In fact, anovulatory cycles were present in 55% of women with primary generalized epilepsy receiving valproate monotherapy (n = 19), which is a significantly greater incidence rate than in any other epilepsy/antiepileptic group. A high prevalence of menstrual disorders and anovulatory cycles in women with epilepsy taking valproate has been reported in several other studies.[4,9,10,13]

Valproate is associated with increases in serum androgen levels and, in about 50% of women, increased BMI.[4,10–15] In this study, both weight and BMI increased in the women treated with valproate, and statistically significant differences between lamotrigine and valproate were observed for weight and BMI. In an analysis of the primary end point by BMI (<25, ≥25), incidence of components of PCOS was significantly greater in the valproate group. This finding is consistent with the possibility that factors other than body weight were responsible for the greater rates of ovulatory dysfunction and hyperandrogenism with valproate therapy.

Women with epilepsy treated with valproate have consistently been shown to have increased serum testosterone levels. This observation was originally made in women of childbearing age with epilepsy,[4] and later confirmed both in cross-sectional[10,12,13,15] and prospective[27] studies in adult women with epilepsy, as well as in a cross-sectional study in young female subjects with epilepsy during pubertal development.[11] Increased serum levels of adrenal androgens DHEA-S and androstenedione have been reported in valproate-treated women with epilepsy in some cross-sectional studies.[4,14] This prospective, randomized study confirmed the increase in serum testosterone levels during the first year of treatment with valproate. At least two mechanisms are likely to contribute to valproate-associated

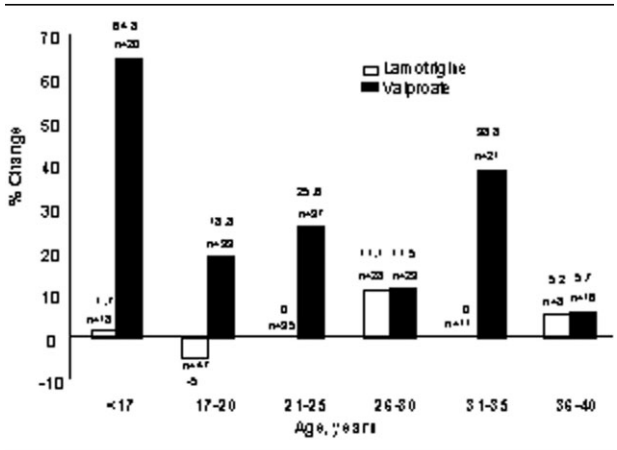

Fig 4. Median percentage change from screening in serum total testosterone during valproate (black bars) *or lamotrigine* (white bars) *treatment by age (post hoc intent-to-treat population).*

increases in androgens: inhibition of hepatic metabolism of androgens by valproate and direct stimulation of androgen synthesis in ovarian thecal cells.[28–30]

Endocrine changes may arise soon after valproate therapy is initiated. In a previous study of 10 women initiating valproate monotherapy for newly diagnosed epilepsy, the mean serum concentration of testosterone, LH, and FSH increased after 1 month whereas the mean concentration of SHBG increased and DHEA-S decreased after 3 months.[27] However, none of the women experienced clinical symptoms of hormonal disorders during the 3-month follow-up period. Substituting lamotrigine for valproate was associated with normalization of serum testosterone levels in 2 months.[16] In this study, similar changes were seen for SHBG and DHEA-S, and statistically significant differences between lamotrigine and valproate were observed. There was no difference between treatment groups in free testosterone. The clinical significance of these modest changes in SHBG and DHEA-S levels remains unclear.

The likelihood of developing components of PCOS with valproate treatment appears to depend on the age at which valproate is introduced. In this study, women with epilepsy beginning treatment with valproate at age younger than 26 years were at greatest risk for developing components of PCOS, whereas those women beginning treatment with valproate at age 26 years or older had no greater risk than women with epilepsy receiving lamotrigine. Other investigators have made similar observations regarding the particular vulnerability of younger women. In one cross-sectional investigation, more than 60% of women with epilepsy receiving valproate before age 20 had polycystic-appearing ovaries, as determined by transvaginal ovarian ultrasound, in contrast with 27% of women with epilepsy receiving other antiepileptic drugs.[4] In another cross-sectional study, increase in serum testosterone levels was found only in women who had started treatment with valproate before age 25 years.[12] In this study, the women who started valproate at the younger age had a prominent increase in serum testosterone levels. This observation is consistent with the possibility that a direct effect of valproate on ovarian androgen secretion may lead to development of components of PCOS in women with epilepsy, and that the younger ovary may be more vulnerable to this effect.

The possibility that epilepsy itself also alters reproductive endocrine function is supported by the high prevalence of polycystic ovaries at baseline before initiation of study medication in this study. Epilepsy and its associated disturbances in cortical function may contribute to reproductive dysfunction through alterations in the hypothalamic-pituitary-gonadal axis.[2,26] The severity of epilepsy could impact the likelihood of developing reproductive health dysfunction, a possibility not examined in this study. This study did not control for duration of epilepsy, seizure type, or seizure frequency. Even in the group of women with newly diagnosed epilepsy, the actual onset of seizures could have been some time before the diagnosis was established. Impact of treatment on seizure frequency was not a primary target in this study, and the seizure data capture was not rigorous. Response to treatment as measured by the proportion of participants who became seizure free was greater in the valproate group (46 vs 37%), but this finding does not explain the endocrine changes in the study. Although epilepsy itself may be a contributing factor to the occurrence of PCOS components, the impact of valproate as a causal factor is supported by a retrospective study of oligomenorrhea and hyperandrogenism in women with bipolar disorder.[31] Women receiving valproate for bipolar disorder had a fivefold greater prevalence of oligomenorrhea with hyperandrogenism than did women receiving nonvalproate anticonvulsants or lithium.

Use of hyperandrogenemia alone, rather than clinical hyperandrogenism and/or hyperandrogenemia, may have underestimated the incidence of this component of PCOS. However, because the study was conducted in culturally diverse settings and was open label, use of the more objective measure of hyperandrogenemia was believed to be advantageous. Inclusion of polycystic ovaries in the definition of PCOS remains controversial. The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus criteria, which include polycystic ovaries as a marker of PCOS, were not published until 2004, 4 years after the start of this study.[32]

Although this study helps to clarify the relative contributions of epilepsy and antiepileptic drugs to reproductive and metabolic dysfunction in women with epilepsy, unanswered questions remain. Because this study did not include an untreated group or a placebo group, data regarding emergence of ovulatory dysfunction or hyperandrogenism in a healthy population followed prospectively are lacking. Furthermore, the degree to which antiepileptic drug dose affects the likelihood of developing ovulatory dysfunction or hyperandrogenism is unknown. Serum concentrations of lamotrigine and valproate were not measured in this study; however, the doses used for both drugs were relatively low. Further study is needed to assess the clinical effects of valproate-associated changes in ovulatory function and reproductive hormones over time, particularly in younger women. An understanding of possible dose effects would provide important information for patient counseling and for practice. Finally, a better understanding of mechanisms and the population at risk may lead to therapeutic interventions that could

mitigate these effects in women wishing to begin or remain taking valproate.

The results of this study should be interpreted with the knowledge that inclusion in the study was based in part on participant-reported, retrospective data: Only women who reported two consecutive menstrual cycles of between 25 and 35 days in length were eligible. If self-reports were inaccurate, women with baseline ovulatory dysfunction might have been inappropriately included.

In conclusion, in this first prospective, randomized study of emergence of components of PCOS in a large, multinational population of women with epilepsy, women initially treated with valproate were more likely to display treatment-emergent PCOS and its components than were women initiating lamotrigine. This difference was driven by women who initiated treatment at age younger than 26 years. The greater impact of valproate in younger women may reflect age-related vulnerability to valproate effects on the hypothalamic-pituitary-gonadal axis.

Disclosure

C.R.W. and J.I. were employees of GlaxoSmithKline at the time this study was conducted. M. J. Morrell has served as a consultant to GlaxoSmithKline, Pfizer, and Valeant Pharmaceuticals, and has received honorarium from GlaxoSmithKline.

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