Menstrual Abnormalities and Polycystic Ovary Syndrome in Women Taking Valproate for Bipolar Mood Disorder

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Background: Valproate treatment has been associated with high rates of menstrual abnormalities, hyperandrogenism, and polycystic ovaries in women with epilepsy. This pilot study investigated whether valproate treatment had the same associations in women with bipolar disorder.

Method: One hundred forty outpatient women with a DSM-IV diagnosis of bipolar disorder (aged 15–45 years) were surveyed on their medical, psychiatric, and reproductive health history. Thirty-two women met entry criteria for the study and were divided into 2 groups: (1) those currently receiving valproate (valproate, N = 17) and (2) those who were not currently taking valproate (nonvalproate, N = 15). These 2 groups were compared with a normal (never diagnosed with a psychiatric disorder) control group of 22 women. Women in the valproate group with current menstrual problems (N = 7) underwent further assessment for the presence of polycystic ovaries and hyperandrogenism.

Results: The age at onset of menses, mean length of menstrual cycle, and mean length of menses were not significantly different between the groups. Significantly more women reported menstrual abnormalities in the valproate group (47%) than women not receiving valproate (13%) and controls (0%). Forty-one percent of women with bipolar disorder taking valproate had polycystic ovary syndrome.

Conclusion: These results suggest high rates of menstrual disturbances and polycystic ovary syndrome in women with bipolar disorder currently receiving valproate.

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Valproate, a simple branched-chain fatty acid, is an anticonvulsant long used in the treatment of epilepsy. More recently, it has become an alternative to lithium carbonate as a mood stabilizer in the treatment of bipolar disorder.[1,2] Valproate is used to treat as many as 30% of children and adults with bipolar disorder because of its more favorable side effect profile as compared with lithium and because of its particular efficacy in rapid-cycling and mixed-mood states.[3–6]

A number of systematic studies have reported an increased occurrence of reproductive endocrine abnormalities, including hyperandrogenism, hyperinsulinemia, and/or polycystic ovary syndrome (PCOS), among women diagnosed with epilepsy who are taking valproate. While others had previously reported a higher incidence of reproductive endocrine disorders in women with epilepsy,[7–9] Isojarvi and colleagues,[10] in 1993, were the first to correlate these abnormalities with valproate treatment. In a cross-sectional study of 238 women with epilepsy, a high prevalence of polycystic ovaries (43%), menstrual disturbances (45%), and elevated serum testosterone levels (17%) were reported for women receiving valproate when compared with women treated with other anticonvulsants.

These findings were confirmed by Murialdo et al.,[11] who reported that 40% of women with epilepsy who were receiving valproate had polycystic ovaries and 38% had menstrual disturbances. Isojarvi et al.,[10] in their original study, also reported that 80% of the women who were treated with valproate prior to the age of 20 years had polycystic ovaries or hyperandrogenism. High rates of hyperandrogenism in girls with epilepsy treated with valproate between the ages of 8 and 18 years have also been reported, with the frequency of hyperandrogenism increasing with pubertal development.[12] In adults with epilepsy that had preserved menstrual cycles, long-term treatment with valproate was not associated with polycystic ovaries, but was associated with blunted luteal progesterone levels and hyperandrogenism.[13] In contrast to these earlier findings, Bauer et al.[14] in a recent study did not find an association between valproate use in women with epilepsy and either menstrual abnormalities or hyperandrogenism (measured only by testosterone levels). However, this study used a fairly narrow definition of PCOS (hyperandrogenism, measured by testosterone concentration, combined with either oligomenorrhea or amenorrhea) and had a relatively small sample size of 19 women on valproate treatment. It was notable, however, that PCOS was present in 11% of women, compared with a figure of 4% to 7% in the general population.[15]

Isojarvi and colleagues[16] have put forward the theory that the weight gain (mean gain = 21 kg [46.2 lb]) associated with valproate treatment is progressive and is associated with hyperinsulinemia and low serum levels of insulinlike growth-factor–binding protein 1 (IGFBP-1), which may lead to hyperandrogenism and polycystic ovaries. In a small group of women with polycystic ovaries, hyperandrogenism, and dyslipidemia, switching medication from valproate to lamotrigine resulted in the reversal of hyperandrogenism, normalization of ovarian morphology, and improvements in lipid profiles.[17] Moreover, studies in girls with epilepsy found that treatment with valproate was associated with increased weight gain without changes in IGFBP-1 or insulin levels, suggesting that the hyperinsulinemia is a consequence rather than a cause of the valproate-related endocrine changes.[18] Consequently, current evidence points to valproate-related endocrine and menstrual abnormalities in women and young adults with epilepsy but does not rule out that the epilepsy itself leads to a greater susceptibility to develop these abnormalities. Indeed, anatomical connections between the temporal lobe and ventromedial, arcuate, and preoptic nuclei in the hypothalamus, which may be disturbed in epilepsy, may influence the regulation of gonadotropin-releasing hormone (GnRH), thus leading to reproductive endocrine changes.[19]

Many psychiatrists are familiar with and concerned about this potential side effect of valproate treatment and recognize the need for research to be conducted in this area.[20–24] Patients with bipolar disorder, like those with epilepsy, may be at risk for developing reproductive-endocrine disorders because of either the central nervous system pathology or the use of valproate. A possible relationship between affective disorders and PCOS has been suggested by Matsunaga et al.,[25,26] who reported elevated serum luteinizing hormone (LH) levels and androgens in 12 young women who had either an affective disorder or atypical psychosis, none of whom were being treated with valproate. More recently, a preliminary report of 22 outpatients with bipolar disorder has suggested that women with bipolar disorder have high rates of menstrual disturbance irrespective of treatment.[27] Of the 10 subjects on valproate monotherapy and the 2 on valproate/lithium combination treatment, 60% had menstrual dysfunction, 50% were obese, and 10% had an increase in hair growth, yet none of the women had abnormal hormone levels or cystic ovaries.

PCOS is one of the most common endocrine disorders among women of reproductive age, affecting about 4% to 7% of the population.[15] Although there is general agreement that PCOS is a relatively common syndrome, no consensus about how to define PCOS has been reached. First defined by Stein and Leventhal,[28] PCOS was described as the association of polycystic ovaries, amenorrhea, hirsutism, and obesity. Nowadays, the diagnosis is usually made on the basis of a combination of clinical, biochemical, and ultrasonographic criteria.[29] The National Institute of Health Conference on PCOS narrowed the definition to the presence of menstrual irregularity, hyperandrogenism, and the exclusion of other diseases.[30–32] Endocrine abnormalities associated with PCOS include elevated serum LH, testosterone, androstenedione, and LH/follicle-stimulating hormone (FSH) ratios.[32,33] Insulin also affects androgen secretion and metabolism, and a growing body of literature suggests that a subset of patients with PCOS are hyperinsulinemic and insulin resistant and may respond to insulin-lowering medications.[34,35] PCOS is associated with many health risk factors including infertility, non–insulin-dependent diabetes mellitus, ischemic heart disease, dyslipidemia, and endometrial carcinoma.[36] Furthermore, the symptoms associated with PCOS are recognized to cause women psychological distress and decreased quality of life.[37]

Given the association between valproate treatment and PCOS in women with epilepsy, the lack of information in the literature about the prevalence of PCO-like symptoms in women with bipolar disorder treated with valproate and health risks associated with PCOS, we investigated the frequency and type of reproductive endocrine disorders in women with bipolar disorder treated with valproate.

METHOD

Survey of Medical and Reproductive Histories

One hundred forty women between the ages of 15 and 45 years who met DSM-IV criteria for bipolar disorder

Table 1. Characteristics of the Study Sample of Women With Bipolar Disorder Receiving Valproate (valproate) or Not Receiving Valproate (nonvalproate) and Normal Volunteers (control)[a]

Variable	Valproate	Nonvalproate	Control
Sample size, N	17	15	22
Age, mean ± SD, y	29.9 ± 7.4	29.7 ± 8.8	31.5 ± 7.6
Body mass index, mean ± SD	27.5 ± 8.0	27.9 ± 4.8	25.5 ± 4.1
Age at onset of symptoms, mean ± SD, y	19.0 ± 5.5	17.3 ± 6.7	N/A
Age at diagnosis of bipolar disorder, mean ± SD, y	25.3 ± 5.6	24.8 ± 7.4	N/A
Hospitalized for mental illness, N (%)	16 (94)	6 (40)[b]	N/A
No. of hospitalizations, mean ± SD	3.9 ± 4.6	3.1 ± 2.5	N/A

[a]Abbreviation: N/A = not applicable.
[b]Chi-square, $p < .01$, compared with valproate group.

and were outpatients of the principal investigator (C.O.) or coinvestigator (V.K.) were invited to participate in the study. Patients over the age of 18 years were recruited from the Bipolar Mood Disorder Clinic at the Queen Elizabeth II Health Sciences Centre, and patients under the age of 18 years were recruited from the Adolescent Mood Disorder Clinic at the IWK Health Centre for Women, Children, and Families, Halifax, Nova Scotia. Patients were invited to participate by mail; each received an information form and questionnaire from her treating clinician. The questionnaire was designed for the study and consisted of 2 parts: medical history and menstrual history.

Medical history. Medical history included information on date of birth, weight, height, history of illnesses, age at diagnosis of bipolar disorder, number of hospitalizations due to bipolar illness, current and past (more than 6 months ago) medication history, and any prior use of valproate.

Menstrual history. Menstrual history included information on age at first menstruation; current use of oral contraceptive medication or intrauterine device (IUD); history of hysterectomy; average length of menstrual cycle in last 9 months; average length of menses in last 3 months; longest time and date with no menses; problems with excessive body hair, acne, or lactation, and time when these problems occurred.

Three months after the questionnaire was mailed, 40 women (29%) had completed and returned it. A follow-up telephone call was made to women who had not returned the questionnaire, and women could either decline to participate (N = 4) or fill in the questionnaire over the telephone (N = 20). Seventy-six women were unable to be contacted and/or did not return telephone messages. At study completion, 60 women (43% of original sample) had completed the questionnaires, and 28 (47% of the questionnaire completers) were excluded. Reasons for exclusion included having an IUD or taking oral contraceptive medications within the last 3 months (N = 15), taking antipsychotic medications within the last 6 months (N = 7), having an illness that interferes with pituitary-gonadal function (N = 1), or having undergone a hysterectomy (N = 5).

Thirty-two questionnaires were analyzed and the subjects were divided into 2 groups: women who reported currently taking valproate (valproate group, N = 17) and women who reported that they were not taking valproate (nonvalproate group, N = 15). A third group, 34 women who had never been diagnosed or received treatment for a psychiatric disorder, also completed the questionnaire. Twelve of these were excluded from analysis because they were taking oral contraceptive medication (N = 10) or had undergone a hysterectomy (N = 2).

Demographic and clinical characteristics of the 3 groups are shown in Table 1. Most of the subjects were white. The groups did not differ significantly in mean age or body mass index (BMI). However, a significantly higher number of women receiving valproate had been hospitalized when compared with women not receiving valproate. In the valproate group, the women reported on average taking valproate for 25 months (range, 3–120 months) with a mean daily dose of valproate of 1031 ± 352 mg (range, 750–1750 mg). About half of the women in the valproate group (N = 8) were also receiving other psychiatric medications including benzodiazepines (N = 2), antidepressants (N = 4), and other mood stabilizers (N = 3). In the nonvalproate group, 67% (10/15) of the women were currently receiving medications including benzodiazepines (N = 2), antidepressants (N = 4), and mood stabilizers (N = 7). One third of the women in the nonvalproate group (N = 5) reported not currently taking medication treatment. One third of the women in the nonvalproate group (N = 5) also reported taking valproate in the past.

Using the classifications as defined by Kiddy et al.,[38] the following were considered menstrual abnormalities: amenorrhea (no menstruation), oligomenorrhea (cycle length longer than 35 days), prolonged menstrual cycle (cycle length varying from less than 35 days to more than 35 days), and irregular menstrual cycle (cycle length varying more than 4 days from cycle to cycle, between 22 to 35 days). These abnormalities were considered to be "current" if they were present at the time the questionnaire was completed and had been present for at least 6 months. These abnormalities were considered to occur in a patient's "lifetime" if they were either current or had occurred more than 6 months prior to the completion of the questionnaire. BMI was calculated by weight in kilograms divided by the square of the height in meters.

Statistical analyses of the data were performed using SPSS 8.0 for Windows statistical software.[39] For the categorical data from the questionnaires, the χ^2 test was used to analyze any differences between the groups. For numerical data, such as BMI and age, differences between

the groups were analyzed using an analysis of variance (ANOVA), followed by a Tukey test post hoc when group differences were present.

Clinical and Gynecologic Examination

On the basis of a review of the initial questionnaire, women who had been receiving valproate for a minimum of 6 months, were currently not taking any other medications, and had current menstrual disturbances were identified and invited to participate in the second part of this study. Of the 8 patients who met these criteria, 7 volunteered to participate and signed an informed consent after the procedures and possible side effects were fully explained. The patient that did not participate was no longer living in the treatment area. No women declined to participate owing to having to complete a transvaginal ultrasound. This second part of the study involved further data collection and laboratory testing over the course of 3 study visits:

Visit 1. Clinical examination was completed by the primary investigator (C.O.) to specifically assess for features of hyperandrogenism including acne, oily skin, and hirsutism. The participants' questionnaire was reviewed and measurements of body weight and height were taken.

Visit 2. Venous blood sample (30 mL) for hormone and lipid assay were obtained at 8 a.m. after an overnight fast during the early follicular phase of the menstrual cycle (days 3–7) in menstruating women and at random in women with amenorrhea. Assays completed on blood included FSH, LH, prolactin, dehydroepiandrosterone sulfate (DHEAS), thyroid-stimulating hormone (TSH), androstenedione, testosterone (total and free), 17-OH progesterone, and valproate serum level. These assays were analyzed at the hospital laboratory at Queen Elizabeth II Health Science Centre, Halifax, Nova Scotia. The automated chemiluminescence system (ACS:180; Chiron Diagnostics, Bayer, Fernwald, Germany) was used to measure total testosterone, LH, prolactin, and TSH. The immulite analyzer (Immulite, Diagnostic Products Corp., Los Angeles, Calif.) was used to measure DHEA/DHEAS. Radioimmunoassay kits were used to measure both androstenedione (Sanofi-Syntholabo, New York, N.Y.) and 17-OH progesterone (Intermedico, Diagnostic Products Corp., Los Angeles, Calif.). Valproic acid levels were assayed by a fluorescence polarization immunoassay (TDx, Abbott Diagnostics, Irving, Tex.). Free testosterone samples were sent to the Hospital in Common Laboratories (Toronto, Ontario), and laboratory tests were completed at Hormone Laboratory at St. Michael's Hospital (Toronto, Ontario) through a radioimmunoassay methodology.

Visit 3. Gynecologic examination, including a transvaginal ultrasound, was completed by a coinvestigator, G.R.G., who was blinded to medication status. The ultrasound was performed using a Siemens Sonoline SL250 apparatus equipped with a transvaginal 5-MHz curvilinear probe (Siemens, Issaquach, Wash.). The endometrium, uterus, ovaries, and ovarian follicles were scanned. The ovaries were considered polycystic if they contained a total of at least 10 cysts 2 to 8 mm in diameter either arranged peripherally around a dense core of stroma or scattered throughout an increased amount of stroma.[40] PCOS was defined as the presence of menstrual abnormalities in combination with hyperandrogenism and excluding other diseases as defined by the National Institute of Health Conference on PCOS.[30–32] While polycystic ovaries were documented, they were not an essential criterion.

Table 2. Menstrual Characteristics and Abnormalities in Women With Bipolar Disorder Receiving Valproate (valproate) or Not Receiving Valproate (nonvalproate) and Normal Volunteers (control)

Characteristic	Valproate (N = 17)	Nonvalproate (N = 15)	Control (N = 22)
Age at first menses, mean ± SD, y	12.9 ± 1.3	12.1 ± 1.7	13.0 ± 1.3
Length of cycle within last 9 mo, mean ± SD, d	24.1 ± 13.0	29.5 ± 4.6	28.1 ± 3.0
Length of menses within last 3 mo, mean ± SD, d	4.8 ± 1.0	5.2 ± 1.5	5.1 ± 1.2
Current rate of abnormalities, N (%)[a]			
Amenorrhea	0 (0%)	0 (0%)	0 (0%)
Oligomenorrhea	7 (41%)	2 (13%)	0 (0%)
Irregular menstruation	1 (6%)	0 (0%)	0 (0%)
Total	8 (47%)[b]	2 (13%)	0 (0%)
Lifetime rate of abnormalities, N (%)[a]			
Amenorrhea	3 (18%)	1 (7%)	0 (0%)
Oligomenorrhea	9 (53%)	8 (53%)	6 (27%)
Irregular menstruation	1 (6%)	0 (0%)	0 (0%)
Total	13 (77%)[c]	9 (60%)[c]	6 (27%)

[a]For current (occurring and present for 6 months) and lifetime (current or occurring more than 6 months ago), the rate represents number of women self-reporting abnormalities. All types of menstrual abnormalities are mutually exclusive.
[b]In total rates of current disturbances, women in the valproate group had significantly more disturbances when compared with the nonvalproate and control groups, chi-square, $p < .05$.
[c]In lifetime rates of disturbances, women in the valproate and nonvalproate groups had significantly more disturbances when compared with the control group, chi-square, $p \leq .05$.

RESULTS

Survey Results

As shown in Table 2, the age at first menses for the 3 groups was 12 to 13 years for the valproate, nonvalproate, and control groups. In the last 9 months, no significant differences in the mean number of days between menses were reported by the women in the 3 groups. As demonstrated by the larger standard deviation for the women with bipolar disorder, these women had a larger range of cycle lengths (valproate 4–52 days, nonvalproate 21–40 days, control 21–35 days). The mean number of days of menses was also not significantly different between the groups.

Table 3. Clinical Data for the Women With Bipolar Disorder in the Valproate Group Participating in the Examination Portion of the Study

Case	Age (y)	Age Diagnosed (y)	Bipolar I/II	Rapid Cycling	Valproate Dose (mg/d)	Length of Time on Valproate	Serum Valproate Level (μmol/L)
1	35	32	I	Yes	1000	3 y	675
2	35	22	I	No	750	1 y	559
3	31	25	I	No	750	2 y	507
4	33	20	I	Yes	1250	3 y	743
5	27	18	I	Yes	750	7 mo	576
6	29	28	I	No	1500	6 mo	599
7	44	21	I	No	750	10 y	222

When examining the rate of current menstrual abnormalities, women with bipolar disorder currently being treated with valproate reported higher rates of abnormalities (47%) compared with women with bipolar disorder not receiving valproate (13%) and controls (0%) (see Table 2). In comparison, when examining the lifetime rate of reported menstrual abnormalities (occurring currently or more than 6 months ago), women with bipolar disorder in both the valproate and nonvalproate groups had high rates of menstrual abnormalities of 77% and 60%, respectively. More than half of these disturbances in each of the groups were accounted for by the high rate of oligomenorrhea.

One explanation for the difference in current versus lifetime rates of menstrual disturbance for the valproate and nonvalproate group may be due to the fact that 33% of the women who were not currently taking valproate had received valproate in the past. To examine this possibility, all the women that were currently taking valproate or had received valproate in the past (N = 17 + 5 = 22) were compared with women with bipolar disorder that had never received valproate (N = 15 – 5 = 10). In the group that had received valproate, 77% (17/22) reported menstrual abnormalities during their lifetime. This rate was significantly higher ($p < .01$) when compared with only 50% (5/10) who had never received valproate and 27% (6/22) of controls.

For the 17 women treated with valproate that had menstrual abnormalities, use of the self-reported date for start of menstrual problems and valproate medication allowed analysis of the temporal association between the start of valproate and menstrual abnormalities. Fifty-nine percent (10/17) of women with menstrual problems reported onset of their menstrual problems *after* starting valproate.

Although there was no significant difference in mean BMI between the 3 groups (see Table 1), the valproate group and nonvalproate group did have a mean BMI greater than 25, and the valproate group had a larger standard deviation when compared with the other 2 groups. A chi-square analysis revealed no significant differences between the 3 groups in the number of women with BMI greater than 25 (rates of 53%, 57%, and 46% for the valproate, nonvalproate, and control group, respectively). Differences in index scores over 30 revealed a trend toward more women in the nonvalproate group (40%, 6/15) to have a score over 30, as compared with women taking valproate (18%, 3/17) or controls (18%, 4/22) (chi-square test not performed, N < 5). Mean BMI scores over 25 for the control group, 27 for the valproate group, and 28 for the nonvalproate group were not associated with the presence of menstrual problems for the 54 women in the study.

Within the 3 groups, there was a trend for more women in the valproate group (24%, 4/17) to report difficulties with excessive body hair when compared with the nonvalproate group (13%, 2/15) and controls (9%, 2/22) (chi-square test not performed, N < 5). Of the 6 women with bipolar disorder that reported difficulties, 2 women reported that these problems started after taking valproate. In 1 case, the hirsutism was prominent and severe on the back, face, and chest and started 2 months following valproate treatment. A small number of women (< 5%) within each group also reported problems with breast lactation, although this was associated with pregnancy or antipsychotic medication that was taken more than 6 months before study participation.

Examination Results

From the initial questionnaires included in the analysis, 7 of the 8 women that were eligible to participate in the second part completed the study. As shown in Table 3, the range of the clinical and demographic characteristics of the 7 women was diverse. The mean age of the women was 33.5 years, and the diagnosis of bipolar disorder had been made between the ages of 18 and 32 years. All women were currently stable and were being seen at the outpatient department for maintenance therapy. They were currently receiving no medication other than valproate, which they had been taking for a range of 6 months to 10 years. A high total testosterone may not seem significant given its binding to sex hormone-binding globulin. However, all but 1 of the 5 with high total testosterone also had other endocrine abnormalities. The mean dose of valproate for the women was 964.3 mg/day, and serum valproate levels were in the therapeutic range except for case 7.

As shown in Table 4, all the women had a BMI score that was under or equal to 25, with the exception of 2 women, case 3 and case 7, who had BMI scores of 40 and 49, respectively. Of the 5 women that had hirsutism, 2 reported that this problem began after starting valproate, and 3 women reported having this problem before starting valproate, although they subjectively reported more hair growth after starting valproate. No women who participated in the examination portion of this study had ab-

Table 4. Number of Women With Bipolar Disorder Currently Being Treated With Valproate Who Had Menstrual Abnormalities[a]

Case	Polycystic Ovaries	High Total Testosterone	High Free Testosterone	High Androstenedione	Hyperandrogenism	LH > FSH	Hirsutism	BMI	PCOS
1	Yes	Yes	Yes	No	Yes	No	Yes	23	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes	No	25	Yes
3	Yes	No	No	Yes	Yes	Yes	Yes	40	Yes
4	Yes	Yes	No	No	Yes	Yes	No	24	Yes
5	No	Yes	No	Yes	Yes	No	Yes	21	Yes
6	Yes	No	No	Yes	Yes	Yes	Yes	22	Yes
7	No	Yes	No	No	Yes	No	Yes	49	Yes

[a]Abbreviations: BMI = body mass index, FSH = follicle-stimulating hormone, LH = luteinizing hormone, PCOS = polycystic ovary syndrome.

normal FSH, prolactin, TSH, DHEAS, or 17-OH progesterone levels. However, all 7 women who participated had hyperandrogenism including 5 women with high total testosterone levels, 2 with high free testosterone levels, 4 with high androstenedione levels, and 4 with high LH:FSH ratio (high LH). By gynecologic examination, 5 women were found to have polycystic ovaries.

Based on these data (see Table 4), all women in the second part of the study had PCOS (menstrual irregularity, hyperandrogenism, and the exclusion of other diseases).[30–32] Therefore, of the 17 women with bipolar disorder that were currently receiving valproate, at least 41% (N = 7) had PCOS and 47% (N = 8) had current menstrual abnormalities.

DISCUSSION

We report higher rates of menstrual abnormalities in women receiving valproate treatment for bipolar disorder than in women not receiving valproate. In our study, the prevalence of current and lifetime menstrual abnormalities in women being treated with valproate is 47% and 77%, respectively. This finding is comparable to the current rate of 45% for epileptic women treated with valproate reported by Isojarvi et al.[10] and lifetime rate of 60% in women with bipolar disorder treated with valproate reported by Rasgon et al.[27]

All of the women who participated in the examination portion of the study (i.e., 7/8 on treatment with valproate with menstrual disturbances) were diagnosed with PCOS. A prevalence of 41% (7/17) for PCOS is higher than the rates in the general population (2%–22% using the widest range of definitions).[41–43] Owing to the lack of a specific definition for PCOS in those studies, it is difficult to compare this rate with the studies of women with epilepsy[10,11] or of women with bipolar disorder treated with valproate.[27]

Polycystic ovaries were present in 71% (5/7) of these cases, which is similar to a rate of 60% reported by Isojarvi et al.[10] It should be noted that Isojarvi et al. also studied women taking valproate for epilepsy with normal menstrual cycles, and 31% of these had polycystic ovaries, which is somewhat higher than the rate in the general population,[31,44] although of doubtful clinical significance.[45] These findings are in contrast with those of Murialdo et al.,[13] who reported that only 10% of women with normal menstrual cycles taking valproate for epilepsy had polycystic ovaries. Some of this variation in results may be due to the use of suprapubic transabdominal ultrasound (rather than the transvaginal ultrasound used in our study), which is less likely to detect cysts. However, differences in ultrasound technique cannot explain the differences in our results and those of Rasgon et al.,[27] who reported that no women with bipolar disorder treated with valproate had polycystic ovaries.

The other core feature of PCOS—abnormally high androgen levels—was found in 100% of the women with bipolar disorder that had menstrual abnormalities. Hirsutism was also present in 71% of our sample clinically. These findings are similar to the findings of Murialdo et al.[13] and Isojarvi et al.[10,16] who reported high androgen levels in women taking valproate that are being treated for epilepsy. Associated PCOS features—high LH levels and LH:FSH ratio—were also found in 57% (4/7) of women with bipolar disorder on treatment with valproate. These results are again in opposition to Rasgon et al.,[27] who found no abnormal hormonal values when comparing women with bipolar disorder treated with valproate. The mean length of valproate exposure and daily dose did not appear to differ between these studies. In fact, it is notable how early in treatment with valproate the clinical findings occurred in our study (see Table 3).

Similar to the findings of Rasgon et al.,[27] we found that 43% of women treated with valproate were obese (BMI > 25). However, we also had a high rate of obesity in our other 2 groups: 57% of the nonvalproate group and 46% of controls. Unlike the study by Isojarvi et al.,[16] we were unable to find a statistical difference between the groups in the number of women that were obese as measured by mean BMI scores or examining the number of women that had BMI scores over 25, 27, or 30. This finding argues against a causal link between valproate, obesity, and the presence of PCOS features.

Unfortunately, we did not measure insulin and IGFBP in our study, which would have been interesting, given the theory by Isojarvi et al.[16] that valproate-induced

weight gain causes hyperinsulinemia, which leads to PCOS. Epilepsy medication, with the exception of valproate, does not tend to cause weight gain in comparison to drugs for bipolar disorder; this finding might allow us to tease out the relevancy of obesity to hyperinsulinemia. The women with bipolar disorder taking medications other than valproate who were equally obese had significantly lower rates of menstrual abnormalities (47% vs. 13%) than the valproate group, but higher rates than controls (13% vs. 0%). We did not test this 13% any further.

Women with bipolar disorder in our study, independent of current medication, had a high lifetime rate of menstrual abnormalities (69% = 22/32). This is the same as the rate of 69% in epileptic women,[8] although lower than the 90% in the study by Rasgon et al.[27] Furthermore, 59% (10/17) of women with menstrual abnormalities recalled onset after starting valproate and 60% (9/15) who were not currently receiving valproate had a lifetime history of menstrual problems.

The similarity in figures with the epilepsy sample makes it less likely that prior use of antipsychotics can explain these high rates. Thus, it is possible that bipolar disorder itself is a risk factor for menstrual abnormalities and/or PCOS with a similar temporal lobe-hypothalamic-gonadal abnormality as suggested in the epilepsy literature.[19] Our study design does not allow us to tackle this question.

Unfortunately for young adults, this study is unable to address the question of whether the use of valproate is associated with polycystic ovary syndrome and hyperandrogenism in their age group, since only 6 participants in the study were under the age of 20. Although 12 young women replied to the study questionnaire, 50% of these were excluded due to their use of birth control, leaving an insufficient number to analyze. Clearly, the studies by Isojarvi et al.,[10] Vainionpaa et al.,[12] and Rattya et al.[18] all suggest concern regarding valproate-induced PCOS-like symptoms in the younger population, and larger samples in this age group will be required for further studies, due to the high use of contraception.

Why is treatment with valproate associated with high rates of menstrual abnormalities, hyperandrogenism, and polycystic ovaries? A variety of mechanisms have been suggested to explain valproate's alteration of reproductive-endocrine functioning, albeit none of these theories has been proven. Valproate has been well demonstrated to increase γ-aminobutyric acid (GABA) concentrations at clinically relevant dosages in specific brain regions.[46,47] Through central effects on GABAergic neurotransmission, investigators have been exploring whether (in animal models) valproate acts on the neuroendocrine axis at the level of GnRH in cells within the medial preoptic area.[48,49] This hypothesis is supported by studies that report increased luteal LH levels and LH:FSH ratios, as well as impaired E2/SHBG ratios and impaired progesterone surges.[13] Conversely, some human studies find normal basal gonadotropin levels in healthy ovariectomized women[50] and patients with epilepsy receiving valproate during the follicular phase.[13] Alternatively, as suggested earlier in human studies by Isojarvi et al.,[16,17] hyperinsulinemia with low levels of IGFBP-1 may be influencing ovarian steroidogenesis. While weight gain is one possible cause of this, valproate is also known to stimulate growth hormone release, which may lead to insulin resistance.[51] As reviewed by Sozen and Arici,[34] hyperinsulinemia and hyperandrogenism can act through a vicious cycle that can cause PCOS-like symptoms. Although it is clear that substantial changes in sex hormones take place during treatment with valproate, it is unknown how specific these effects are for valproate when compared with other anticonvulsants or mood stabilizers, and if these changes are a consequence or the initiator of changes in endocrine-reproductive functioning. Therefore, any hypothesis of cause derived from clinical data at this time is speculative because of the relatively small amount of experimental evidence on the effects exerted by valproate on sex steroid synthesis, metabolism, and peripheral organs.

Although the data suggest that bipolar adult women treated with valproate may be at high risk for developing PCOS or PCOS-like features, the interpretation of the data must be done with caution. The retrospective design of the study and use of self-report may be inaccurate, as it may be difficult for women to remember exact times and periods in which they had menstrual abnormalities. However, it must be said that in this study the self-report information from the women in the examination portion of the study correlated 100% with the information in their charts, where available. The women with bipolar disorder in this sample are also from a tertiary care center, and this may limit our ability to apply these findings to all women with bipolar disorder.

Only 40 (29%) initially responded to the questionnaire. At study completion, 60 (43%) had completed it, upon follow-up with telephone calls. The large number of women not completing the questionnaire is a significant limitation to this study, since it is possible that the women who did not respond had no menstrual concerns. Women in the negative study reported by Rasgon et al.[27] appear to have been recruited directly from their specialty clinic, and of those who met criteria, 74% agreed to participate. Furthermore, in our study only 7 women completed the examination portion (7 of 8 who had menstrual abnormalities). To be able to differentiate problems for women with bipolar disorder compared with women receiving valproate, a larger sample and control group for the second part of the study would be necessary.

While the evidence is mounting that valproate treatment is associated with PCOS features, whether bipolar disorder is a risk factor is still unclear. Of note is the high lifetime prevalence of menstrual disturbances in women

with bipolar disorder, which cannot be clearly linked with valproate use in studies to date. The literature to date has focused on an either/or hypothesis, which may be too simplistic. Clearly, only prospective studies can answer this question. The clinical significance of the epilepsy and bipolar findings to date is unclear. Evidence to date suggests decreased fertility in epileptic women and increased morbidity in women with bipolar disorder (over and above suicide risk), but we do not know if these risks reflect clinically significant concomitants of PCOS, i.e., anovulation, hyperlipidemia, endometrial carcinoma, or other risk factors. A study by Polson et al.[45] suggests that 23% of the general population has PCOS-like features without obvious clinical significance. Hence, current stringent guidelines for valproate-treated women that suggest baseline and yearly lipid profile as well as BMI calculation each visit[24] may be premature and excessive. We recommend that all women on treatment with valproate be followed longitudinally for menstrual abnormalities, and, if present, be screened biochemically for TSH, prolactin, serum (total), testosterone, androstenedione, and LH, with subsequent referral to a specialist. This recommendation is a slightly broader endocrine screen than that proposed by Rasgon et al.,[27] but reflects the abnormalities we found and specific recommendations based on a hormonal study of 63 diagnosed cases of PCOS.[33] At this time, the clinical relevance of screening those without menstrual abnormalities is unclear.

Drug name: lamotrigine (Lamictal).

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