Medication Status and Polycystic Ovary Syndrome in Women With Bipolar Disorder: A Preliminary Report

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Background: In patients with epilepsy, polycystic ovary (PCO) syndrome has been reported to be associated with the use of the anticonvulsant divalproex sodium. Whether PCO syndrome is associated with divalproex use in patients with bipolar disorder has not previously been explored.

Method: Twenty-two female outpatients with a DSM-IV diagnosis of bipolar disorder who were between the ages of 18 and 45 years (inclusive) and who were taking lithium and/or divalproex (10, divalproex monotherapy; 10, lithium monotherapy; 2, divalproex/lithium combination therapy) were evaluated. Patients completed questionnaires about their medical, psychiatric, and reproductive health histories, and body mass indices were calculated. In the early follicular phase of their menstrual cycle, women were examined for hirsutism, given a pelvic ultrasound, and/or assessed for changes in laboratory values such as serum levels of testosterone, free testosterone, estradiol, estrone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, luteinizing hormone, follicle-stimulating hormone, and 17-OH progesterone.

Results: All 10 patients on lithium monotherapy, 6 of 10 patients on divalproex monotherapy, and both of the patients on divalproex/lithium combination therapy reported some type of menstrual dysfunction, which, in 4 cases, had preceded the diagnosis of bipolar disorder. Hirsutism was not common in any group, but obesity was prominent in all groups. Ovarian ultrasound revealed an increased number of ovarian follicles in 1 patient taking lithium and in none of the patients taking divalproex. Hormonal screening did not indicate PCO-like changes in any patient.

Conclusion: In this pilot study of bipolar patients, PCO-like changes were not seen in women receiving divalproex or lithium. However, independent of therapeutic agent used, the bipolar women in this study reported high rates of menstrual disturbances, suggesting that the hypothalamic-pituitary-gonadal axis may be compromised in some women with bipolar disorder.

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Bipolar disorder is an illness with a usual age at onset during the reproductive years. Lithium and anticonvulsant agents (carbamazepine, divalproex sodium) have demonstrated excellent antimanic efficacy and are prescribed for chronic use in patients with bipolar disorder. However, anticonvulsants have been reported to change the metabolism of reproductive hormones, including estrogen, progesterone, and testosterone, with resultant alterations in circulating blood levels of these hormones and secondary effects on the feedback loop of the hypothalamic-pituitary-gonadal (HPG) axis.[1] This, in turn, may influence serum levels of reproductive hormones and consequently affect menstrual cyclicity and reproductive function.[1,2]

Recently, concerns have been raised about an association between the use of divalproex and polycystic ovary (PCO) syndrome.[3] PCO syndrome has been defined clinically as the association of hyperandrogenism with chronic anovulation in the absence of specific underlying diseases of the adrenal and pituitary glands.[4] The diagnosis of PCO syndrome is usually made on the basis of a combination of endocrinologic, clinical, and ultrasonographic criteria.[5,6] Endocrinologically, women with PCO syndrome have chronically elevated plasma testosterone (hyperandrogenism), increased luteinizing hormone (LH) secretion due to enhanced pituitary sensitivity to gonadotropin-releasing hormone (GnRH) stimulation, and low or normal plasma follicle-stimulating hormone (FSH) levels.[4,7,8] Many of these women additionally have hyperinsulinemia and peripheral insulin resistance. Clinically, hyperandrogenism is manifested as hirsutism, acne, alopecia, or anovulation (Table 1). Women with anovulation may present with menstrual disturbances such as amenor-

Table 1. Clinical and Endocrine Abnormalities in Women With Polycystic Ovary Syndrome[a]

Clinical	Hormonal
Hirsutism/acne/alopecia	Increased serum testosterone (total and bioavailable)
Menstrual abnormalities:	
Oligomenorrhea	Decreased FSH
Amenorrhea	Increased LH and LH/FSH (> 2)
Anovulation	Increased prolactin
Obesity	Insulin resistance
	Increased fasting glucose
	Hyperlipidemia

[a]Abbreviations: FSH = follicle-stimulating hormone, LH = luteinizing hormone.

rhea, oligomenorrhea, or dysfunctional uterine bleeding. Infertility may result from chronic anovulation. The metabolic abnormalities of hyperinsulinemia and peripheral insulin resistance may contribute to obesity, which is common but not universal in this disorder.[4,7] Obesity in itself contributes to insulin resistance, which is quite common in women with PCO syndrome.[4,5,7] On ultrasound the ovaries appear to have multiple small cysts. However, the term "polycystic ovaries" itself is misleading, because in women with PCO syndrome, the ovaries are studded with atretic (involuted) follicles, not with cysts.

PCO syndrome is the most common cause of menstrual disturbances in women of reproductive age.[4] Polycystic ovaries per se, however, do not necessarily mean a woman has the PCO syndrome. Polycystic ovaries were detected in more than 20% of premenopausal women with regular menstrual cycles using ultrasound[9] and in 87% of women with "idiopathic hirsutism" (e.g., hirsutism, yet with regular menstrual cycles).[10] Women with polycystic ovaries, hyperandrogenism, and regular menses do not fit the classic definition of PCO syndrome, which includes menstrual disturbance, but they may have PCO syndrome–like changes.

Menstrual disturbances, including amenorrhea and oligomenorrhea, have been reported as a side effect of divalproex therapy.[2] A recent article[3] has raised concern about the association of divalproex and PCO syndrome. Isojarvi et al.[3] studied 238 women on treatment with antiepileptic medications; they found that menstrual disturbances were most common in the 29 women receiving divalproex monotherapy (45%) compared with those receiving other antiepileptic medications (13%–19%). Polycystic ovaries or elevated serum testosterone concentrations were found in most of the women with menstrual disturbances who were taking divalproex monotherapy.[3] Polycystic ovaries or elevated serum testosterone or both were also common in women with regular menstrual cycles who took divalproex as monotherapy or in combination with other anticonvulsants (56%). Further, 80% of women treated with divalproex before the age of 20 years had polycystic ovaries or elevated serum testosterone[3] compared with 27% of women treated with other antiepileptic drugs; 56% of women treated with divalproex after the age of 20 had polycystic ovaries or increased serum testosterone compared with 20% of women treated with other antiepileptic drugs after the age of 20.

Because of the common use of divalproex in bipolar women of reproductive age, we sought to assess for PCO syndrome in women taking divalproex. We report the results of a cross-sectional study assessing the presence of PCO syndrome and evaluating reproductive function in women with bipolar illness taking mood stabilizers. In this article, we use the term "PCO-like changes" to refer to any of the clinical, endocrinologic, or ultrasonographic changes seen in PCO syndrome.

METHOD

Subjects

Women 18 to 45 years old from the University of California Los Angeles (UCLA) Mood Disorders Clinic, UCLA Women's Clinic, and the Women's Outpatient Clinic of the West Los Angeles Veterans Affairs who were taking lithium and/or divalproex for a DSM-IV diagnosis of bipolar disorder were recruited for the study. Because both antipsychotics and oral contraceptives are known to affect the normal menstrual cycle,[8,11] patients were included in our study only if they had not taken either antipsychotics or oral contraceptives for at least 6 months beforehand. Of 115 women screened, 31 met these criteria. Of these, 9 (26%) refused to participate for personal reasons. Thus, 22 women (71%) who met the inclusion criteria participated in the study. All gave informed consent to be interviewed and to undergo venipuncture and vaginal ultrasound.

Procedures

Patients completed a questionnaire assessing their medical, psychiatric, and reproductive health histories, including menstrual history, family history of menstrual and/or reproductive problems, and family psychiatric histories. Information about infertility problems, miscarriages, and menstrual disturbances was collected. Menstrual disturbances were defined as the presence for at least 6 months of amenorrhea, oligomenorrhea (cycle length longer than 35 days), menorrhagia (heavy menstrual bleeding for more than 3 days), or dysmenorrhea (recurrent pain during menses interfering with daily functioning).

All patients were examined for hirsutism using the Ferriman-Gallwey hirsutism scale.[12] Obesity was calculated using body mass index (BMI; the weight in kilograms divided by the square of the height in meters). Patients with a BMI exceeding 25 were considered obese.[13]

A pelvic ultrasound using a vaginal transducer was performed by a radiologist blinded to the medication status of the patient. The ovaries were considered polycystic

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if they contained a total of at least 10 cysts 2 to 8 mm in diameter arranged either peripherally around a dense core of stroma or scattered throughout an increased amount of stroma.[14]

Venous blood samples were collected between days 4 and 7 of the menstrual cycle (early-to-mid follicular phase) from women who did not have amenorrhea (N = 18) and at random from those with amenorrhea (N = 4). Serum samples were kept frozen at –20°C until analyzed. Serum levels of testosterone, free testosterone, estradiol, estrone, LH, FSH, dehydroepiandrosterone/dehydroepiandrosterone sulfate (DHEA/DHEAS), and 17-OH progesterone were obtained. The methods described by O'Conner et al.[15] were used to measure testosterone, bioavailable testosterone, and estradiol. For testosterone, the respective intra-assay and interassay coefficients of variation of replicate samples were 3.3% and 4.3%.[15] For free testosterone, the intra-assay coefficients of variations of replicate samples were 1.8% and 2.6%, and the interassay coefficients of variations were 2.9% and 4.8%. For estradiol, the respective intra-assay and interassay coefficients of variations for replicate samples were 3.2% and 4.6%.

The 1–125 radioimmunoassay method by Diagnostic System Laboratories (Webster, Tex.) was used to analyze the estrone, DHEA, DHEAS, and progesterone assays. The intra-assay and interassay coefficients of variation of replicate samples of DHEAS were 3.32% and 5.06%, respectively. The intra-assay and interassay coefficients of variation for replicate samples of DHEA were 1.54% and 6.43%, respectively. The intra-assay and interassay coefficients of variation for replicate samples of estrone were 1.83% and 9.1%, respectively. The intra-assay and interassay coefficients of variation for replicate samples of 17-OH progesterone were 1.78% and 5.7%, respectively.

Luteinizing hormone was measured using the immunoradiometric assay (IRMA) described by Miles et al.[16] The intra-assay and interassay coefficients of variation for replicate samples were 7.1% and 5.75%, respectively. Follicle-stimulating hormone was also measured using the IRMA.[16] The intra-assay and interassay coefficients of variation for replicate samples of FSH were 3.29% and 6.75%, respectively.

Hormonal values of patients were compared with normative data obtained from persons with no known psychiatric, neurologic, or endocrinologic abnormality by Diagnostic System Laboratories (N = 20) using the same assays.

RESULTS

Demographic and historic information are presented in Table 2. Nineteen of the 22 women underwent both ovarian ultrasound and hormonal screening. Two refused the blood draw but agreed to an ultrasound, and 1 completed only the physical examination and history review. Ten patients were on lithium monotherapy, 10 were on divalproex monotherapy, and 2 were taking both lithium and divalproex. Patients' ages ranged from 19 to 44 years. The mean ± SD age in the lithium group was 34.1 ± 6.4 years and in the divalproex group, 37.0 ± 6.0 years. Daily dose of lithium ranged from 600–1500 mg/day (mean = 1029.9 mg), and the mean length of drug exposure was 68.8 ± 51.0 (range, 12.0–144.0) months. The daily dose of divalproex ranged from 750 to 1500 mg/day (mean = 1112.5 mg), and the mean length of exposure was 34.1 ± 30.4 (7.0–108.0) months.

Table 2. Clinical Characteristics of Bipolar Women Taking Mood Stabilizers

Characteristic	Lithium (N = 10)	Divalproex Sodium (N = 10)	Lithium + Divalproex Sodium (N = 2)
Daily dose, mg, mean ± SD	1029.9 ± 330.0	1112.5 ± 291.4	Lithium: 1350 ± 0 Divalproex: 1500 ± 0
Length of exposure, mo, mean ± SD	68.8 ± 51.0	34.1 ± 30.4	12 ± 0
Body mass, kg, mean ± SD	68.4 ± 19.0	71.9 ± 16.9	59.1 ± 0
Menstrual disturbances,[a] N (%)	10 (100)	6 (60)	2 (100)
Post-medication weight gain by self-report, N (%)	6 (60)	8 (80)	1 (50)
Family history of menstrual disturbances, N (%)	3 (30)	3 (30)	0
Positive family psychiatric history for mood disorders, N (%)	7 (70)	6 (60)	1 (50)
Age, y, mean ± SD	34.1 ± 6.4	37.0 ± 6.0	26.0 ± 11.3
Body mass index, mean ± SD	25.5 ± 6.9	26.7 ± 6.0	23.5 ± 0.5

[a]Menstrual disturbances included amenorrhea, oligomenorrhea, menorrhagia, and dysmenorrhea.

None of the patients in the lithium monotherapy group had reported previous intake of other mood stabilizers, while 70% of patients taking divalproex reported prior use of lithium at a dose range of 900 to 1200 mg/day for 36 to 144 months. Twenty percent of patients in this group had not taken mood stabilizers other than divalproex, and 10% reported sporadic lithium intake for a few months plus prior use of carbamazepine for 9 years. Patients taking the combination of lithium and divalproex had used lithium as a sole agent for 2 to 3 years before taking combination therapy.

Reproductive histories of patients and their families are shown in Table 2. No patient met criteria for PCO syndrome. Analysis of reproductive complaints showed that all patients taking lithium alone or in combination with

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Table 3. Hormonal Values of Bipolar Women Taking Mood Stabilizers (N = 19)[a]

Measurement	Normative Values, mean (range)[b]	Lithium (N = 9)	Divalproex Sodium (N = 9)	Lithium + Divalproex Sodium (N = 1)
Testosterone, ng/dL	(20–80)	19.8 ± 10.9	26.2 ± 17.7	26.4
Bioavailable testosterone, ng/dL	< 5	3.3 ± 3.5	4.5 ± 4.5	5.4
Estrone, pg/mL	70.7 (37.2–137.7)	38.6 ± 20.7	31.9 ± 10.7	16.8
Estradiol, pg/mL	(30–100)	30.0 ± 20.7	26.0 ± 12.6	23.9
DHEA, ng/dL	3.6 (0.8–10.5)	6.3 ± 2.6	4.9 ± 3.0	2.2
DHEAS, mg/dL	1637 ± 846	2237.5 ± 1367.1	1354.1 ± 830.2	1101.7
17-OH Progesterone, ng/mL	0.7 (0.4–1.0)	0.7 ± 0.4	0.6 ± 0.3	0.5
LH, mIU/mL	5.5 (1.0–18.5)	6.5 ± 5.4	5.7 ± 2.4	6.6
FSH, mIU/mL	3.4 (2.5–8.0)	6.9 ± 4.6	4.9 ± 0.8	4.5

[a]Abbreviations: DHEA = dehydroepiandrosterone, DHEAS = DHEA sulfate. All values reported as mean ± SD unless indicated otherwise.
[b]When presented as a range, normative values are based on the normative values of the laboratory kit for that particular assay. When presented as a mean ± SD, normative values are based on the normative data for controls for the laboratory performing the assays. The experimental values are presented as mean and range, except DHEAS values are presented as mean ± SD and estradiol and testosterone values are presented as ranges.

divalproex had some type of menstrual dysfunction in their histories; 67% of women taking divalproex reported menstrual dysfunction histories (6 of 10 from the divalproex monotherapy group and 2 of 2 in the combined lithium/divalproex group). The most common complaints in the lithium group were dysmenorrhea (60%), followed by oligomenorrhea (20%), miscarriages (20%), and infertility (10%). In all but 1 case, these abnormalities preceded the development of bipolar illness and thus preceded lithium use. In the divalproex group, the most common complaints were oligomenorrhea (30%) and menorrhagia (30%), followed by amenorrhea (10%). One patient in the lithium group, 2 in the divalproex group, and 1 in the combined group had amenorrhea. In these patients, amenorrhea preceded the onset of bipolar disorder and thus preceded the use of mood stabilizers. One patient in the divalproex group reported oligomenorrhea after treatment with this mood stabilizer; she also reported menstrual disturbances (dysmenorrhea, menorrhagia, and endometriosis) before the development of bipolar disorder, i.e., since puberty. Perimenstrual mood changes, e.g., complaints of "premenstrual syndrome," accompanied menses in 50% of women in the lithium group and 20% of women in the divalproex group. Thirty percent of patients in the lithium group and 30% of patients in the divalproex group had knowledge of reproductive dysfunction in their first-degree relatives (see Table 2). Additionally, 70%, 60%, and 50% of patients in respective groups of lithium, divalproex, or combination treatment reported a history of mood disorders in first-degree female relatives.

Results of the physical examination did not reveal significant hirsutism in any patient in either group. Only 1 patient in the divalproex group reported an increase in hair growth as a result of therapy. When obesity was operationalized as BMI > 25, it was present in 50% (N = 6) of patients taking divalproex versus 30% (N = 3) of those taking lithium. Most patients attributed their increased weight to medication intake. Ovarian ultrasound indicated an increased number of follicles in the ovaries of 1 patient in the lithium monotherapy group. None of the patients on divalproex treatment had an increased number of follicles on ultrasound. Hormonal screening did not reveal abnormalities compared with normative values (Table 3).

DISCUSSION

In this small pilot study of patients with bipolar disorder, we did not find significant hormonal or radiological evidence of PCO-like changes in women treated with either divalproex or lithium. Although women taking divalproex in our study had elevated concentrations of total and bioavailable testosterone and DHEA when compared with women treated with lithium, none of the differences were significant. Given the small sample size, a type II error cannot be ruled out. However, the absolute hormonal concentrations of this group were low compared with age- and menstrual phase–matched normative data (see Table 3).

The lack of PCO-like changes seen in the 12 bipolar patients exposed to divalproex differs from the results of the Isojarvi et al.[3] study in epileptic patients, in which 40% of 29 women receiving divalproex as monotherapy had hyperandrogenism, polycystic ovaries, or both. In that study, the length of exposure to divalproex was longer (approximately 7 years) than in our study (approximately 3 years), although the mean dose for bipolar patients in our study was somewhat higher. Both studies are limited by small numbers of patients and by cross-sectional designs.

The long-term impact of divalproex on female reproductive function is an important area for future research since there is increasing recognition that bipolar disorder can begin in both the prepubertal and adolescent time and that both divalproex[17–19] and lithium[20] are effective in the treatment of mania in adolescents. In humans, the only published report[21] described a case of reversible, delayed puberty onset associated with divalproex treatment. In rodents, chronic administration of divalproex delayed reproductive and skeletal maturation in genetically epilepsy-prone mice.[22] In our study, no patient was started on divalproex therapy prior to age 20 years, making it dif-

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ficult to compare with the Isojarvi et al.[3] study, where the patients treated prior to age 20 were most at risk for developing PCO syndrome. The impact of both length and timing of exposure to divalproex on reproductive functioning merits further study with larger sample sizes, longitudinal designs, and longer lengths of exposure. It is possible that the PCO-like changes reported in the epileptic patients may be due to epilepsy per se or a therapy-epilepsy interaction.[1,2,23] Future studies should therefore also examine whether patients' diagnoses (epilepsy vs. bipolar disorder) influence the likelihood of an association between divalproex use and PCO-like changes.

In our study, obesity was common in women taking both medications, but was more likely in the divalproex group. Menstrual irregularities were also common and present in all women taking lithium and 70% of women treated with divalproex. It is possible that our sample reflects some selection bias, with women who had menstrual problems preferentially electing to participate (26% of the eligible sample population declined to participate). If this is the case, the lack of PCO syndrome findings in our patient sample is even more reassuring. Alternatively, the occurrence of menstrual disturbances in bipolar women may represent a trait marker of HPG dysregulation in women with bipolar illness. Our preliminary findings might suggest that women with bipolar disorder have a high prevalence of menstrual disturbances independent of therapeutic agent used and, in some cases, preceding the onset of bipolar disorder. The relationship between the reproductive endocrine system and bipolar illness in women is poorly defined. One case report and 1 case series have described reproductive hormone changes in bipolar women.[24,25] Matsunaga and Sarai[24] reported reproductive endocrine changes in 12 women with manic-depressive or psychotic symptoms exacerbated by menstrual cyclicity. They described both radiological (polycystic changes by ovarian ultrasound) and biochemical (e.g., elevated basal LH, decreased basal FSH, elevated serum testosterone) evidence of PCO syndrome in 8 of 12 women with affective disorder with and without psychotic features. Three of the 8 women were diagnosed with PCO syndrome several years before the onset of a psychiatric disorder.[24] Their findings, however, may be confounded by the use of antipsychotic medication at the time of the investigation, which is known to alter HPG function (via hyperprolactinemia), and use of oral contraceptives in 1 case. Further, hormonal sampling was done during both phases of the menstrual cycle, and the ultrasonography was performed in the luteal phase of the menstrual cycle in every woman, which does not allow for comparison with our data or that of Isojarvi et al.[3]

The results of our study, although negative, are based on a small number of patients, and larger studies are needed to make definitive conclusions. At present, clinicians treating bipolar women should assess for obesity, menstrual abnormalities (e.g., oligomenorrhea, amenorrhea), and iatrogenic hair growth. If a clinical psychiatrist has a female patient who is being or will be treated with divalproex therapy, he or she should consider a diagnostic workup if the patient presents with at least 2 of the following symptoms: hirsutism, menstrual disturbances (oligomenorrhea, amenorrhea), obesity, alopecia, or infertility. The workup should be limited to a blood test for bioavailable testosterone and DHEA, with a subsequent referral to a specialist. Pelvic ultrasounds are not necessary, nor are they diagnostic of PCO syndrome. Divalproex may influence hormonal homeostasis through both peripheral (liver metabolism) as well as central (increasing LH pulses) mechanisms.[26]

Whether PCO-like changes can be induced in bipolar women with exposure to divalproex over many years remains to be determined and might be able to be evaluated in a large, longitudinal multicenter study. A recent study,[27] however, suggests that if such changes occur, they are reversible. Isojarvi et al.[27] found that BMI and serum concentrations of insulin and testosterone as well as the number of ovarian follicles were decreased within 1 year in epileptic women who were switched from divalproex to lamotrigine.[24] Our findings, as did those of Isojarvi et al.,[27] indicate a need for a longitudinal controlled evaluation of reproductive function in women taking mood stabilizers, whether they have epilepsy or bipolar disorder. Our data also suggest that some women with bipolar disorder may have compromise in reproductive endocrine function even prior to treatment, as do women with epilepsy.[23,26] The clinical manifestation of a menstrual disturbance may represent a marker for an underlying HPG axis dysregulation. Certainly the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes have been studied in bipolar women and have been found, in many cases, to be dysregulated. We are continuing to assess the reproductive function in young women with bipolar disorder in our current studies.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), lamotrigine (Lamictal).

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