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Polycystic ovary syndrome in women using valproate: A review

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Abstract

Valproate (VPA) is a highly effective drug successfully employed in several neuropsychiatric diseases. In the last 15 years, an increased prevalence of polycystic ovary syndrome (PCOS) associated with VPA use has been reported in both women with epilepsy and women with bipolar disorders. However, data on this subject are contrasting and it is possible that different factors might play a role in the development of PCOS in these patients. The risk of developing PCOS during VPA treatment seems to be higher in women with epilepsy than in women with bipolar disorders, and this might be due to an underlying neuroendocrine dysfunction related to the seizure disorder. Gynecologists must be aware of the possibility that PCOS in these populations of patients might be related to VPA use, and a careful multi-specialist approach is required for evaluating the risks and benefits of this treatment in the presence of features of PCOS.

Keywords: *Polycystic ovary syndrome, valproate, epilepsy, bipolar disorder, review*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of fertile age [1] and has been considered the most common cause of oligo-ovulatory infertility [2]. Patients with PCOS are at higher risk for developing infertility and endometrial carcinoma, besides several metabolic disorders including insulin resistance, diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease [3,4]. Despite the vast amount of clinical, laboratory and experimental data that have been accumulated, the pathogenesis of PCOS remains a subject of speculation [5], with both genetic and environmental factors being implicated [6].

While the 'classical' syndrome is usually easily recognized in women displaying hyperandrogenism, irregular menstruations, obesity and a polycystic ovarian morphology, the diagnosis of PCOS in women who present with fewer of the classical symptoms has caused considerable controversy [7]. Many efforts were devoted in the last 20 years to reach uniformity in the diagnostic criteria, since the use of a standardized definition of PCOS is clearly very important for comparing epidemiological data and treatment outcomes in different studies. Most commonly, PCOS is defined according to the proceedings of an expert conference sponsored by the National Institutes of Health (NIH) in 1990, which requested for diagnosis hyperandrogenism and/or hyperandrogenemia, menstrual dysfunction and exclusion of known disorders [8]. More recently, another expert conference held in Rotterdam in 2003 proposed diagnosis of PCOS – after the exclusion of related disorders – in the presence of any two of the following: hyperandrogenism and/or hyperandrogenemia, oligo- or anovulation, or polycystic ovaries [9]. In essence, the Rotterdam criteria expanded the NIH criteria, including in the diagnosis of PCOS also ovulatory women with polycystic ovaries and hyperandrogenism as well as normoandrogenic oligoanovulatory women with polycystic ovaries. At the present time, several authors underline that the metabolic and possibly the reproductive implications of the two additional phenotypes of PCOS patients proposed by the Rotterdam criteria are unclear and relatively poorly characterized [10,11]. For this reason, the Rotterdam 2003 criteria are still debated; modification of the

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NIH 1990 criteria is strongly proposed, but the NIH criteria are still widely accepted and usually employed in papers dealing with the diagnosis and epidemiology of PCOS. It is worth noticing that the most recent reports on PCOS prevalence in premenopausal women, obtained following the NIH criteria for diagnosis, describe remarkably similar values, with a prevalence of 6.6% in the USA [12], 6.5% in Spain [13] and 6.8% in Greece [14].

Valproate (VPA) is one of the most commonly used antiepileptic drugs throughout the world, being a drug of first choice in many seizure types. Besides to being an effective drug in the treatment of epilepsy, VPA is also used by psychiatrists for the treatment of bipolar disorders, and several reports suggest that this medication is becoming a widespread therapy for these conditions, both in the acute and in the long-term treatment, in adult and in child/adolescent populations.

Concern about the use of VPA in women has been spreading after reports suggesting the possibility that this drug might give rise to reproductive endocrine disturbances. In fact, in the last 15 years several reports have suggested that chronic use of VPA in women might be associated with an increased frequency of menstrual disorders and/or polycystic ovaries and/or hyperandrogenism, realizing in some cases a clear-cut picture of PCOS. These findings, first reported in women with epilepsy and more recently also described in females with bipolar disorders, have received growing attention and raised concern among neurologists and psychiatrists. The possibility that an effective, widely used drug may give rise to unwanted endocrine side-effects, possibly evolving into reduced fertility and increased cardiovascular risk, actually deserves full consideration also from endocrinologists and gynecologists.

The present paper briefly examines data from the literature regarding the association between VPA use and PCOS in women with epilepsy and with bipolar disorders.

Polycystic ovary syndrome in women using valproate: A critical review of the literature

The first warnings of a possible association between VPA use and menstrual dysfunction came from several anecdotal reports of individual or small series of women with epilepsy using VPA, in whom menstrual disturbances, often disappearing after discontinuation of the drug, were observed [15–19]. In 1993 Isojarvi and colleagues [20] described an increased prevalence of polycystic ovaries, hyperandrogenism and menstrual irregularities (not necessarily associated in the same patient and, consequently, not necessarily giving rise to a picture of PCOS) in women with epilepsy treated with VPA; several reports from the same group in the subsequent years confirmed their earlier data (see [21]). At this point, the possible association between PCOS and VPA received wide attention from the scientific community, and research groups from all over the world investigated the effect of VPA on the reproductive endocrine status of women with epilepsy or bipolar disorders.

Unfortunately, no consistency of diagnostic criteria and diagnostic tools is found in these papers, and consequently the results are very often difficult to interpret and virtually impossible to compare. Many authors still confuse the concept of PCOS with that of polycystic ovaries; others still invoke a supposed lack of uniformity of criteria for diagnosis of PCOS as an excuse to use personal views on this subject, completely ignoring the results of the 1990 NIH conference or other authoritative guidelines. The wide variability observed in the characteristics of the patient series in the different reports also gives rise to possible inaccuracies and poor comparability of results. Moreover, additional problems arise when dealing with papers evaluating VPA effects in women with epilepsy, since in epileptic patients a possible deranging effect of epilepsy itself on the hypothalamus leading to neuroendocrine dysfunction has been suggested by several reports, actually earlier than the ones suggesting a role of VPA [22–26].

With these limitations in mind, however, some tentative conclusions can be proposed. In consideration of the possible role played by the epileptic disease, we now review separately reports dealing with VPA use in women with epilepsy and in women with bipolar disorders.

Polycystic ovary syndrome, valproate and epilepsy: A complex association

Many reports assessing the reproductive endocrine status in epileptic women and evaluating the occurrence of PCOS in these populations can be traced in the literature [20,22,23,24,27–44], but comparing the results emerging from these studies is not an easy task. Apart from the difficulties arising from lack of consistency in criteria employed for diagnosing PCOS, the comparative analysis of these reports is problematic because many authors, even when performing a complete evaluation of patients, present the results only as means of hormonal values or as percentages of abnormal findings observed in different subgroups, without giving any information on individual data which allow to determine the prevalence of PCOS in the studied sample. In an earlier review [21] we examined in detail most of the literature on this subject. In the present paper therefore we discuss only the results of a comparative analysis of the literature. Some reports have been totally or partially left out of this analysis for several reasons: pre-selection of patients with menstrual

irregularities [20,27]; insufficient data for diagnosing PCOS [29]; inconsistencies of methodology [23,36,40,43]; and evaluation of a population of adolescent patients [30,41,44], in contrast with the remaining literature that deals with adult women.

A high occurrence of menstrual dysfunctions in women with epilepsy has long been reported [45–51] and this finding is confirmed in most of the recent literature. With the exception of Murialdo and associates [29], who report a prevalence of 10.8%, in all the other series in which such information is offered [23,24,28,31,33,34,35,37,38,42] the prevalence of irregular menstruations, ranging from 21.8% to 65.0%, is quite higher than the 7% prevalence described in the general population in a recent epidemiological study [52]. Menstrual irregularities are observed also in drug-free epileptic patients; in treated patients it does not seem related to the use of VPA, since in most reports the distribution of menstrual irregularities is quite similar in different therapy groups.

Individual data on hyperandrogenism are more rarely given [23,24,33–35,37,38,42] and only in some of these reports [23,24,33–35,42] are laboratory data offered. In these latter, hyperandrogenism is usually over-represented, with a single report describing a 4.5% prevalence [35] and the others a prevalence ranging from 15.0% to 26.0% [23,24,33, 34,42]. When a comparison among VPA users and non-VPA users is performed [24,33–35, 37,38,41,42,44], the prevalence of hyperandrogenism is higher in VPA patients in most reports [34,35,37,38,41,42,44] even if not always significantly.

Finally, a high prevalence of polycystic ovaries ($>30\%$) is reported in half of the studies [32–34,39,42] in which this finding was systematically evaluated, most of which employed transvaginal scanning or magnetic resonance imaging rather than transabdominal scanning which is associated with a lower prevalence [24,28,29,37,38]. Most reports describe a higher, but not significant, prevalence of polycystic ovaries in non-VPA users [24,29,32, 37,38,42].

While, even with the caution due to methodological differences in the collection and analysis of data, it is altogether possible to compare the prevalence of findings such as menstrual dysfunction, hyperandrogenism and polycystic ovaries in different series of women with epilepsy, comparing the prevalence of PCOS in such reports is much more difficult due to the methodological issues underlined above. If we consider only reports in which PCOS in patients with epilepsy is diagnosed, or may be diagnosed employing available data using the NIH criteria [22–24,28,33–35,42], we notice in most of these series that the prevalence of PCOS in epileptic females is higher than the 6.6% prevalence reported in the general population with the same diagnostic criteria. Only in the report from Stephen and co-workers [35] is a considerably low prevalence of PCOS (2.3%) observed in epileptic females (a certain degree of underestimation could derive from lack of evaluation of clinical features of hyperandrogenism). In the other reports, the prevalence (often corrected according to NIH guidelines) is 12.5% [34], 15% [22,24,28], 20% [23,42] and 26% [33]. It must be stressed that the highest prevalence of 26% is reported in a study in which the endocrine evaluation of patients with epilepsy is particularly accurate [33], including assessment not only of menstrual cyclicity but of ovulation status as well, and evaluation of both clinical and laboratory hyperandrogenism. The influence of VPA use on PCOS prevalence is difficult to evaluate if we consider only the reports in which a NIH diagnosis can be obtained, due to the small number of observations; widening our analysis to all reports [24,31–35,37–39] in which the prevalence of PCOS is given, even if with different criteria, and in which a comparison among therapy groups is carried out, we observe that most reports dealing with epileptic women describe a higher prevalence of PCOS in VPA-treated patients [32,34,35,37,39], even if this finding is statistically significant only in two reports [34,39].

In summary, we can conclude that in women with epilepsy the increased prevalence of menstrual disturbances and of polycystic ovaries do not seem associated with the use of any antiepileptic drug and might more probably be related to the epileptic disorder per se. On the other hand, the finding of hyperandrogenism is more often related to the use of VPA. The prevalence of PCOS (NIH-defined) in women with epilepsy is elevated in the majority of reports, even if with a considerable variability among series. The association of PCOS (in this case, also when diagnosed with non-validated criteria) with VPA treatment is found in most of the reports investigating this finding.

Polycystic ovary syndrome related to valproate use in women with bipolar disorders

In recent years the possible effect of chronic VPA use has been evaluated also in women receiving this drug for bipolar disorders. Reports dealing with this subject are relatively few when compared with those devoted to the endocrine status of epileptic females under VPA treatment. However, reports on bipolar patients have the advantage of studying a population of VPA users in which the potential influence of epilepsy has been removed.

Rasgon and collaborators [53] evaluated the endocrine status of 80 bipolar women, comparing subjects treated with VPA (alone or in association) with subjects treated with other antimanic agents.

PCOS was found in 8% of VPA users and in 0% in non-VPA users: this difference was not statistically significant, possibly because of limited statistical power. The same group [54] successively reported a 2-year longitudinal evaluation in 25 women with bipolar disorder, treated with VPA, lithium or atypical antipsychotics, and described high rates of menstrual abnormalities, hyperandrogenemia and insulin resistance in the whole group. Valproate use was associated with an increase in total testosterone over time, but rates of oligomenorrhea and clinical hyperandrogenism did not differ between medication groups.

Joffe and co-workers [55] evaluated 230 women with bipolar disorder, comparing the incidence of oligo-/amenorrhea with hyperandrogenism that developed after antimanic treatment. Before treatment the prevalence of PCOS in the whole group was similar to that reported in the general population (4.7%). After treatment was started, oligo-/amenorrhea with hyperandrogenism developed in nine (10.5%) of 86 women on valproate and in two (1.4%) of 144 women on other treatments ($p = 0.002$), suggesting a significant association of PCOS with VPA use in bipolar women. In a subsequent study [56] the authors performed a follow-up evaluation in nine women who had developed PCOS while taking VPA, four of whom had discontinued the drug after developing PCOS features. This study showed that reproductive features of PCOS, such as menstrual irregularities and hyperandrogenism, improved in three out of four of VPA discontinuers, in spite of unchanged body weight. Since these results support that VPA use is associated with new-onset PCOS in women with bipolar disorders, the authors suggest that this may be the case also in women with epilepsy, attributing the higher prevalence of PCOS described in epileptic patients to the lack of accepted criteria for the diagnosis of PCOS in reports describing these latter subjects. However, Joffe's report is specifically focused on patients with new-onset of PCOS symptoms developed after medication use, and consequently reports incidence of PCOS rather than prevalence. Consequently, caution must be employed in comparing the results from this study with those coming from studies describing prevalence.

Other studies on bipolar women receiving VPA [57–59] contrast with the results of Rasgon's group [53] and Joffe's group [55], since they describe a considerably higher prevalence of PCOS in VPA users with bipolar disorders. We do not review the data coming from the reports of O'Donovan and colleagues [57,58], since they present several shortcomings which warrant caution in the interpretation of results (for a detailed analysis, see [21,60]). The report from McIntyre and associates [59], describing 38 bipolar female patients treated with VPA or lithium, shows a very high prevalence of PCOS in bipolar patients, especially in VPA users (39%) but with high values also in the lithium group (19%), with a non-significant difference between groups. However, this study presents some problems in methods (poor definition of menstrual irregularities, lack of evaluation of clinical hyperandrogenism) which might be of concern in evaluating PCOS prevalence in the different treatment groups.

In conclusion, bipolar patients seem to show an increased risk of developing PCOS when treated with VPA in respect to other antimanic medications. However, in reports evaluating large series of women with validated diagnostic criteria, the prevalence of PCOS in VPA-treated bipolar patients is not much higher than what is reported in the general population and quite lower than what is reported in epileptic populations. The hypothesis of Joffe and co-workers that the difference between PCOS prevalence in bipolar and epileptic patients should be attributed to the lack of validated criteria for PCOS diagnosis in epileptic populations is interesting. However, in several studies on epileptic patients in which well accepted criteria for diagnosis of PCOS have been employed [22–24,28,33–35,42], the PCOS prevalence is quite higher than what is reported in bipolar patients. In particular, as we have mentioned above, the study reporting the highest prevalence of NIH-defined PCOS in epileptic patients (26%) [33] employed a very careful endocrine evaluation of subjects. Quite interestingly, in this series PCOS does not show a significant association with the use of VPA.

Akdeniz and collaborators [61] compared the endocrine status of women with epilepsy and women with bipolar disorder, describing 15 bipolar patients treated with lithium, 15 bipolar patients treated with VPA and 15 epileptic patients treated with VPA. Menstrual irregularities were observed in 46.7% of VPA-treated epileptic women, 20% of VPA-treated bipolar women and 0% of lithium-treated bipolar women. Laboratory hyperandrogenism was observed in both VPA groups but not in the lithium group; however, only in women with epilepsy was this finding associated with hirsutism. The authors conclude that even if VPA treatment is associated with raised testosterone levels in both bipolar and epileptic women, these latter have an increased susceptibility to develop a clinical endocrine dysfunction.

One could speculate that the impact of VPA on endocrine status is not as strong in bipolar patients as in women with epilepsy, suggesting that these latter may have additional risk factors leading to the development of PCOS under the influence of VPA use [62].

Valproate and polycystic ovary syndrome: Possible links

The mechanism of action of VPA is not entirely clear. It increases synaptosomal γ-aminobutyric acid (GABA) concentrations through activation of the GABA-synthesizing enzyme glutamic acid decarboxylase and also inhibits GABA catabolism through inhibition of GABA transaminase and succinic semialdehyde dehydrogenase. Moreover, VPA also inhibits excitatory neurotransmission mediated by aspartic acid, glutamic acid and γ-hydroxybutyric acid, and reduces cellular excitability through modulation of voltage-dependent sodium currents.

Several theories have been proposed to explain the possible pathogenic mechanisms of VPA-induced endocrine disturbances. A significant increase in body weight has been reported in nearly 40% of cases during VPA use [63–66], both in adults and children and without sex-related differences. Apparently, this phenomenon is not related to VPA oral dosage and is poorly influenced by dietary changes or physical exercise, being responsive, conversely, to VPA discontinuation [65]. The pathogenesis of VPA-related weight increase is still unclear, and several possible mechanisms have been proposed, such as increased appetite [63], changes in catecholamine response to glucose load [67] and enhanced availability of long-chain fatty acids as a result of VPA binding to serum albumin [68]. In their first report describing VPA-related endocrine dysfunction [20], Isojarvi and co-workers suggested that weight gain could be the main pathogenic factor leading to reproductive endocrine disturbances, proposing that VPA-induced obesity might lead to insulin resistance and consequently hyperinsulinemia, resulting in direct and/or indirect hyperstimulation of the ovaries, hyperandrogenism and finally in ovarian polycystic changes. However, further studies from the same group [34] challenged the theory that VPA-induced obesity might have a primary role and suggested that increase of androgen production might be the first abnormal finding originating from VPA use. Results coming from VPA discontinuation in bipolar patients [56], who showed improvement of menstrual regularity and hyperandrogenism without changes in body weight, also support this hypothesis.

How could VPA use lead to hyperandrogenism? A possible effect on gonadotropin release, mediated by a VPA-induced increase of GABA levels affecting secretion of gonadotropin-releasing hormone, is considered unlikely since VPA-treated hyperandrogenic patients have normal luteinizing hormone (LH) levels [20]. Alternatively, a direct effect of VPA on androgen formation has been suggested [20]. Long-term VPA treatment in female rats has been associated with a pronounced reduction in estrogen levels, a marked increase in testosterone to estrogen ratio and only a minor effect, if any, on gonadotropins [69], suggesting a direct effect of VPA on peripheral sex hormone production in the ovary [70]. An inhibitory effect of VPA on the aromatase complex, the enzyme system which converts androgens to estrogens, has also been recently reported [71].

Recently, Nelson-Degrave and associates [72], testing the activity of VPA on androgen biosynthesis in ovarian theca cells isolated from follicles of normal cycling women, reported data suggesting that VPA may increase ovarian androgen biosynthesis by inducing changes in chromatin modifications (histone acetylation) that augment transcription of steroidogenic genes. The same research group [73], in a subsequent paper in which the gene expression profiles of untreated normal, VPA-treated normal and untreated PCOS theca cells were compared, reported that VPA-induced and PCOS-induced changes in gene expression were similar, resulting in enhancement of Akt/PKB signal transduction in human theca cells. These important data provide the first biochemical evidence to support a role for VPA in the genesis of PCOS-like symptoms.

A possible direct effect of VPA on insulin metabolism, not mediated by increase in weight, has also been suggested [74,75] as a possible additional cause leading to endocrine dysfunction in VPA-treated women with epilepsy. In a study directed to evaluate the role of insulin in VPA-related obesity, Pylvanen and co-workers [74] reported serum insulin levels being higher in VPA-treated epileptic subjects compared with BMI-matched controls; this phenomenon was observed not only in obese but also in lean VPA-treated subjects. In a subsequent study, the same group [75] reported fasting hyperinsulinemia and lower fasting glucose levels in epileptic patients on VPA monotherapy: these findings were similar regardless of whether the patients had gained weight or not during VPA treatment or whether they were obese or not at the time of the study. Fasting serum proinsulin and C-peptide levels did not differ significantly between patients and controls. The authors conclude that the changes in insulin metabolism seen in VPA-treated epileptic subjects are not due to weight gain or obesity, and that VPA might interfere with insulin metabolism in the liver, inhibiting insulin degradation with resulting higher insulin concentrations in the peripheral circulation and consequently reduced plasma glucose concentrations. It must be underlined that the same authors in earlier reports [20,27,34] had described results which contrast with their later view on this issue, reporting a significant association between hyperinsulinism and obesity in VPA-treated epileptic females [20,27] or increased insulin levels only in obese, but not in lean, VPA-treated women when compared with normal controls [34].

Insulin metabolism in VPA-treated epileptic subjects has been evaluated by other groups as well [41,44,76–79], the majority of which [41,44,77–79] do not distinguish between obese and lean patients and evaluate mean values of insulin and body weight in the whole group of studied patients. While most of these studies report hyperinsulinism and weight gain in VPA-treated patients compared with controls [44,79] or patients treated with other antiepileptic drugs [77] or in comparison to pre-treatment values [78], de Vries and collaborators [41] do not report any difference in body weight, insulin levels and fasting glucose levels in VPA-treated and untreated epileptic patients. When obese and lean patients are examined separately [76], insulin resistance is described only in obese but not in lean VPA-treated epileptic females. On the whole, these findings are in disagreement with those reported recently by Pylvanen's group [74,75] and do rather support the view that insulin resistance is related to obesity and is found only when weight gain occurs.

In conclusion, VPA seems to present different potential adverse effects on metabolism, since it has been associated, via different and not necessarily related mechanisms, to weight gain, hyperandrogenism and hyperinsulinemia. As underlined by Joffe and co-workers [55], obesity and insulin resistance alone, even if VPA-related, are unlikely to explain the association of VPA with PCOS, since PCOS is uncommon in women with obesity or type 2 diabetes. However, both weight gain and hyperinsulinemia are associated with an increased cardiovascular risk and must be considered severe adverse effects independently from their association with PCOS. At the present time, however, while the association between weight gain and VPA use is well documented, data in favor of a possible direct effect of VPA on insulin metabolism come only from a single group, who had earlier reported contrasting results on this issue. More studies are needed to clarify the complex subject of VPA use, insulin metabolism and body weight.

Conclusions

Valproate is a highly effective drug, widely employed in different neuropsychiatric conditions such as epilepsy, bipolar disorders, migraine and chronic neuropathic pain. Women with epilepsy and women with bipolar disorders are most likely to receive VPA for prolonged periods of time, often encompassing most of their reproductive life, and are consequently particularly at risk for developing reproductive endocrine disturbances related to VPA use.

On the other hand, when reviewing the studies regarding the possible effect of VPA on reproductive functions in these populations of patients, the possible role of the specific disease must be taken into consideration. A reduction of fertility, independent from marriage rates, and a high prevalence of menstrual disturbances have been described in women with epilepsy since 50 years ago, far before the introduction of VPA in clinical practice. More recently, a possible role of seizure disorders in altering the regular function of the hypothalamic–pituitary–ovary axis has been suggested by reports describing significant increases in plasma prolactin and, less consistently, gonadotropins after epileptic seizures, which are suggested to result from spreading of paroxysmal discharges within the hypothalamic areas which control pituitary reproductive hormones (see [21,62]). Further support to this theory comes from the evaluation of untreated women with epilepsy, in whom both an abnormal LH pulsatility pattern and a significant rise of gonadotropin secretion during increase of subclinical paroxysmal activity has been reported [25,80].

Our review of the literature devoted to assessing the endocrine status in women with epilepsy has showed that, while menstrual disturbances and polycystic ovaries are over-represented in these patients independently from the use of VPA, hyperandrogenism and PCOS are usually more frequent in epileptic females treated with VPA. These data might suggest that both the seizure disorder and the use of VPA could play a role in the development of PCOS in women with epilepsy [62]. Due to neurotransmitter dysfunctions and/or to spreading of paroxysmal activity within the hypothalamus, women with epilepsy seem to have an increased susceptibility to hypothalamic dysfunction: as a result of that, a high percentage of these patients will present with menstrual disorders, and, possibly, polycystic ovaries. The further possible evolution towards a definite clinical disease, specifically PCOS, seems conversely to be often related to the use of antiepileptic drugs, and in particular of VPA. This VPA effect is most probably due to its hyperandrogenic activity, recently demonstrated *in vitro* on human theca cells; weight gain, often associated with VPA use, may also play an additional role.

At the present time studies in bipolar patients using VPA are considerably fewer. However, two of them have the advantage of describing large study populations and of employing validated methods for diagnosis of PCOS [53,55]. Both these studies show an increased prevalence of PCOS in bipolar patients using VPA when compared with patients using other antimanic medications. However, the prevalence of PCOS described in VPA-treated bipolar women is only slightly higher than what is reported in the general population, and lower than what is reported in many epileptic populations evaluated with validated criteria. This could suggest that bipolar patients lack the specific susceptibility to reproductive endocrine dysfunction which is present in epileptic women, and that consequently VPA has a

weaker impact on their endocrine status. The available literature on this issue is contradictory, since while Rasgon and colleagues describe a very high prevalence of treatment-unrelated menstrual abnormalities and hyperandrogenism in bipolar women [53,54], the pre-treatment assessment in the population described by Joffe and associates does not seem to show any difference from the general population [55]. In a recent study, Klipstein and co-workers [81] screened women diagnosed with PCOS for the presence of bipolar illness, reporting in this population a higher rate of bipolar disorder than what is expected in the general population, independently from the use of VPA. These results could suggest that also bipolar women could present with an increased susceptibility to develop PCOS, independently from VPA treatment. However, the authors themselves report several methodological constraints in their study and warrant caution in the interpretation of their results.

In conclusion, in spite of several issues still needing clarification, prolonged use of VPA seems to be associated with an increased risk of developing PCOS in predisposed women. The relative weight of individual predisposition, associated neuropsychiatric diseases, duration and doses of VPA treatment are still to be fully understood. When dealing with patients with PCOS, the gynecologist must be aware of this possibility and investigate about the present or past use of VPA. Patients with PCOS using VPA must receive a multi-specialist approach and a careful evaluation about the balance between risk and benefits of continuing therapy with this highly effective drug.

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