The Reproductive Safety Profile of Mood Stabilizers, Atypical Antipsychotics, and Broad-Spectrum Psychotropics

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There has been growing concern about the potential iatrogenic effects of several newer psychotropic drugs on reproductive health safety in women. Areas of particular concern in this regard include (1) controversies about a potential association between the use of valproate and development of polycystic ovary syndrome (PCOS), (2) the safety of use of newer psychotropic medications during pregnancy, and (3) safety issues with these medications in women while breastfeeding. This review summarizes current information about each of these areas. In particular, existing data suggest that (1) PCOS very likely represents a complex neuroendocrine disorder with multiple determinants; (2) menstrual irregularities may be a frequently seen phenomenon in women with bipolar illness, at least partially independent of psychotropic drug therapy; (3) potential central nervous system teratogenicity remains substantial during first-trimester exposure to valproate or carbamazepine; (4) with newer agents used for bipolar disorder and schizophrenia, safety data during pregnancy, while not definitive, are most abundant with olanzapine and with lamotrigine; relatively less is known about systematic pregnancy outcomes with other atypical antipsychotics or newer anticonvulsants; and (5) risks for neonatal safety during lactation continue to appear substantial with lithium, are of potential concern with lamotrigine and clozapine, are quite likely minimal with valproate or carbamazepine, and are indeterminate with most other new anticonvulsants or atypical antipsychotics. Recommendations are presented for clinical management in each of these instances. *(J Clin Psychiatry 2002;63[suppl 4]:42–55)*

Female reproductive health safety has become a growing focus of concern amidst the expanding psychotropic pharmacopoeia. The modern range of options for mood stabilization now includes, in addition to lithium, over a dozen anticonvulsants, atypical antipsychotics, and broad spectrum psychotropics. Advances in treatment options have been especially welcome for women with bipolar disorder, for whom complex illness presentations such as rapid cycling,[1,2] mixed states,[1–3] bipolar depression,[1,2] and comorbid alcohol abuse[4] pose disproportionately frequent obstacles to standard lithium therapy.[5] Yet, limited clinical experience with some newer agents has aroused uncertainty and debate about reproductive health safety issues in several key domains. In this article, we will examine current evidence for drugs commonly used to treat bipolar disorder with regard to controversies about women's health, focusing specifically on ovarian function, pregnancy, and lactation.

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POLYCYSTIC OVARY SYNDROME

In 1993, an initial report by Isojarvi and colleagues[6] identified a high point prevalence of polycystic ovaries (PCO) anatomically among epileptic women taking valproate. This observation has important potential implications for the use of valproate and possibly for the use of other psychotropic medications as well. Although unreplicated, this finding has prompted hesitation on the part of some clinicians to use valproate in women of childbearing potential. Moreover, some authors[7–9] have advised or strongly cautioned against using valproate as a first-line agent in women under age 20 years, those for whom the frequency of PCO was especially high in the group described by Isojarvi et al.[6] Other authors have disputed recommendations contraindicating the use of valproate in young women, often citing the lack of reliable and consistent data at this point.[10–12] What has come out of this remarkable debate is the fact that this singular case series of 289 epileptic women, only 23 of whom were taking valproate, has served less to demonstrate a causal relationship between valproate use and the pathogenesis of PCO than to highlight the complex interrelationships between PCO and its multiple potential determinants.

Definitions: PCO vs. PCOS

A first consideration involves the distinction between the often normal presence of PCO versus polycystic ovary syndrome (PCOS). PCO, diagnosed radiographically by pelvic ultrasound, is defined by the presence of at least 10 subcapsular follicular cysts, measuring 2 to 8 mm in diameter, arranged around or within thickened ovarian stroma.[13,14] Others have required 8 or more follicular cysts.[15] Estimates have varied, but PCO seems to

occur in about 17% to 22% of the general population (reviewed by Genton et al.[10]). PCO is not an intrinsically pathologic condition, and in fact, up to 25% of patients with this radiographic finding have no endocrine or menstrual irregularities.[16]

PCOS, by contrast, constitutes a clinical syndrome, first reported in 1935 by Stein and Leventhal.[17] At that time, it was characterized by amenorrhea, hirsutism, and bilaterally enlarged ovaries. After much debate, it was later formally defined in 1990 by the National Institutes of Health (NIH) as involving (1) ovulatory dysfunction (e.g., chronic anovulation, oligomenorrhea, or amenorrhea); (2) clinical evidence of hyperandrogenism, and (3) exclusion of other endocrinopathies such as thyroid disorders, hyperprolactinemia, and nonclassic adrenal hyperplasia.[18] Anatomical evidence of subcapsular cysts (e.g., by ultrasonography) is not considered a diagnostic criterion for PCOS.

Clinical features associated with PCOS include hirsutism, alopecia, acne, menstrual irregularity, and obesity. Hormonally, women with PCOS manifest increased levels of total and free serum testosterone, decreased or normal follicle-stimulating hormone (FSH), increased serum prolactin, increased luteinizing hormone (LH), and LH/FSH ratios > 2.[15,19-21] Insulin resistance, hyperlipidemia, impaired glucose tolerance, and hyperinsulinemia are further potential endocrinologic correlates of PCOS. Correspondingly, morbidities associated with PCOS may include non–insulin-dependent diabetes mellitus (NIDDM), infertility, endometrial hyperplasia or malignancy, hypertension, coronary artery disease, and adverse lipid profiles.

In interpreting clinical studies, it is important to distinguish between PCO, PCOS, and menstrual irregularities, since non-pathologic irregular menses occur in about 18% of women,[22] and this base rate must be considered when assessing prevalence rates in the context of medications, clinical predispositions, or other PCOS risk factors. The distinct constellation of menstrual irregularities with hyperandrogenism (i.e., PCOS) has been reported in approximately 3% to 7.6% of women,[23] although rates may vary across distinct clinical subgroups. PCOS is thought to be the most common cause of anovulatory infertility and hirsutism affecting women of reproductive age.

POSSIBLE ETIOLOGIES OF PCOS

The etiology of PCOS remains unknown, although the available data suggest important roles for a number of factors, including genetic predisposition, ovarian defects, epilepsy, and insulin resistance. These may interact with environmental or iatrogenic factors such as psychotropic medications and obesity. Each of these factors merits further consideration.

Psychotropic Drugs

It has long been known that drugs such as anabolic steroids and progestins are associated with androgen excess and menstrual irregularity. As early as 1981, menstrual disturbances were reported as a side effect of treatment with valproic acid, an antiepileptic drug and mood stabilizer.[24] Recent literature (as summarized in Table 1A) associating valproate use with the development of polycystic ovaries and/or hyperandrogenism has prompted further interest and concern regarding possible drug-induced changes in reproductive health safety. As previously noted, Isojarvi et al.[6] cross-sectionally diagnosed PCO via ultrasound criteria alone in 10 (43%) of 23 epileptic women taking valproate, as contrasted with 11 (22%) of 49 patients taking carbamazepine and 9 (18%) of 51 normal control women. Of particular concern to many readers of this study was the finding that PCO was more common in women who had begun taking valproate before age 20 years. Isojarvi et al.[25] recently published similar findings in a study that included some patients from the initial study as well as a new group of Finnish patients. In this study, PCO was diagnosed by ultrasound in 23 (62%) of 37 valproate-treated epileptic patients, 5 (14%) of 35 epileptic patients taking carbamazepine, and 9 (17%) of 52 healthy controls. Only 24% of valproate-treated women had hyperandrogenism, however, compared with 17% of those taking carbamazepine and 6% of controls. Importantly, 3 other independent studies that evaluated ovarian anatomy and menstrual function among epileptic women taking valproate failed to replicate these findings, with reported rates of PCO of 0% among 11 women[26] and 10% among 21 women,[27] and PCOS in 11.1% of 20 women.[28] Corresponding rates of PCO or PCOS among epileptic women taking carbamazepine were comparable to (or even higher than) those for women taking valproate, ranging from 10% for PCOS[28] to 21.4% for PCO.[26]

As summarized in Table 1B, menstrual disturbances per se (regardless of anatomic evidence of multiple follicles) were noted in 45% to 59.5% of epileptic women using valproate studied by Isojarvi et al.,[6,25] compared with 19% of women taking carbamazepine, 15% to 16% of controls, and 0% of untreated epileptic patients. Bauer et al.[28] found a similar incidence of menstrual irregularities among valproate users, while the 2 studies by Murialdo et al.[26,27] found a much lower incidence of menstrual disturbances. These differences in incidence rates very likely reflect subtle differences in study design or the patient population.

Although these studies are often compared in head-to-head fashion, it is important to note that the studies by Isojarvi et al.[6,25] and Murialdo et al.[26,27] used PCO as a primary outcome measure, while the investigation by Bauer et al.[28] focused on PCOS. As mentioned above, the sheer anatomical presence of PCO need not be clinically significant. In fact, a full one third of the women with PCO in the initial study by Isojarvi et al.[6] had normal menstrual cycles, and none met the NIH clinical criteria for PCOS. Of note, in the later study, Isojarvi et al.[25] report that "most of the valproate-treated women with polycystic ovaries or hyperandrogenism had menstrual disorders,"[(p293)] but do not report specific numbers for each of these groups. Furthermore, limitations of all of the studies cited above include (1) lack of pretreatment data regarding ovarian structure and function, (2) retrospective design, (3) few data on untreated epileptics, and (4) exclusive focus on epileptic women, curtailing the generalizability of findings to other potential groups taking valproate (e.g., migraine sufferers, women with bipolar disorder). These design features

Table 1A. Summary of the Literature Investigating Antiepileptic Drug Use and the Prevalence of Polycystic Ovaries (PCO) or Polycystic Ovary Syndrome (PCOS)[a]

Study	N	Diagnosis	Untreated Epileptic Patients	Phenobarbital Monotherapy	Valproate Monotherapy	Carbamazepine Monotherapy	Multiple Antiepileptic Drugs	Healthy Controls
			Percentage of Subjects With PCO or PCOS					
Isojarvi et al[6]	289	PCO	Not reported	...	43	22	(VPA ± CBZ) 50	18
Isojarvi et al[25]	124	PCO	...	...	62	14	...	17
Murialdo et al[26]	101	PCO	...	12.5	0	21.4	+VPA: 40; −VPA: 13	...
Murialdo et al[27]	65	PCO	...	10	10	18	...	Not reported
Bauer et al[28]	93	PCOS	10.5	...	11.1	10	0	...

[a]Abbreviations: CBZ = carbamazepine, VPA = valproate.

Table 1B. Summary of the Literature Investigating Antiepileptic Drug Use and the Prevalence of Menstrual Cycle Abnormalities[a]

Study	N	Untreated Epileptic Patients	Phenobarbital Monotherapy	Valproate Monotherapy	Carbamazepine Monotherapy	Multiple Antiepileptic Drugs	Healthy Controls
		Percentage of Subjects With Menstrual Cycle Abnormalities					
Isojarvi et al[6]	289	0	...	45	19	(VPA ± CBZ) 25	16
Isojarvi et al[25]	124	...	...	59.5	Not reported	...	15.4
Murialdo et al[26]	101	...	5.3	18	20	+VPA: 38; −VPA: 24	...
Murialdo et al[27]	65	...	4.8	4.8	21.7	...	Not reported
Bauer et al[28]	93	42	...	39	45	25	...

[a]Abbreviations: CBZ = carbamazepine, VPA = valproate.

limit interpreting the data in order to differentiate the role of the medications from the role of epilepsy itself.

Three theories have been described to account for why valproate might confer an increased risk for PCO or PCOS. A first explanation involves the potential for hyperandrogenism and menstrual abnormalities to result from weight gain or obesity during valproate therapy.[29] Favoring this explanation is the relatively high incidence of weight gain associated with valproate therapy (approximately 44%–57% of all patients),[30,31] which in turn may promote hyperinsulinemia, ultimately resulting in hyperandrogenism.[32–34] Of note, Isojarvi et al.[29] reported that epileptic women who gained weight on valproate treatment were significantly more likely to have PCO than those who did not gain weight. Also, in a later study, Isojarvi et al.[35] observed a reversal of PCO when overweight epileptic women taking valproate lost weight after being switched to lamotrigine. On the other hand, in a different study,[25] PCO and/or hyperandrogenism were found in a large number of nonobese, nonhyperinsulinemic epileptic women taking valproate (65%, compared with 79% of obese, hyperinsulinemic women). Moreover, the use of other psychotropic drugs associated with weight gain has not been described in association with PCO and/or PCOS, suggesting that drug-induced weight gain and subsequent hyperinsulinemia may not be a robust explanation for the development of PCO and/or PCOS.

A second model proposes that increased levels of γ-aminobutyric acid (GABA) resulting from valproate use may contribute to the development of PCO and/or PCOS by affecting gonadotropin-releasing hormone (GnRH) release from the hypothalamus, which could in turn affect the secretion of the gonadotropins LH and FSH.[6] This model is theoretical and based on the finding that GABAergic neurons modulate noradrenergic inputs to GnRH neurons[36] and that valproate seems to modify GABAergic neurotransmission.[37] However, PCO and/or PCOS above baseline population levels has not been noted with predominantly GABAergic drugs other than valproate (e.g., gabapentin or tiagabine).

A third explanation is that valproate could have a direct effect on the formation of androgens in the ovary, hypothetically by inhibiting the conversion of testosterone to estradiol or by stimulating the production of more androgens. High serum testosterone levels can arrest follicular maturation, which could eventually lead to the development of PCO.[25]

Whether or not psychiatric drugs, including valproate and others, might directly affect ovarian function remains a source of controversy. Conventional antipsychotics, as well as some atypical antipsychotics such as risperidone, have been associated with menstrual dysfunction predominantly via their elevation of serum prolactin levels. Package insert data for other atypical antipsychotics (i.e., quetiapine, clozapine, ziprasidone) or broad-spectrum psychotropics (i.e., olanzapine) describe menstrual irregularities as occurring in < 1% of premenopausal women during short-term premarketing studies. To our knowledge, as noted previously, no specific association has been reported in the literature between weight gain induced by lithium, anticonvulsants, or atypical antipsychotics and reproductive-endocrine abnormalities. Our group also conducted a preliminary study of menstrual irregularities among premenopausal

women taking clozapine (obviating potential effects of hyper-prolactinemia) and observed no significant correlation between menstrual cycle length and body mass index.[148]

Epilepsy

A second, critical dimension for interpreting current literature linking PCO and/or PCOS with psychotropic medications involves the clinical population under study. Importantly, the incidence of menstrual irregularities and PCO both appear to be higher among premenopausal epileptic than nonepileptic women, confounding the ability to draw inferences pertinent to other clinical groups or otherwise healthy women. For example, Herzog and colleagues found PCOS in 20% of 50 women with temporal lobe epilepsy[38] and in 25% of 20 with complex partial seizures,[39] most of whom were unmedicated. In addition, Bilo et al.[40] reported PCOS in 15% of 20 patients with primary generalized epilepsy. Menstrual irregularities per se were evident in 56% of epileptic women studied by Herzog and colleagues.[38] There was no significant relationship between the use of antiseizure medication and the occurrence of menstrual irregularities (60% untreated and 53% treated).

Several factors related to epilepsy could account for its intrinsic role in reproductive dysfunction. First, epileptic discharges from the amygdala (a limbic structure) to the hippocampus may affect the secretion of GnRH and may thereby induce the development of reproductive endocrine disorders.[38] In support of this theory, one clinical study found individual changes in the menstrual cycle in 50% of epileptic women after epilepsy surgery.[41]

A second line of evidence suggests that reproductive endocrine disorders favor the occurrence of seizures in predisposed patients.[38] Progesterone, which is protective against seizures, is not made in anovulatory conditions such as PCOS. This leaves temporal lobe limbic structures exposed to unopposed estrogen, a hormone that is known to have a pro-seizure effect. Thus, anovulatory cycles themselves can trigger limbic seizure discharges. In support of this theory, Sharf et al.[42] observed electroencephalogram (EEG) abnormalities in 56.5% of women with anovulatory cycles or amenorrhea. Treatment with clomiphene citrate, an antiestrogenic agent, restored normal EEG findings in 54% of them. Lending further support, Harden and colleagues[43] found that synthetic hormone replacement therapy may be associated with an increase in seizure frequency in menopausal women with epilepsy.

Third, limbic seizure discharges can reduce serum dopamine levels, in turn producing hyperprolactinemia,[38] and these phenomena could further promote elevated levels of LH with consequent androgenization. Finally, it is possible that both epilepsy and reproductive endocrine disorders might be caused by a common dysfunction in neurotransmission or genetic vulnerability.

Obesity

It has long been known that obesity is associated with menstrual cycle abnormalities (reviewed in Pasquali and Casimirri[32]). As early as 1952, Rogers and Mitchell[44] showed

that 43% of women affected by menstrual and fertility problems were overweight or obese. More recently, Hartz et al.[45] found a significantly higher prevalence of anovulation, oligomenorrhea, and hirsutism in obese than normal-weight women. An intrinsic link has been described between PCOS and obesity as well, and up to 50% of women with PCO and/or PCOS are moderately obese or overweight to some degree,[32] further complicating the ability to draw causal inferences about the effects of medications or other clinical predispositions without controlling for the contributing influence of obesity. Obese women with PCOS are more likely to be hirsute and have menstrual irregularities than nonobese women with the same condition.[46,47] Obesity is also associated with decreased levels of sex hormone binding globulin and elevated levels of estrogen.[32,48] Mechanisms by which increased body weight might promote PCOS include increased peripheral aromatization of androgen to estrogen within adipose tissue and consequent sensitization of gonadotropins by constant acyclic estrogen feedback. In addition, decreased levels of sex hormone binding globulin associated with obesity may produce increased relative levels of free serum testosterone.[32] Notably, weight loss has been associated with reduced levels of serum androgens (as well as insulin) and the restoration of fertility.[47,49]

Hyperinsulinemia

Related to concepts about obesity as contributing to PCOS is the potential for androgenization to occur from elevated serum insulin levels. Important clues to the pathogenesis of PCOS came from the finding that women with PCOS are hyperinsulinemic, suggesting the presence of insulin resistance.[33] Although obesity itself is associated with insulin resistance, women with PCOS have greater levels of insulin resistance than obese women in the general population.[50] Furthermore, even underweight women with PCOS can have insulin resistance, although this is relatively uncommon.[34,50] A genetic defect might be responsible for this insulin resistance. Defects in insulin receptor phosphorylation have been reported in up to half of women with PCOS along with a decrease in tyrosine phosphorylation and an increase in serine phosphorylation, all cumulatively leading to impaired insulin activity.[51] There is substantial evidence to suggest that, in addition to insulin resistance, dysfunction of beta-cells (responsible for pancreatic insulin production) is also evident among women with PCOS.[52] Beyond insulin resistance, PCOS is associated with a higher incidence of impaired glucose tolerance (31%–35% vs. 7.8%) and undiagnosed type 2 diabetes mellitus (7.5%–10% vs. 1%) than is found in the general U.S. female population.[53,54]

A complex interaction has been noted between insulin resistance and PCOS, inasmuch as high insulin levels may lead to increased androgen levels (due to direct ovarian stimulation and suppression of sex hormone binding globulin); but, at the same time, high androgen levels may promote elevated levels of insulin (as shown when anti-androgen therapy improves sensitivity to insulin; reviewed by Dunaif[34]). Hence, although PCOS has been described as a potential risk factor for the development of type 2 diabetes mellitus,[53,54] insulin resistance or impaired

glucose tolerance may also confer an elevated risk for the development of PCOS. Further studies of menstrual irregularities among diabetic women—particularly with versus without additional risk factors for PCOS—are needed to better elucidate this interrelationship.

Genetic Factors

Several lines of evidence suggest that PCOS may derive at least in part from hereditary elements. In human pedigree studies, women with PCOS have been found to be more likely to have mothers or sisters with PCO and/or PCOS than would be expected in the general population.[55] Similarly, Polson and colleagues[22] observed concordance for menstrual irregularities between probands and their mothers or sisters in 44% of cases. It has been difficult to determine the mode of transmission for PCOS, given the absence of a clear male phenotype, but various modes, including autosomal dominant,[56] X-linked, and polygenic, have been proposed.[57] Defects in different enzymes involved in steroidogenesis have been associated with PCOS. These defects appear to lead to the accumulation of androgens in the ovaries (reviewed in Diamanti-Kandarakis[19]). For example, a single base change in the gene coding for the cytochrome P450 C17 enzyme, a key enzyme involved in ovarian and adrenal androgen biosynthesis, has been identified in PCOS and seems to be associated with a significant risk of developing the condition.[58,59] Relatedly, as mentioned above, the insulin resistance observed in PCOS has been associated with genetic defects in insulin receptor phosphorylation.

Ovarian vs. Hypothalamic Defect

In the past, the primary pathologic defect associated with PCOS was thought to be inappropriate GnRH secretion by the hypothalamus, leading to increased LH release from the pituitary, which ultimately was thought to cause disproportionate androgen production from the ovaries. The prevailing belief now, however, is that ovarian dysfunction is the primary cause of PCOS and impaired gonadotropin release is secondary. More specifically, as mentioned above, PCOS may result in the context of a defect in the P450 aromatase gene, the enzyme product of which is responsible for the conversion of androgens to estrogens in the ovaries.

PCOS and Bipolar Disorder

Although many of the data examining valproate use in women of reproductive age relate to epileptic patients, there is additionally a limited database for bipolar women. Efforts to isolate possible iatrogenic ovarian effects of valproate from other clinical factors (such as epilepsy) are usefully informed by examining nonepileptic women taking valproate on a regular basis. Rasgon et al.[21] reported a 0% incidence of PCOS or PCO in 22 bipolar women taking lithium, valproate, or a combination of the two. The study authors did, however, observe menstrual irregularity in 10 (100%) of 10 lithium, 6 (60%) of 10 valproate, and 2 (100%) of 2 combination patients, suggesting a possible relationship between bipolar disorder and menstrual irregularities,

independent of specific treatment. Similarly, Sachs (G. S. Sachs, M.D., written communication, November 2001) found a 0% prevalence of PCOS in 189 bipolar women (106 on valproate treatment, 83 never on valproate treatment), while McIntyre et al.[60] recently presented data suggesting a 58% prevalence of menstrual irregularities in bipolar women taking valproate compared with just 15% of those taking lithium. In keeping with the majority of the epilepsy literature, these data in bipolar patients support a possible association between valproate use and menstrual irregularities but not PCO and/or PCOS, although the menstrual irregularities could also be secondary to bipolar disorder itself, independent of drug therapy. Hence, the report by Isojarvi et al.[6] remains the only study in the literature reporting an association between valproate use and PCO.

Some authors have begun to raise the possibility of a direct association between PCO and/or PCOS and affective disorders,[61,62] in line with formulations about other endocrinopathies associated with bipolar illness (e.g., thyroid dysfunction, adrenocortical dysfunction). A 1993 case report[63] observing ultrasonographic evidence of PCO in 8 (67%) of 12 women with bipolar affective disorder first suggested the association between bipolar disorder and PCO. Hormonal abnormalities in a significant percentage of bipolar women compared with those who had other psychiatric diagnoses were also reported. More recently, 27% of 78 women identified with a primary diagnosis of PCOS were found to screen positively for features of bipolar illness,[61] only 1 of whom had been previously exposed to valproate. In a similar study, Rasgon et al.[62] observed that the prevalence of depression in women with known PCOS exceeds that in the general population. It has been hypothesized that a common neuroendocrine defect may be responsible for the pathogenesis of both PCO and/or PCOS and affective illness,[64] but there is no direct evidence as yet in support of this theory.

Management of PCOS

Guidelines for the management of PCOS are summarized in Table 2. PCOS is managed by addressing each of the various components of this complex syndrome (reviewed by Diamanti-Kandarakis[19] and Tan et al.[65]). Medications such as oral contraceptives or, in more severe cases, long-acting GnRH agonists (e.g., leuprolide) are used to suppress elevated androgen levels and control menstrual irregularities. Antiandrogens, such as spironolactone, a mineralocorticoid and androgen receptor antagonist, may also be considered to manage the symptoms of androgen excess. Clomiphene citrate has been shown to be successful at inducing ovulation in 80% of women with PCOS through its inhibitory effects on estrogen-binding receptors. Only 20% of these women, however, will conceive. If infertility persists, human menopausal gonadotropin combinations may be used. A decrease in weight by as little as 5% to 15% may also be helpful in restoring fertility and reducing hyperandrogenism.[49,66] Given the risk of dysfunctional uterine bleeding and endometrial cancer in women with conditions of unopposed estrogen such as PCOS, intermittent use of oral progestins can, in some cases, be used to induce withdrawal bleeding and protect the endometrial lining. The various metabolic

Table 2. Management of Polycystic Ovary Syndrome[a]

1. Correct hyperandrogenemia: oral contraceptives, long-acting gonadotropin-releasing hormone agonists, antiandrogens (eg, spironolactone)
2. Promote induction of ovulation: clomiphene citrate, human menopausal gonadotropin combinations
3. Optimize endometrial protection: intermittent use of oral progestins
4. Manage metabolic abnormalities: oral hypoglycemics, diet, exercise, weight loss
5. Screen for medical comorbidities: hypertension, cardiovascular disease, impaired glucose regulation

[a]Based on Diamanti-Kandarakis[19] and Tan et al.[65]

abnormalities associated with PCOS are treated as they would be ordinarily. Oral hypoglycemics along with diet and exercise are usually effective in lowering blood glucose levels.

Management of Valproate-Treated Women

While larger, prospective studies are needed in order to make definitive treatment guidelines for the use of valproate in women of reproductive age, the following recommendations are presented in Table 3. At present, women starting valproate treatment should be informed about the possibility of reproductive-endocrinologic side effects.[9] Additionally, baseline body weight should be measured prior to initiation of treatment, and the patient should be told of the risks and consequences of valproate-induced weight gain. Weight should be monitored and weight gain should be evaluated.[10] Isojarvi et al.[67] also recommend obtaining baseline and subsequent information about ovarian structure and serum sex hormone concentrations in epileptic women taking valproate, although detection of PCO by ultrasound is not a diagnostic criterion for PCOS. Rasgon et al.[21] suggest that clinicians regularly assess for menstrual irregularities, obesity, and hirsutism in their reproductive-aged female bipolar patients taking valproate. A workup consisting of a blood test for dehydroepiandrosterone (DHEA) and bioavailable testosterone should be initiated, along with referral to a reproductive endocrinologist, if the patient has 2 or more of the following symptoms: hirsutism, menstrual disturbances, obesity, alopecia, or infertility. In the presence of such features, consideration should be given to discontinuing valproate after a thorough risk-benefit analysis. Other clinical management strategies include counseling on proper nutrition and weight maintenance strategies, body mass index (BMI, defined as height in meters squared divided by weight in kilograms) calculations at each visit, and measuring both baseline and annual serum lipid profiles.[68]

While some clinicians debate the use of valproate in women < 20 years of age, Isojarvi et al.[67] and others agree that the current data do not appear conclusive enough to contraindicate the use of valproate. While many authors recommend simple caution and observation, Soares[9] suggests doing a pretreatment workup consisting of serum testosterone level and pelvic ultrasound and repeating it annually. Among women with bipolar disorder, changing to a different mood stabilizer should be considered, if psychiatrically appropriate, when clinical symptoms of hyperandrogenism or PCOS appear.

Table 3. Recommendations for Treatment of Premenopausal Women Taking Valproate

1. Discuss possibility of reproductive-endocrinologic side effects with female patients prior to beginning valproate treatment
2. Measure baseline body weight/body mass index and follow both at each visit; evaluate weight gain
3. Obtain baseline information about menstrual cycle and assess for menstrual irregularities at each visit
4. Consider obtaining baseline and subsequent information about ovarian structure and serum sex hormone concentrations[67]
5. Obtain baseline and annual serum lipid profiles[68]
6. Evaluate at baseline signs of androgen excess (eg, hirsutism, alopecia, acne) and follow up at each visit
7. Do blood test for dehydroepiandrosterone (DHEA) and bioavailable testosterone and refer to a reproductive endocrinologist if ≥ 2 of the following symptoms are found: hirsutism, menstrual disturbances, obesity, alopecia, or infertility[21]; consider discontinuing valproate after a thorough risk-benefit analysis
8. Counsel patient on nutrition and weight management strategies

For women < 20 years old:
  Valproate is not contraindicated, but use with caution and follow the recommendations as above
  Consider pretreatment workup consisting of serum testosterone level and pelvic ultrasound, and consider repeating it annually[9]
  Consider changing to a different mood stabilizer if clinical symptoms of hyperandrogenism or polycystic ovary syndrome appear

PREGNANCY

Psychopharmacologic management decisions with newer psychotropic agents represent another fundamental yet controversial aspect of treating women with bipolar and other affective or psychotic disorders. While most mood stabilizers and/or atypical antipsychotic drugs have been identified by the American Academy of Pediatrics (AAP)[69] and the U.S. Food and Drug Administration (FDA)[70,71] as either Category C (i.e., human fetal teratogenicity cannot be ruled out) or Category D (i.e., positive risk of human fetal teratogenicity has been demonstrated), most existing information about human pregnancy outcomes derives from small, select case registries reported by industry or else from tertiary care academic centers. The pregnancy classification system is summarized in Table 4.

With most psychotropics, decisions about often-unknown relative risks must be balanced on an individualized basis in light of potential benefits and likely morbidity and/or mortality associated with untreated (or otherwise-treated) forms of psychopathology. It is of further importance to note the base rate for major congenital malformations (2%–4%) in the general population when assessing relative risks during medication exposures.[72,73] Moreover, the possibility exists that some forms of severe psychopathology, including affective disorders, may themselves confer some elevation of risk for complications during pregnancy, regardless of psychotropic drug use.[74–77]

In addition, specific drug exposures during first versus second or third trimesters also may vary in relation to the developmental periods of organogenesis, as well as windows of greater or lesser risk for breakthrough psychopathology (e.g., risk of manic relapses off lithium treatment appears higher in pregnant bipolar women after the 41st week postconception as compared

with nonpregnant women followed for comparable durations[78]). As summarized in Table 5, several distinct anatomical abnormalities have become recognized with specific psychotropic agents, although the cumulative extent of data available in each instance is variable. The table also reviews the FDA pregnancy class for each agent. Notably, only clozapine is a class B drug, indicating no known evidence of risk in humans when administered during pregnancy.

Lithium

In the case of lithium, the risk for Ebstein's anomaly, a congenital malformation of the tricuspid valve, has for several decades been of notorious concern during first-trimester lithium exposures, although the potential for its actual occurrence appears substantially less than was originally believed (i.e., while once thought to approximate a 400-fold increased risk, the revised likelihood appears to be closer to 1- to 8-fold[79]). Other forms of teratogenicity historically associated with lithium use during the second and third trimesters of pregnancy include polyhydramnios, premature delivery, thyroid abnormalities, nephrogenic diabetes insipidus, and floppy baby syndrome (reviewed by Llewellyn et al.[80]). In general, it is estimated from cohort studies that the risk of major congenital anomalies in lithium-exposed babies is 4% to 12%, compared with the 2% to 4% rate in the untreated comparison groups.[79]

A recent guideline described by Cohen and colleagues[79] to aid decision making with lithium use in pregnancy suggests gradual (i.e., ≥ 2 weeks) prepregnancy tapering of lithium to minimize rebound relapses[110] in women with relatively mild, stable forms of bipolar disorder; tapering and discontinuing lithium during embryogenesis (i.e., 4–12 weeks after the last menstrual period) only in women with severe forms of bipolar illness at moderate risk for relapse; and maintaining lithium throughout pregnancy in those with severe illness for whom the risks of lithium teratogenicity are substantially outweighed by the risks associated with lithium discontinuation and relapse. The latter group of women, however, should get appropriate reproductive risk counseling and prenatal diagnosis. High-resolution ultrasound and fetal echocardiography at 16 to 18 weeks of gestation should be performed in women treated with lithium during the first trimester.

Valproate

Valproate readily crosses the placenta.[111] Use of valproate during pregnancy confers an approximately 5-fold increased risk for major malformations or other substantial pregnancy complications; the incidence of major congenital malformations is 11%.[81] Commonly associated risks (reviewed by Iqbal et al.[82]) include spina bifida (1%–2%),[83–85] skeletal abnormalities,[86] fetal valproate syndrome (up to 53%),[87–89] cardiovascular abnormalities,[90–92] developmental delays in up to 71%,[93] intrauterine growth retardation,[91,93,94] neonatal hypoglycemia,[95] coagulopathies,[96] neonatal hepatotoxicity and/or hyperbilirubinemia,[97] and neonatal withdrawal symptoms.[87,95]

Contraindications to valproate use during pregnancy, particularly the first trimester, are relative rather than absolute. In

Table 4. U.S. Food and Drug Administration Classification System for Administration of Drugs During Pregnancy[a]

Category	Interpretation
A	Controlled studies in humans show no risk
B	No evidence of risk in humans (human data reassuring [animals positive] OR animal studies show no risk)
C	Risk cannot be ruled out (human data lacking; animal studies positive OR not done)
D	Positive evidence of risk (human data show risk; benefit may outweigh risk)
X	Contraindicated in pregnancy (animal or human data positive)

[a]Based on references 69–71.

pregnant women with first-trimester exposures to valproate, a high-resolution fetal ultrasound and echocardiogram should be performed at 16 to 18 weeks of gestation, along with a serum α-fetoprotein level to detect neural tube defects, followed by amniocentesis if necessary to detect spina bifida. Supplementation with folic acid (4–5 mg/day) is advisable from preconception through the 12th week of pregnancy,[112] along with prophylactic oral vitamin K supplementation (10–20 mg/day) in the last month before delivery (as well as 1 mg of intramuscular vitamin K administered to neonates) because of the potential for valproate-induced coagulopathies.[113] Risks for teratogenicity are thought to be further minimized by using doses < 1000 mg/day, with serum levels < 70 μg/mL, administered in 3 or more equal doses.[81,114]

Carbamazepine

Similar to valproate, carbamazepine has been associated with an approximately 0.5% to 1.0% risk of spina bifida,[98] in addition to an overall 5.7% incidence of congenital malformations.[81] Common teratogenic effects include coagulopathies, microcephaly and other craniofacial defects, growth retardation, cardiac abnormalities, and possible developmental delays (reviewed in Iqbal et al.[82]). A prospective study by Jones et al.[99] found craniofacial defects in 11%, fingernail hypoplasia in 26%, and developmental delay in 20% of 35 children exposed prenatally to carbamazepine. Multiple reports suggest a higher frequency of congenital anomalies when carbamazepine is administered in conjunction with valproate.[81,115,116] As a potential human teratogen, carbamazepine should be avoided if possible during the first trimester.

Gabapentin

Since gabapentin is one of the newer anticonvulsants to emerge in the past decade, less naturalistic experience has accrued with its use during pregnancy than with anticonvulsants such as those mentioned above. Preclinical studies suggest potential fetotoxicity (e.g., delayed bone ossification, hydronephrosis, and/or increased rates of hydroureters in rodents and an elevated potential for postimplantation fetal loss in rabbits).[101] In the absence of adequate studies, human risks for teratogenicity are unknown.

Table 5. Teratogenicity Risk Classification and Reported Adverse Events Associated With Mood Stabilizers and/or Atypical Antipsychotics

Drug	Class	Adverse Events
Lithium[79,80]	D	Cardiac anomalies (Ebstein's anomaly); polyhydramnios; floppy baby syndrome; thyroid abnormalities; nephrogenic diabetes insipidus
Valproate[81–97]	D	11% risk of congenital defects; neural tube defects in first trimester; 1%–2% risk of spina bifida; fetal anticonvulsant syndrome; cardiovascular defects; developmental delay; intrauterine growth retardation; coagulopathy; neonatal effects
Carbamazepine[81,82,98,99]	D	5.7% risk of congenital defects; neural tube defects in first trimester; 0.5%–1% risk of spina bifida; fetal anticonvulsant syndrome; craniofacial defects; developmental delay; coagulopathy
Lamotrigine[100]	C	1.8% risk of major congenital defects
Gabapentin[101]	C	Fetotoxic effects in rodents
Topiramate[101]	C	Craniofacial and skeletal anomalies and decreased fetal weight in animals; case reports of hypospadias in male infants
Olanzapine[a]	C	1% risk of major defects
Risperidone[101]	C	1 case report of agenesis of corpus callosum; fetotoxic in animals
Quetiapine[101]	C	No reported data
Ziprasidone[101]	C	Developmental toxicity and possible teratogenic effects in animals
Clozapine[102–109]	B	No known association with congenital anomalies; 2 reports of new-onset or worsening gestational diabetes with shoulder dystocia

[a]M. J. Bernauer, R.Ph.; R. W. Baker, M.D., Eli Lilly and Company, written communication, July 2001.

Lamotrigine

Although lamotrigine is a relatively new anticonvulsant, data on its use during pregnancy are available from a prospective, naturalistic study of first-trimester exposure with known outcomes under ongoing collection by the manufacturer.[100] In lamotrigine monotherapy during the first trimester, the risk of malformations was 1.8% (95% confidence interval = 0.5% to 5.5%). This sample size is too small to rule out small increases in frequency of all major malformations or large increases in frequency of rare major malformations. Since lamotrigine has been shown to decrease fetal folate concentrations in rats,[101] folate supplementation should be considered for all women of reproductive age who are taking lamotrigine.[117]

Topiramate

Craniofacial and skeletal abnormalities have been described in animals, along with decreased fetal weight.[101] Data regarding possible teratogenic effects of topiramate in humans remain indeterminate without adequate studies.

Olanzapine

Data from a case registry of olanzapine exposures during pregnancy was provisionally reported by Goldstein and colleagues.[118] An expanded description of this case registry, maintained by Eli Lilly and Co., presently includes pregnancy outcome data for 96 prospectively reported cases (M. J. Bernauer, R.Ph.; R. W. Baker, M.D., Eli Lilly and Company, written communication, July 2001). Among these, 69 (71.9%) resulted in normal births; 12 (12.5%) resulted in spontaneous abortions; 2 (2.1%) led to premature deliveries, 3 stillbirths occurred (3.1%), and major malformations occurred in 1 case (1.0%). An additional incidence of perinatal complications was seen in 7 cases (7.3%). These are all within the range of normal historical control rates. There are several case reports of healthy infants born without complications despite prenatal exposure to olanzapine.[119,120]

Risperidone

There are no adequate human studies to determine teratogenicity of risperidone. An increased incidence of rat pup deaths and stillborns, however, has been described in animal studies, as has 1 reported case of agenesis of the corpus callosum in a human infant exposed in utero.[101]

Quetiapine

At present, no data are available from human studies to indicate risk for the potential teratogenicity. There is some evidence of delays in skeletal ossification, reduced fetal weight, and increased fetal and pup death in preliminary animal studies.[101]

Ziprasidone

Developmental delays, possible teratogenic effects, and increased stillbirths have been described in animal studies at doses similar to human therapeutic doses,[101] although data from human studies are lacking.

Clozapine

The potential for clozapine-induced agranulocytosis warrants monitoring of white blood cell counts in newborns, although there have been no reports of leukopenia or agranulocytosis in infants exposed during pregnancy or lactation. Several published case reports[102–106] and 3 case series[107–109] collectively suggest no definitive association between clozapine exposure and congenital anomalies in either animals or humans. However, there were 2 cases of new-onset or worsening gestational diabetes with shoulder dystocia[103,104] and a suggestion that the accumulation of clozapine in fetal serum may increase the risk of floppy infant syndrome[105] and neonatal seizures.[106] In a review, Dev and Krupp[108] reported 5 congenital malformations and 5 perinatal syndromes in 61 children exposed to clozapine. Some of the mothers, however, had taken other medications during pregnancy.

Summary: Pregnancy

In summary, possible neurotoxic and other organ system malformations have been described with several anticonvulsant drugs, although their possible therapeutic advantages in some instances may outweigh the relative and often inestimable risks of first-trimester pregnancy exposure. Valproate, carbamazepine, and lithium should be avoided during the first trimester if possible. Risks for adverse pregnancy outcomes most likely are substantially less during second- and third-trimester exposures, after the completion of organogenesis, although the absence of extensive case registry data with most compounds limits the certainty with which conclusions about safety can be drawn. Similarly, relative risks for teratogenicity or perinatal complications are largely unknown with the use of atypical antipsychotics, although the largest recorded case registry, with olanzapine, describes a relatively low risk for adverse events in comparison with rates for spontaneous malformations, premature deliveries, or spontaneous abortions.

Since the neural tube typically closes by the end of the first month, anatomic teratogenicity may have already occurred before a woman knows she is pregnant. Ideally, women of childbearing age taking psychotropic medications should be counseled prior to conception regarding the risk of congenital anomalies secondary to fetal exposure in utero. Prepregnancy counseling may be especially important among sexually active women with bipolar disorder who may unexpectedly place themselves at risk for pregnancy during periods of impulsivity or hypersexuality.

Llewellyn et al.[80] recommend that regardless of medication choice, in all reproductive-aged women with bipolar disorder (and presumably with other psychiatric illnesses as well), the clinician should (1) document the birth control method; (2) document discussion of risks for pregnancy exposure; (3) encourage proper nutrition, exercise, and vitamins; (4) discourage use of tobacco, alcohol, or > 300 mg/day of caffeine; (5) inquire about the use of nutritional/herbal supplements and advise the patient of the lack of data for use during pregnancy; and (6) inquire about plans for pregnancy and emphasize the need for pre-pregnancy consultation. This consultation should include education about the risk of psychiatric illness in the offspring, a treatment plan for managing a relapse during pregnancy and the postpartum period, and a good history including the patient's illness course and response to treatment.

Once a patient becomes pregnant, the risks and benefits of continuing a medication must be carefully weighed and should include the severity of the illness and past response to treatment. Each pregnancy should be closely monitored, and the appropriate screening tests (i.e., fetal ultrasound, α-fetoprotein levels) should be performed. Treatment alternatives such as conventional antipsychotics, antidepressants, and electroconvulsive therapy can also be considered.[121]

LACTATION

The postpartum period is thought to be a relatively high risk period in terms of experiencing an affective episode for all women, but particularly for women with preexisting psychiatric illness. As reviewed by Chaudron and Jefferson,[122] between 5% and 20% of all women will experience a postpartum depression within the first 6 months, and 0.1% to 0.2% will experience a postpartum psychosis. From 40% to 70% of bipolar women will experience postpartum mania or depression.[123] This rate is decreased to 10% with mood-stabilizer prophylaxis.[124–126] Given the risks of relapse and the many associated consequences for mother and newborn, it is advisable to continue psychotropic medications during this vulnerable time. However, many women choose to breastfeed. This choice brings with it the many documented medical and psychosocial benefits of breastfeeding as well as the risk of infant exposure to the medication.

Most psychotropic medications are excreted into breast milk, but there is great variability in the amount of drug received by the infant. Factors such as route of administration, pH, absorption rate, and lipid content, some of which vary throughout the postpartum period and even during a single feeding, are among the many factors that can affect medication concentration in breast milk.[122,127] The amount of medication actually received by the infant can depend on such factors as milk yield, differences in either breast, concentration of the medication in the milk, and absorption and excretion by the infant.[128] The following formula is often used to calculate the amount of drug transferred to the infant: dose/24 hours = concentration of drug in milk × weight in kg of the infant × volume of milk per kg ingested in 24 hours.[122] It is recommended for safe breastfeeding that the ratio of infant dose exposure to maternal dose be no greater than 10%.[129]

Unfortunately, with the exception of several case reports or small case series, there are very few data on the safety of psychotropic medications during breastfeeding (reviewed in Table 6). Additionally, most of the data come from epileptic women. It is important to note that recommendations for breastfeeding while being treated with psychotropic medications have generally been made based on these limited data.

Lithium

The AAP cautions against using lithium while breastfeeding.[130] Lithium has consistently been found in high concentrations in breast milk and infant serum, with reported breast milk concentrations ranging from 24% to 72% of maternal serum levels (reviewed by Chaudron and Jefferson[122] and Iqbal et al.[82]). Nursing infants' serum lithium concentrations have been reported to range from 5% to 200% of the mother's serum concentration.[122] There have been several reports of adverse events experienced by nursing infants of mothers who were taking lithium.[131–133] Reported symptoms have included cyanosis, hypotonia, heart murmur, T-wave changes on electrocardiogram, lethargy, and hypothermia. Linden and Rich[146] recommend that nursing infants of mothers taking lithium be monitored for hypotonia, lethargy, and cyanosis. Hydration status should also be monitored,[80] as dehydration can increase the risk of lithium-related adverse events. While most reports discourage breastfeeding during lithium use, there is limited information about the

Table 6. Medication Exposure Effects in Nursing Infants of Mothers Treated With Mood Stabilizers and/or Atypical Antipsychotics[a]

Drug	Reported Adverse Events	Milk/Maternal Serum, %	Baby/Maternal Serum, %	Specific Events	AAP Recommendation[130]
Lithium[22,122,131–133]	3	24–72	5–200	ECG changes, cyanosis, lethargy, murmur, hypotonia	Use caution; associated with adverse effects
Valproate[122,123,134,135]	1	< 1–10	0–40	Thrombocytopenia and anemia	Compatible with lactation
Carbamazepine[122,136–142]	9	7–95	6–65	Hepatic dysfunction, drowsiness, poor feeding, hyperexcitability, seizure-like activity	Compatible with lactation
Lamotrigine[117,122,143,144]	0	60	23–33	No events; increased rashes in children	Effect unknown, but may be of concern
Gabapentin[122]	0	100	?	No events	None
Topiramate	0	?	?	No events	None
Olanzapine[b]	4	?	?	Jaundice, sedation cardiomegaly; shaking, lethargy; protruding tongue; rash, diarrhea, poor sleep	None
Risperidone[145]	0	?	Infant/maternal dose = 4.3	No events	None
Quetiapine	0	?	?	No events	None
Ziprasidone	0	?	?	No events	None
Clozapine[82,102]	0	?	?	No events; potential for sedation, irritability, seizures, and cardiovascular instability	Effect unknown, but may be of concern

[a]Abbreviations: AAP = American Academy of Pediatrics, ECG = electrocardiogram. Symbol: ? = no information available.
[b]M. J. Bernauer, R.Ph., R. W. Baker, M.D., Eli Lilly and Company, written communication, July 2001.

actual effects of lithium on the infant during lactation, and both the mother and the physician should fully review the risks and benefits prior to making a decision. Burt et al.[127] advise avoiding lithium until the infant is at least 5 months of age due to decreased renal clearance, although careful monitoring of infant clinical status and serum lithium concentrations is recommended if the mother is at high risk for decompensation if lithium were discontinued.

Valproate

Although valproate is excreted into human breast milk, the AAP considers its use to be compatible with breastfeeding.[130] In contrast to lithium, limited data suggest that valproate is measurable in breast milk at acceptable concentrations, ranging from less than 1% to 10% of the maternal serum level (reviewed by Kuller et al.[134] and Chaudron and Jefferson[122]). Data from just 10 reported cases suggest that infant serum valproate levels range from undetectable to 40% of maternal levels (reviewed by Chaudron and Jefferson[122]). One case series[123] reported infant serum levels of just 0.9% to 2.3% of maternal serum levels. There is just one published report of an adverse event potentially related to valproate use during breastfeeding. Stahl et al.[135] reported a case of thrombocytopenic purpura and anemia in a 3-month-old infant whose mother used valproate during pregnancy and lactation. Symptoms resolved after discontinuation of breastfeeding. There are also reports of increased risk of fatal hepatotoxicity in children under 2 years of age who are treated with valproate, which have prompted some authors to advise against breastfeeding while the mother is on treatment with valproate.[134,147] Burt et al.[127] recommend monitoring pediatric clinical status, liver enzymes, and platelets.

Carbamazepine

Similar to valproate, carbamazepine is considered compatible with breastfeeding by the AAP,[130] despite excretion into breast milk and limited data. In a review of 50 published cases of carbamazepine exposure during breastfeeding, Chaudron and Jefferson[122] report breast milk concentrations from 7% to 95% of maternal serum levels. Data from 8 case reports, also reviewed by Chaudron and Jefferson,[122] show that infant serum carbamazepine levels ranged from 6% to 65% of maternal serum levels. There have been 2 reports of transient hepatotoxicity,[136,137] 1 report of seizure-like activity,[138] 1 report of drowsiness, irritability, and a high-pitched cry,[139] 2 reports of hyperexcitability,[140,141] and 3 reports of poor feeding in breastfed infants exposed to carbamazepine.[140,141] By contrast, 1 early study from 1979 reported no adverse events in 94 infants exposed to carbamazepine during lactation.[142]

Generally, many of the women in the case series reported above were on anticonvulsant polytherapy, which makes interpretation and generalization of the data difficult. Chaudron and Jefferson,[122] however, recommend a reassessment of the safety of carbamazepine given the reports of adverse events. Iqbal et al.[82] recommend monitoring concentrations of carbamazepine and its 10,11-epoxide metabolite in maternal plasma and breast milk and infant plasma. Nursing should be discontinued if any adverse reactions are observed.

Lamotrigine

There are no reports of adverse events associated with lamotrigine use during breastfeeding, but the milk-to–maternal serum ratio was approximately 60% in 3 published reports.[117,143,144] The infants' serum levels were 25% to 30% of maternal serum

concentrations.[143,144] Hence, lamotrigine has been designated as a drug "for which the effect on nursing infants is unknown but may be of concern" by the AAP.[130] There is also a theoretical concern about exposure of infants to lamotrigine because of the increased risk of potentially life-threatening rashes (such as Stevens-Johnson syndrome or toxic epidermal necrolysis) in epileptic children treated with lamotrigine.[122]

Gabapentin

There are no published data on exposure to gabapentin during breastfeeding. An unpublished case series conducted by the manufacturer noted that the amount of gabapentin in breast milk was approximately equivalent to that in maternal serum (data on file, Parke-Davis, cited in Chaudron and Jefferson[122]). Given the lack of published data, the AAP in its recently published report on the use of medications during lactation did not make a specific recommendation regarding the use of gabapentin during lactation.

Topiramate

At present, there is no known published information regarding infant exposure to topiramate through breastfeeding. Hence, caution is warranted in using topiramate among women who are breastfeeding.

Olanzapine

There are 20 reports of breastfed infants exposed to olanzapine (M. J. Bernauer, R.Ph.; R. W. Baker, M.D., Eli Lilly and Company, written communication, July 2001). These elaborate on the 2 retrospectively ascertained cases of lactation exposure reported by Goldstein et al.[118] Four of 20 noted adverse events, which included (1) jaundice, sedation, cardiomegaly, and a heart murmur; (2) shaking, poor sucking, and lethargy; (3) protruding tongue; and (4) rash, diarrhea, and sleeping disorder. No definitive conclusions were made regarding the role of olanzapine in contributing to these events. In one published case report of olanzapine use during breastfeeding,[120] serum concentrations were measured at "below detection limit" (39.5 ng/mL at 2 weeks and 32.8 ng/mL at 6 weeks) in the mother and < 2 ng/mL in the infant. The manufacturer advises patients taking olanzapine not to breastfeed until more information is ascertained.

Risperidone

There is 1 published case report of risperidone use during lactation.[145] Used in a young woman with puerperal psychosis, risperidone was found to have just a modest distribution into breast milk. The infant dose exposure was noted to be just 4.3% of the maternal dose. No adverse effects were reported in the infant. Nevertheless, the authors made a conservative recommendation to discontinue nursing.

Quetiapine

There is no known information regarding infant exposure to quetiapine through breastfeeding, prompting caution in its use during lactation.

Ziprasidone

There is no known information regarding infant exposure to ziprasidone through breastfeeding, prompting caution in its use during lactation.

Clozapine

In a case reported by Barnas et al.[102] of clozapine treatment of a schizophrenic woman during pregnancy and lactation, relatively high concentrations of clozapine were found in breast milk. Milk-to–maternal serum ratios were noted to be 432% on the day following delivery, and 279% 1 week after delivery. The authors attributed this to the higher lipid concentration of breast milk in combination with the lipophilic properties of clozapine and advised against breastfeeding during clozapine use. As mentioned above, the theoretical risk for leukopenia or agranulocytosis has not been demonstrated in neonates exposed to clozapine via breast milk. There is, however, the potential for clozapine to cause sedation, decreased suckling, restlessness or irritability, seizures, and cardiovascular instability in the nursing infant.[82] Given these concerns, clozapine, like lamotrigine, has been designated as a drug "for which the effect on nursing infants is unknown but may be of concern" by the AAP.[130]

Summary: Lactation

In summary, infants exposed to valproate received the lowest concentration of medication, followed by those exposed to carbamazepine. Both are considered "compatible with breastfeeding" by the AAP,[130] although in general the recommendations made by the AAP and other sources are based on very limited information, and there are reports of adverse events, particularly in infants exposed to carbamazepine. Lithium should be used with extreme caution and only if necessary, while concern should be exercised when deciding to use lamotrigine and clozapine. The newer anticonvulsants and atypical antipsychotics have not been studied sufficiently for any definitive recommendations to be made at present. The most conservative approach is thus to avoid breastfeeding while using these medications until more information is known.

Recognizing the importance of breastfeeding to some mothers, various authors, however, have made general recommendations regarding the use of psychotropics during the postpartum period. Chaudron and Jefferson[122] recommend choosing a mood stabilizer based on the patient's clinical status and past response, regardless of breastfeeding status. The risks and benefits of breastfeeding, of not taking medication, and of nursing while taking medication should be discussed with all new mothers. If a mother has taken medication through the pregnancy, a 1- or 2-day washout period (without breastfeeding) is recommended for the infant. Breastfeeding mothers should be informed about the symptoms of drug toxicity, and formula supplements should be used during any periods of infant illness or dehydration. If toxicity is suspected, infant and maternal serum drug levels should be drawn and breastfeeding should be temporarily stopped. Polypharmacy should be avoided if possible, and lowest effective doses should be used. Chaudron and Jefferson[122] also state that

following milk and infant serum levels is not indicated unless there are clinical symptoms of toxicity. Llewellyn et al.,[80] on the other hand, recommend monthly monitoring of the indices affected by the individual medication in an exposed infant for 2 to 3 months, after any increase in maternal daily dose, or if side effects are observed in the infant. They also warn of the risks of changing to a new medication during this high-risk period.

CONCLUSION

The advent of many new pharmacotherapies has led to renewed optimism about the prognosis and treatment outcome for women with psychiatric illnesses, as well as new concerns about reproductive health safety issues. While provisional data with some agents raised suspicions about possible detrimental effects on menstrual function, a wide-ranged perspective now acknowledges the complex interrelationships between pharmacologic, neuroendocrine, genetic, neurologic, reproductive, and other health issues in distinct clinical populations. An emerging database on reproductive health safety factors for women with bipolar and psychotic disorders has begun to shed light on maximizing clinical benefits while realistically appraising medication side effects, both short- and long-term, for women with childbearing potential.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), divalproex (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), leuprolide (Lupron and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), tiagabine (Gabitril), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, carbamazepine, clozapine, gabapentin, lamotrigine, quetiapine, risperidone, tiagabine, topiramate, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder, and leuprolide and spironolactone are not approved for antiandrogen use.

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