Reproductive Biology and Psychotropic Treatments in Premenopausal Women With Bipolar Disorder

Hadine Joffe, M.D., M.Sc.

Treating women with bipolar disorder during the reproductive years requires special consideration because of the reproductive risks associated with specific psychotropic drugs and drug interactions with hormonal contraceptives. Some psychotropic drugs can disrupt the menstrual cycle, alter pregnancy potential, and increase the risk for chronic conditions associated with hormone changes, such as prolactin elevation and polycystic ovarian syndrome (PCOS). Valproate has been associated with an increased risk of PCOS features. Typical antipsychotics and risperidone can increase prolactin production, which may also disrupt the menstrual cycle. When the menstrual cycle is altered, fertility is reduced, and medical conditions such as osteoporosis and endometrial hyperplasia can result. This article advises establishing the regularity of menstrual cycles and discussing the potential reproductive impact of specific psychotropic medications before initiating treatment in women with bipolar disorder who are of reproductive age. *(J Clin Psychiatry 2007;68[suppl 9]:10–15)*

Treatment considerations in bipolar disorder differ between men and women. One important difference arises because of factors specific to the reproductive system.[1,2] Some psychotropic medications that are used commonly to treat bipolar disorder can affect the hypothalamic-pituitary-gonadal (HPG) axis. Some of these medications can also interact with contraceptive hormones (e.g., birth control pills), with important effects on their contraceptive efficacy.

When psychiatric medications affect the HPG axis (Figure 1), menstrual cycle patterns may change in women who are in the childbearing years (from menarche to menopause). Disruption of the menstrual cycle can have important effects, including reduced fertility. Hormonal changes associated with menstrual irregularities may also increase the risk for specific chronic medical conditions, such as osteoporosis in the case of prolactin disorder or endometrial hyperplasia and diabetes mellitus in the case of polycystic ovarian syndrome (PCOS). Additionally, interactions may occur between psychiatric drugs and contraceptive hormones. As a result of these interactions, the efficacy of contraceptive hormones may be reduced, or the contraceptives may alter the blood levels of certain psychiatric drugs, which may reduce their efficacy. In this review, the evidence supporting the associations between valproate and PCOS features, the effect of antipsychotics on prolactin, as well as drug interactions between hormonal contraceptive agents and psychotropic medications used commonly in bipolar disorder, will be discussed. Clinical assessment of reproductive function and recommendations about management of reproductive side effects and drug interactions will also be addressed.

ASSESSMENT OF REPRODUCTION FUNCTION IN WOMEN OF CHILDBEARING AGE

It is important to determine the patient's menstrual cycle pattern before starting a medication to know if the prescribed medication is responsible for menstrual cycle changes or if the patient coincidentally has menstrual abnormalities for reasons unrelated to the psychiatric medication. Studies[3] have shown that approximately 15% to 20% of premenopausal women have irregular menstrual cycles. Cycles are considered normal if they occur every 25 to 35 days at predictable intervals; cycles outside of this range are considered abnormal. Menstrual cycle irregularities are more common in women under 20 years old and over 40 years old than in other age groups because of recent menarche in younger women and the perimenopause in older women. Because of the high prevalence of menstrual cycle irregularities in women of reproductive age, women seeking treatment for bipolar disorder may have cycle irregularities before they initiate treatment with psychotropic medications.

Irregular cycles may occur because of normal, physiologic reasons and because of pathologic disorders

From the Perinatal and Reproductive Psychiatry Clinical Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston.

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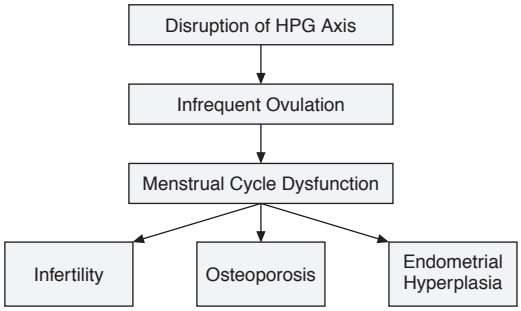
Corresponding author and reprints: Hadine Joffe, M.D., M.Sc., Massachusetts General Hospital, 185 Cambridge St., Boston, MA 02114 (e-mail: hjoffe@partners.org).

Figure 1. Hypothalamic-Pituitary-Gonadal (HPG) Axis Disruption in Women



(Table 1).[4] Normal, physiologic reasons include recent menarche (≤ 2 years), pregnancy, breastfeeding, and perimenopausal status. The most common pathologic reasons for abnormal cycles are PCOS and prolactin elevation. In rare cases, hypothyroidism can lead to abnormal cycles. Hypothalamic or stress amenorrhea can occur in women who exercise excessively or who have anorexia nervosa. Temporary periods of psychosocial stress can also lead to transient cycle abnormalities.

Women with bipolar disorder may be more likely to have menstrual cycle irregularities than women with unipolar depression and healthy individuals. In a study (Figure 2) of menstrual cycle dysfunction prior to initiation of psychiatric medication, 34.2% of 295 women with bipolar disorder reported a history of menstrual cycle abnormalities, which was significantly higher than that reported by healthy control subjects (21.7%) and women with unipolar depression (24.5%).[5] The results of this study suggest that approximately one third of women with bipolar disorder have irregular cycles before they start treatment. Other smaller studies[6,7] of women with bipolar disorder have been somewhat contradictory, with some reporting an even higher rate of menstrual abnormalities in women already taking psychiatric medications and others finding no difference relative to general population estimates of menstrual irregularities.

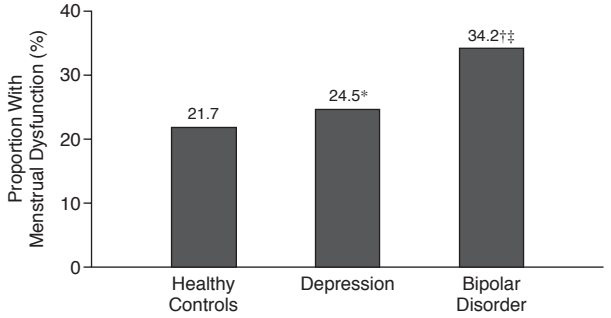
RELATIONSHIP BETWEEN VALPROATE AND PCOS

Valproate has been reported to be associated with PCOS features in women taking the medication for treatment of bipolar disorder and epilepsy.[8–10] PCOS is a chronic reproductive-endocrine disorder that occurs in 4% to 10% of reproductive-aged women.[11–14] This disorder is diagnosed when menstrual cycle irregularities, reflecting infrequent ovulation, and evidence of hyperandrogenism are both present.[15] Evidence of hyperandrogenism includes either clinical or biochemical evidence of elevated androgens or heightened sensitivity to androgens.

Table 1. Common Causes of Irregular Menstrual Cycles in Premenopausal Women

Physiologic	Pathologic
Recent menarche	Polycystic ovarian syndrome
Pregnancy	Prolactin elevation
Lactation	Hypothyroidism
Perimenopause	Hypothalamic/stress amenorrhea

Figure 2. Prevalence of Early-Onset Menstrual Cycle Dysfunction Retrospectively Reported by Women With Bipolar Disorder (N = 295), Women With Depression (N = 245), and Healthy Controls (N = 619)[a]



[a]Adapted with permission from Joffe et al.[5]
*Depression vs. healthy controls, p = .37.
†Bipolar disorder vs. healthy controls, p < .0001.
‡Bipolar disorder vs. depression, p = .01.

Clinical manifestations are hirsutism (excess hair growth on the face), acne, and male-pattern balding. Biochemical evidence consists of elevated serum levels of total or free testosterone or the adrenal androgen dehydroepiandrosterone sulfate (DHEAS). Obesity is present in approximately half of women with PCOS. The abnormal polycystic ovary morphology pattern seen on ultrasound is not required for the diagnosis of PCOS, but this pattern is observed in almost all women with PCOS. However, the presence of polycystic ovary morphology alone does not constitute a diagnosis of PCOS, since it is present in one quarter of women who have regular menstrual cycles and no hyperandrogenic features.[16] Health risks associated with PCOS include insulin resistance and diabetes mellitus, endometrial hyperplasia (as a precursor to endometrial cancer), reduced fertility, and possibly cardiovascular disease.[11]

The association between valproate use and PCOS features was first observed in women with epilepsy.[9,10,17] Studies in epileptic populations were controversial because some found an association between valproate and PCOS features,[18] while others reported an association with the disorder of epilepsy, rather than valproate.[19] Growing evidence of an association between valproate use and PCOS features in women with bipolar disorder emphasizes that the association is likely to be medication specific.[8]

In a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[20] substudy,[8] PCOS features were compared between 86 premenopausal women taking valproate and 144 premenopausal women taking other anticonvulsants or lithium. The results of this study showed that 10.5% of women taking valproate developed new-onset menstrual cycle irregularities and had evidence of hyperandrogenism while taking valproate, which was significantly higher than the 1.4% incidence of new-onset PCOS features among women taking other anticonvulsants or lithium. All women who developed PCOS features while taking valproate developed irregular menstrual cycles within the first year of valproate use.

The incidence of PCOS features observed among valproate users with bipolar disorder is much lower than the initial report in women with epilepsy that 56% of valproate users had PCOS features.[9] However, the diagnostic criteria used in the STEP-BD study were more stringent and consistent with current conventional definitions of PCOS.[15] Results of other smaller studies in women with bipolar disorder[6,21–23] examining the association between valproate and PCOS have been mixed, with some finding an association and others observing no association. The second largest study[24] to examine this association evaluated 50 women taking valproate and 22 women taking medications other than valproate. This study found an 8% prevalence of PCOS in women taking valproate compared with 0% for medications other than valproate, but this difference was not statistically significant because of sample size limitations.

Several explanations for how valproate might induce PCOS have been proposed.[9,25,26] First, valproate has been shown[9,25] to induce higher levels of androgens in the ovary, which is the primary source of male hormones in women, and may be the basis of hyperandrogenism and irregular menstrual cycles in woman taking valproate who develop PCOS features. Another hypothesis[27] is that valproate may indirectly lead to PCOS via weight gain and insulin resistance; however, there is little direct evidence to support this hypothesis. Others[27] have proposed that hepatic effects of valproate lead to higher testosterone levels or that central nervous system effects of valproate may alter the gonadotropin-releasing hormone, which controls the hypothalamic-pituitary-ovarian axis. Currently, the strongest evidence suggests that a direct ovarian effect of valproate is the basis for the PCOS risk.

When starting a premenopausal woman on valproate treatment, clinicians should discuss the risk of developing PCOS, assess pretreatment menstrual cycle patterns, hirsutism, acne, and weight. After the initiation of treatment, these PCOS features should be monitored closely, especially during the first year of valproate use. The risk for developing new-onset PCOS features may pass after 1 year on valproate treatment. Evidence suggests that PCOS features associated with valproate resolve after valproate is discontinued,[9,28] but that menstrual cycles may not normalize until up to 1 year after the patient has discontinued taking valproate. If menstrual cycle irregularities or amenorrhea develop when taking valproate, a woman should be evaluated for common causes of menstrual dysfunction, including pregnancy, elevated prolactin levels, perimenopause, and PCOS. Hyperprolactinemia should be carefully considered as many of these women may also be taking prolactin-elevating antipsychotics that can affect menstrual cycle patterns. Details about the temporal relationship between initiation of valproate and the development of PCOS features are key to establishing that valproate may be etiologically related to PCOS. If PCOS symptoms emerge, options include changing the mood stabilizer or continuing the mood stabilizer while seeking an endocrinology consultation for management of PCOS.

MANAGING WOMEN TAKING PROLACTIN-ELEVATING ANTIPSYCHOTICS

Serum levels of prolactin increase in pregnancy and lactation but can also be increased by specific medical conditions and medications. Antipsychotic agents are a common cause of prolactin elevation (hyperprolactinemia). Prolactin is a hormone that is produced and secreted by cells in the anterior pituitary. Its secretion is tonically inhibited by dopaminergic neurons from the hypothalamus acting on dopamine-2 (D_2) receptors in the anterior pituitary. Antipsychotics that have a strong affinity for D_2 receptors block these receptors in the anterior pituitary, which increases prolactin secretion.[29] Normal levels in adults are under 20 ng/mL.

The antipsychotics most strongly associated with hyperprolactinemia are the typical agents and risperidone, with hyperprolactinemia seen in 48% and 88% of users, respectively.[30] The other atypical antipsychotic agents[31] (clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole), which have a low affinity for D_2 receptors, are mostly prolactin-sparing, with modest transient elevation in prolactin seen occasionally.[29] Risperidone is a strong D_2 receptor inhibitor that is associated with the greatest elevation in prolactin levels.[30]

Tremendous individual differences in prolactin elevation exist in the setting of antipsychotic medication exposure. In addition, when prolactin levels are elevated, the clinical presentation varies widely, with some individuals being highly symptomatic and others asymptomatic. The risks associated with hyperprolactinemia differ based on whether the condition is symptomatic or not.

In premenopausal women, a common symptom of hyperprolactinemia is infrequent menstrual cycles or amenorrhea, which is estimated to occur in at least one quarter of women taking typical antipsychotics and one half of women taking risperidone.[29,30] Infrequent menses

reflect infrequent ovulation and reduced production of ovarian estrogen, which can lead to infertility and osteoporosis if untreated for a prolonged period of time. Other symptoms of hyperprolactinemia in premenopausal women include galactorrhea, which occurs in approximately 19% of women taking typical antipsychotics.[29,30] Sexual dysfunction can occur in 33% of women taking typical agents and 43% of women taking risperidone.[30] Elevations in prolactin after initiation of antipsychotics occur rapidly, with disruption of the menstrual cycle frequently presenting within a few months of the development of hyperprolactinemia.

A small increase in the risk of breast cancer has been observed in a large study of women using long-term typical antipsychotics.[32] The authors hypothesized that antipsychotic agents may increase the risk for breast cancer because of their prolactin-elevating effects but did not measure prolactin levels.[32] The prolactin hypothesis was based on an increased risk of breast cancer that they also observed in women taking prolactin-elevating antiemetic dopamine antagonist drugs.[32] No increased risk for breast cancer was observed in a small sample of women with prolactin-secreting pituitary adenomas,[33] and no data are available on breast cancer risk in women using atypical antipsychotics. The association between use of prolactin-elevating medications and breast cancer is difficult to reconcile with the likely estrogen-deficient state resulting from hyperprolactinemia, because estrogen-deficiency should provide relative protection against breast cancer. More studies are needed to address this potential risk of hyperprolactinemia.

The potential reproductive effects of hyperprolactinemia warrant assessment of reproductive function prior to initiating treatment with antipsychotic agents in premenopausal women. For women not taking a hormonal contraceptive, it is important to determine if menstrual cycle patterns are regular. Measuring pretreatment prolactin levels can be helpful to compare with prolactin levels during treatment. If menstrual cycles become irregular, it is important to establish if a high prolactin level is the cause and, if so, if the antipsychotic is the cause of the elevation. Knowing that menstrual cycles (and possibly prolactin levels) were normal before antipsychotic treatment was started provides useful information about the possible causative link between menstrual dysfunction and use of the antipsychotic agent.

Because prolactin-secreting pituitary adenomas (prolactinomas) are the most common cause of hyperprolactinemia, they may sometimes account for menstrual irregularities or galactorrhea in premenopausal women taking antipsychotic medications. Prolactinomas are benign growths in the pituitary that are diagnosed with brain magnetic resonance imaging (MRI). In contrast, hyperprolactinemia resulting from an antipsychotic agent is physiologic and does not result in an anatomic abnormality in the pituitary. Brain MRIs can be used to exclude the possibility of a prolactinoma when the diagnosis of antipsychotic-induced hyperprolactinemia cannot be established based on the temporal relationships between the initiation of the medication and the onset of hyperprolactinemia and menstrual cycle irregularities. However, obtaining clinical information about menstrual cycles and galactorrhea prior to initiation of treatment with the antipsychotic can sometimes be used to avoid this radiographic procedure.

Management strategies for premenopausal women who develop symptoms from prolactin-elevating antipsychotics can be derived from approaches to the management of women with prolactinomas. If menstrual cycles are infrequent or if amenorrhea is present, it is important to consider how long the antipsychotic will be used. Because of the long-term risks of chronic estrogen-deficiency, if the medication is expected to be used for only a few months, the treatment decisions are different than if the antipsychotic is to be administered chronically. Bone mineral density studies can be helpful to assess the potential effects of prolonged menstrual dysfunction on bone health.

Treatment options for symptomatic hyperprolactinemia induced by antipsychotics include adding a hormonal contraceptive to replace estrogen and reduce the risk of osteoporosis, changing the antipsychotic to a prolactin-sparing antipsychotic or a mood stabilizer, reducing the dose of the antipsychotic, and adding a dopamine agonist to directly lower the prolactin level. This decision rests on the specific clinical scenario, including the presence of contraindications to use of hormonal contraceptives (e.g., thrombotic tendencies, cigarette smoking in women over 35 years of age), the psychiatric risks inherent in reducing the dose of or discontinuing a medication that may have particular efficacy in an individual, and the risk for psychosis induced by dopamine agonists. Women who have irregular but frequent cycles (e.g., every 6–8 weeks) may not necessarily require treatment for medical reasons unless they are bothered by unpredictable menstrual cycles. Galactorrhea can be treated by adding a dopamine agonist or by changing to a prolactin-sparing antipsychotic or a mood stabilizer.

In premenopausal women who have asymptomatic antipsychotic-induced hyperprolactinemia, it is not clear that treatment is required. For example, asymptomatic women with prolactinomas are frequently left untreated. However, recent data[34–36] regarding the association of antipsychotics and breast cancer risk may lead some to avoid long-term hyperprolactinemia even if it is asymptomatic, particularly if there is a personal or strong family history of breast cancer. In addition, management of hyperprolactinemia in prepubertal and peripubertal children, unlike in premenopausal women, requires careful attention to maintain normal serum prolactin because of the possible effects on growth and pubertal development.

DRUG INTERACTIONS BETWEEN PSYCHOTROPIC MEDICATIONS AND HORMONAL CONTRACEPTIVES

Notable interactions exist between hormonal contraceptive agents and specific psychotropic drugs that warrant clinical consideration. Carbamazepine, topiramate, oxcarbazepine, and modafinil can lower the efficacy of birth control pills (and the contraceptive vaginal ring) via induction of hepatic CYP450 3A4 isoenzymes that metabolize the exogenously administered estrogen. These interactions are important because they can result in unexpected pregnancies. Contraception can be improved in these individuals by changing to another hormonal contraceptive that does not undergo extensive hepatic metabolism (e.g., the birth control patch), using barrier methods or intrauterine devices for birth control, or by administering a birth control pill that has a higher dose of estrogen. High-dose birth control pills are less well tolerated and are associated with more adverse events. Their efficacy can also be reduced with concomitant use of hepatic CYP450 3A4 enzyme inducers, although contraceptive failure is expected to occur less commonly than with the low-dose birth control pills used today. The psychiatric medication can also be changed if clinically appropriate. The contraceptive efficacy of birth control pills used in combination with CYP450 3A4 enzyme inducers is unpredictable because of interindividual differences in hepatic isoenzymes.

Another drug interaction between hormonal contraceptives and psychotropic drugs warrants attention because of the potential effect on stability of psychiatric symptoms. Birth control pills reduce serum levels of lamotrigine by approximately 50%.[37–39] This effect occurs because the estrogen in combination (estrogen and progesterone) birth control pills increases the clearance of lamotrigine. As a result, the dose of lamotrigine may need to be increased when a birth control pill is added, the dose can sometimes be decreased after discontinuation of a birth control pill, and those receiving treatment with both lamotrigine and estrogen-based hormonal contraceptives may require high doses of lamotrigine for efficacy. Lamotrigine is not known to significantly reduce serum levels of exogenously administered estrogen or the contraceptive benefit of combination birth control pills. However, it reduces serum levels of some synthetic progestins, which may reduce the efficacy of progesterone-only birth control pills.[38]

SUMMARY AND RECOMMENDATIONS

Treatment of bipolar disorder in women of reproductive age requires attention to the potential effects of psychotropic drugs on reproductive biology. Before initiating treatment, clinicians should encourage contraceptive practices and emphasize the importance of planning pregnancies in the context of clinical stability and psychotropic medication use. In addition, in women not taking hormonal contraceptives, clinical review of the regularity of menstrual cycles is a simple way to screen for the possibility that an endocrine disorder affecting the reproductive system is present prior to or during treatment. Self-monitoring of menstrual cycles can be valuable. The potential effects of valproate on PCOS features, of selected antipsychotics on prolactin elevation, and of drug-drug interactions between specific psychotropic medications and hormonal contraceptives should be discussed before initiating treatment and when monitoring medication tolerability. The reproductive side effects reviewed here are not universal and appear to be reversible when medications are discontinued.

When specific medications are selected, reproductive side effects should be considered together with concerns about other health risks, such as weight gain, insulin resistance, and thyroid and renal dysfunction. Management of bipolar disorder in premenopausal women involves complicated decision making about the benefits and risks of medications. The risk for any side effects should be weighed against the risk of undertreating or destabilizing a woman with a severe mental illness when medications are withheld or discontinued. Collaboration with gynecologists, endocrinologists, and/or primary care physicians during consideration of reproductive side effects and drug interactions can help to optimize care in these complicated situations.

Drug names: aripiprazole (Abilify), carbamazepine (Equetro, Tegretol, and others), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), modafinil (Provigil), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperidal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, carbamazepine, clozapine, modafinil, oxcarbazepine, and topiramate are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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