

Bipolar Disorder in Women: Clinical and Metabolic Correlates

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Financial Disclosure

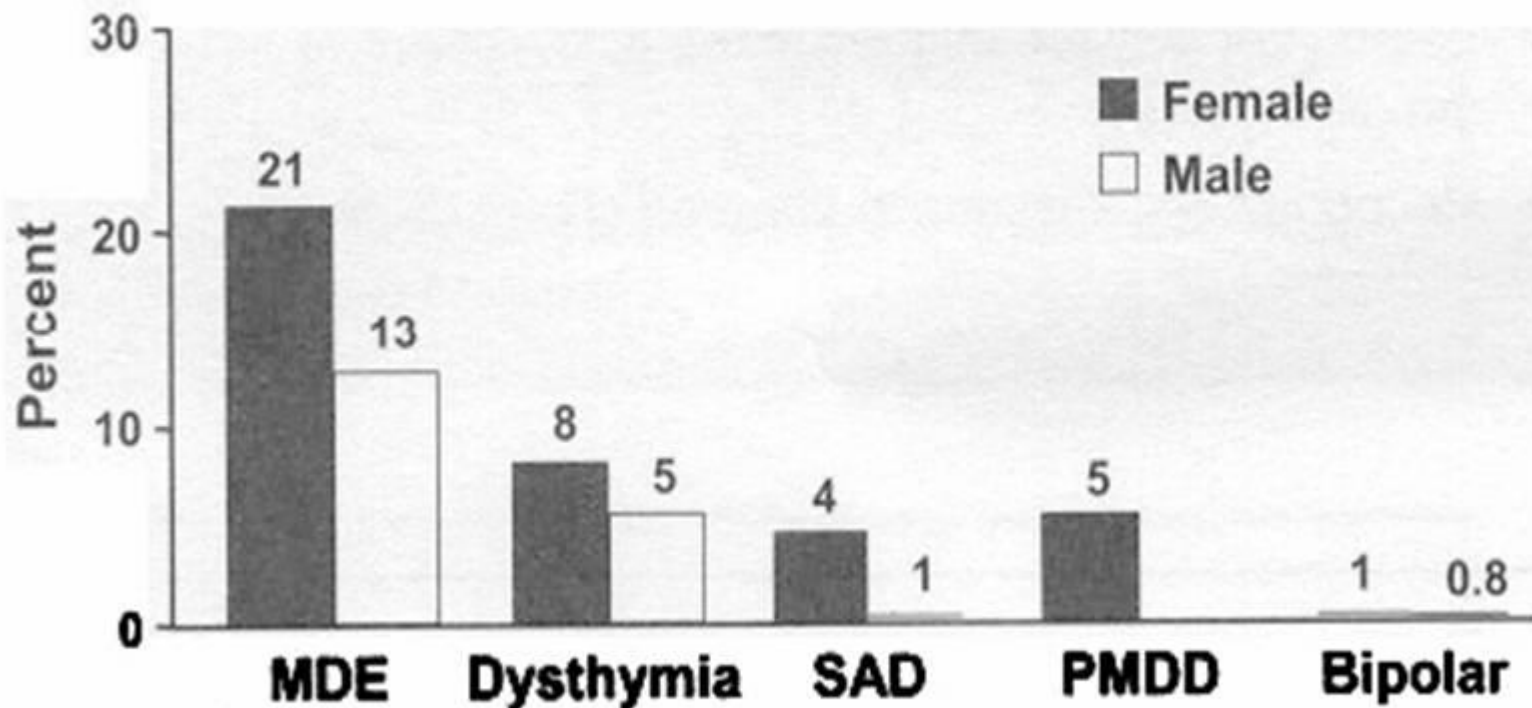
- **Speakers' Bureaus:** Abbott Laboratories, Inc, Bristol-Myers Squibb Company, Forest Laboratories, Inc, GlaxoSmithKline, and Pfizer Inc
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Dr Rasgon will discuss off-label use of pharmaceutical compounds during her presentation.

Outline

- **Gender-specific presentation of bipolar disorder (BD)**
- **Pregnancy and BD**
- **Reproductive endocrine system function and BD**
- **Contraception in patients being treated for BD**

Prevalence of Mood Disorders by Gender



MDE = major depressive episode; SAD = social anxiety disorder; PMDD = premenstrual dysphoric disorder; Kessler RC et al. (1994), *Arch Gen Psychiatry* 51(1):8-19; Rivera-Tovar AD, Frank E (1990), *Am J Psychiatry* 147(12):1634-1636; Weissman MM et al. (1993), *J Affect Disord* 29(2-3):77-84

Gender Differences in Clinical Course of Bipolar Disorder

- **Prevalence rate of Bipolar I Disorder estimated to be 1% and affects men and women in equal proportions¹**
- **Bipolar II and rapid-cycling subtypes overrepresented in women^{2,3}**
- **Women suffer from depressed episodes,¹ mixed episodes,⁴ and rapid cycling² more frequently than men**

Sources: 1. Perugi G, et al. *Br J Psychiatry*. 1990;157:835-841.

2. Tondo L, Baldessarini RJ. *Am J Psychiatry*. 1998;155:1434-1436.

3. Coryell W, et al. *Arch Gen Psychiatry*. 1992;49:126-131.

4. McElroy SL, et al. *Compr Psychiatry*. 1995;36:187-194.

Bipolar Disorder in Pregnancy and Postpartum

Psychiatric Disorders During Pregnancy

- **High estrogen and progesterone levels during pregnancy**
- **12% prevalence of depression in 2nd and 3rd trimesters¹**
- **Pregnancy not protective for most mood and anxiety disorders²**
- **75% of 32 women with prior depression who discontinued antidepressant relapsed during the pregnancy, most during the first trimester³**

Sources:

1. Bennett HA et al. (2004), *Obstet Gynecol* 103(4): 698-709;
2. Levey L et al. (2004), *Neurol Clin* 22(4): 863-893,
3. Cohen LS et al. (2004), *Arch Women Ment Health* 7(4): 217-221

Effects of Untreated Depression in Pregnancy

- **Poor self-care, poor prenatal care**
- **Risk of suicide, substance abuse**
- **HPA axis effects on neurobehavioral developments**
- **Spontaneous abortion, low birth weight, preeclampsia, prematurity, low APGAR scores, neonatal complications**

Sources:

1. Bonari L et al. (2004), *Can J Psychiatry* 49(11): 726-735;
2. Henry AL et al. (2004), *Clin Obstet Gynecol* 47(3): 535-546

Common Misperceptions

- **Ideal pregnancy**
 - Myth propagated in lay literature
- **Higher risk associated with first-trimester exposure**
- **Mental illness improves during pregnancy**
- **Breastfeeding**
 - Natural does not mean easy
 - Impact on sleep often not considered in women with mental illness

Impact of Untreated Depression in Pregnancy on Fetal Outcome

- **Decreased appetite, lower than normal weight gain, increased use of cigarettes, alcohol, drugs**
- **Above behaviors associated with altered birth outcome**
- **Depression associated with preterm labor and low birth weight**
- **Congenital malformation: not known**
- **Neurobehavioral sequelae: not known**

Sources: 1. Zuckerman B, et al. Am J Obstet Gynecol. 1989;160:1107-1111.
2. Zuckerman B, et al. Pediatr Clin North Am. 1991;38:1387-1400.
3. Orr ST, Miller CA. Epidemiol Rev. 1995;17:165-171.
4. Steer RA, et al. J Clin Epidemiol. 1992;45:1093-1099.

What Is Category Labeling?

Key to FDA Use-in-Pregnancy Ratings

<u>Category</u>	<u>Interpretation</u>
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- | | |
|----------|--|
| A | Controlled human studies have demonstrated no fetal risk |
| B | Animal studies indicate no fetal risk, but no human studies OR adverse effects in animals, but not in well-controlled human studies |
| C | No adequate human or animal studies OR adverse fetal effects in animal studies, but no available human data |
| D | Positive evidence of risk, but benefits outweigh risks |
| X | Contraindicated in pregnancy |

Antidepressants and Persistent Pulmonary Hypertension of the Newborn

- **377 women whose infants had PPHN and 836 matched control women and their infants**
- **Neither the use of SSRIs before the 20th week of gestation nor the use of non-SSRI antidepressant drugs at any time during pregnancy was associated with an increased risk of PPHN**
- **Data support an association between the maternal use of SSRIs in late pregnancy and PPHN in the offspring**

Postpartum Psychosis

- **Symptoms of agitation, confusion, mood lability, delusions**
- **Prevalence 1-2/1,000 births**
- **Rapid onset**
- **More linked to bipolar disorder than schizophrenia**
- **Increased risk with previous psychosis**

Medication Use and Pregnancy

- **Weigh risks of fetal exposure to untreated maternal depression and anxiety against risks of exposure to medication**
- **Use the lowest possible effective dose of medications with substantial safety data**
- **Avoid medication use in first trimester if possible**
- **Monotherapy preferable to multiple medications**
- **Although congenital malformations not increased, consequences for neonatal and long-term neurologic, behavioral and cognitive development largely unknown**



The goal is to navigate the safest pregnancy and postpartum for women with mental illness

Reproductive Endocrine System Function and BD

Polycystic Ovary Syndrome

- **Among the most common endocrine disorders in women of reproductive age¹**
- **Affects 4% to 6% of reproductive-age women**
- **Leading cause of anovulatory infertility and hirsutism²**
- **Characterized by increased androgen production and ovulatory dysfunction²**

Oral Contraceptive Issues

Drug Interaction Between Some AEDs and Hormonal Contraceptives

- **Hepatic enzyme–inducing AEDs**
 - Increase metabolism, binding, and clearance of hormones¹
 - Increase failure rate of oral, subdermal, and intramuscularly administered contraceptives¹
 - Associated with a 4% to 6% failure rate of oral contraceptives^{2,3}

Sources: 1. Devinsky O, et al. *Neurol Clin.* 1994;12:479-495.
2. Yerby MS. *Epilepsia.* 1991;32(suppl 6):S51-S59.
3. Schachter SC. *Epilepsia.* 1999;40(suppl 9):S20-S25.

Drug Interaction Between Some AEDs and Hormonal Contraceptives (cont)

- **Clinicians often choose a high-dose 50-mcg pill**
 - Increased risk of serious adverse event?
- **Levonorgestrel-releasing intrauterine system (Mirena[®])**
 - An effective new option
- **Oral contraceptives**
 - Reduce lamotrigine levels by 41% to 64%^{1,2}
- **Newer contraceptive methods (eg, vaginal ring)**
 - Lack of data
- **Hormone replacement therapy issues are controversial**

Mirena is a registered trademark of Berlex Laboratories.

Sources: 1. Sabers A, et al. *Epilepsy Res.* 2001;47:151-154.

2. Sabers A, et al. *Neurology.* 2003;61:570-571.

Contraception and AEDs: Summary

- **Drug interactions between AEDs and oral contraceptives are clinically important**
 - AEDs that induce P450 enzymes may reduce the effectiveness of oral contraceptives
 - These studies have not looked at ovulation or pregnancy rates, however
- **Oral contraceptives will significantly decrease lamotrigine blood levels by up to 64%**

Detection of Reproductive Health Dysfunction in Women Taking AEDs

- **Signs/symptoms**

- Weight gain of greater than 7%
- Hirsutism
- Abnormal menstrual cycle (<23 or >35 days)
- Midcycle menstrual bleeding
- Difficulty conceiving or history of early-term miscarriage

- **Monitoring methods**

- Physical and gynecologic exam
- Menstrual diary
 - Note cycle length, duration of flow
- Fasting glucose, insulin, and lipid profile
- Measurement of serum testosterone levels

Conclusions

- Bipolar women report high rates of menstrual disturbances that, in many cases, *precede* the diagnosis and treatment for the disorder
- Mood stabilizers (eg, valproate) may induce reproductive and metabolic abnormalities in some women with BD
- In pregnancy: to limit exposure to **either** illness or treatment, and help patient decide which exposure path poses the **least risk**