# 18 y.o. female with amenorrhea

Olesya Krivospitskaya, MD

Endorama 08/08/2013

# History of past illness:

- 18 y.o. female presented for the evaluation of a secondary amenorrhea
- Menarche at 12
- Irregular menstrual cycles between 12-14 y.o. (10 cycles per year)
- Stopped having menstrual cycles at 14 and no cycles since then
- Reports a hx of acne on her face, upper chest, upper back since13 y.o.
- Gained 40 lbs since that time and developed stretch marks on her abdomen

# Past medical history:

- ***Past medical history:*** bipolar disorder diagnosed at the age of 14
- ***Home medications:*** Depakote-ER, Risperdal, Vilazodone (Vibrid), Melatonin, Guanfacine (Intuniv ER)
- ***Family history:*** Paternal grand grand father with DM2, no fertility problems in her family.
- ***Social history:*** high school student, has younger brother and sister – both healthy. No smoking, alcohol or illegal drugs.

# Review of systems:

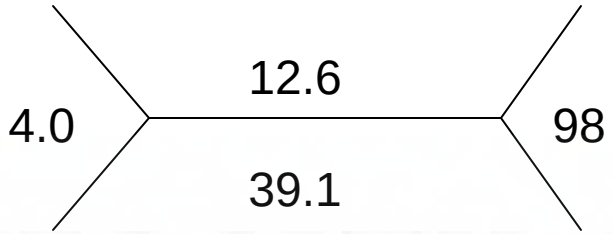
- Constitutional: **gained 40lbs in the last 4 years. Sedentary lifestyle.**
- Cardiovascular: **palpitations in her chest mostly on exertion, but occasionally at rest.**
- Genitourinary: **secondary amenorrhea for the last 4 years.** No galactorhea.
- Musculoskeletal: no weakness.
- Skin: **stretch marks on her abdomen, pale, they appeared with a weight gain. Acne on her face, upper chest and back.** No hirsutism.
- Psychiatric: **anxiety, dysphoric mood.**

# Physical exam:

- Vitals: BP 107/73, pulse, Ht 167.6 cm, Wt 85.05 kg, BMI 30.26 kg/m2
- NEENT: Normocephalic, PERLA.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Soft. Nontender. Bowel sounds are normal. She exhibits no distension and no mass.
- Musculoskeletal/extremities: No weakness, normal range of motion.
- Neurological: AAOx3. Normal DTRs.
- Skin: **Acne face, upper chest and upper back. No significant hirsutism. Stretch marks on her abdomen, less than 0.5cm in diameter, pale color.**

# Labs:

CMP from OSH was reviewed and was unremarkable




TSH 3.11 (0.3-4 mcU/mL)

Free T4 1.12 (0.9-1.7 ng/dL)

Anti-TPO and TG antibodies are negative

Estradiol 25 (30-400 pg/mL)

LH 9.4 mIU/mL

FSH 4.8 mIU/mL

Prolactin 37.02 (4.8-23.3 ng/mL)

Total testosterone 28 (20-60 ng/dL)

Free testosterone 12 (3-9 pg/mL)

Te binding globulin 14 (20-100 nmol/L)

Valproic acid 76 (50-100 mcg/mL)

Urine pregnancy test is negative

# Impressions:

- Does the patient has PCOS?

**Proposed diagnostic criteria for polycystic ovary syndrome**

| NIH consensus criteria 1990[1] (all required) | Rotterdam criteria 2003*[2] (two out of three required) | AES definition 2008[3] (all required) |
|---|---|---|
| Menstrual irregularity due to oligo- or anovulation | Oligo- or anovulation | Clinical and/or biochemical signs of hyperandrogenism |
| Clinical and/or biochemical signs of hyperandrogenism | Clinical and/or biochemical signs of hyperandrogenism | Ovarian dysfunction – oligo-anovulation and/or polycystic ovaries on ultrasound |
| Exclusion of other disorders: NCCAH, androgen-secreting tumors | Polycystic ovaries (by ultrasound) | Exclusion of other androgen excess or ovulatory disorders |

NIH: National Institutes of Health; AES: Androgen Excess Society; NCCAH: nonclassic congenital adrenal hyperplasia; PCOS: polycystic ovary syndrome.
* Rotterdam criteria based upon a 2003 concensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine consensus workshop group).

*References:*

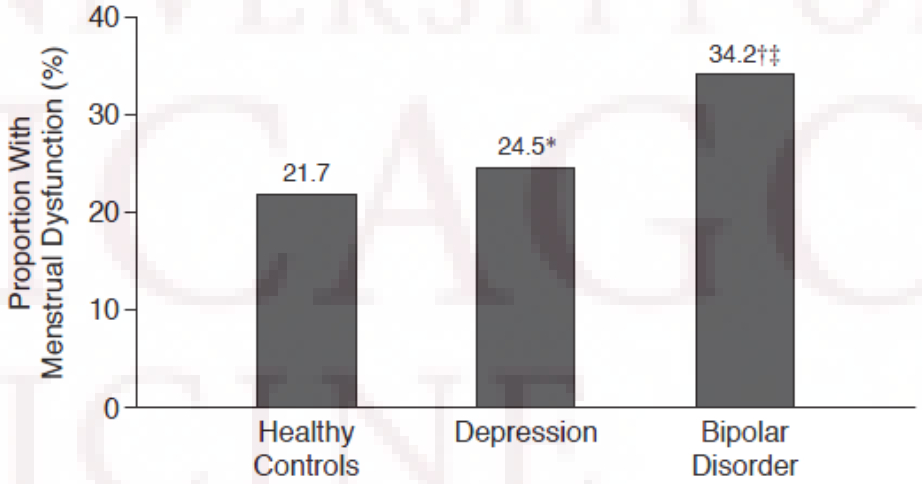
1. *Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In: Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc., Boston 1992. p.377.*
2. *Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19:41.*
3. *Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009; 91:456.*

- PCOS and Bipolar Disorder
- PCOS-like symptoms and hyperprolactinemia in females treated with antiepileptic agents and antipsychotics
- Possible mechanisms of PCOS-like symptoms

# Bipolar disorder and PCOS

- 34.2% of females with bipolar disorder report menstrual abnormalities[1]
- Some authors report that the association between PCOS and bipolar disorder could be related to the use of antiseizure and antipsychotic medication in this population[2]

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.


[1] Joffe H, Kim DR, Foris JM, Baldassano CF, Gyulai L, Hwang CH, McLaughlin WL, Sachs GS, Thase ME, Harlow BL, Cohen LS. Menstrual dysfunction prior to onset of psychiatric illness is reported more commonly by women with bipolar disorder than by women with unipolar depression and healthy controls. J Clin Psychiatry. 2006 Feb;67(2):297-304.

[2] Joffe H, Hayes FJ. Menstrual cycle dysfunction associated with neurologic and psychiatric disorders: their treatment in adolescents. Ann N Y Acad Sci. 2008;1135:219-29.

# Valproic acid and PCOS

**TABLE 1. Studies addressing the association between valproate use and polycystic ovary syndrome (PCOS) features**

| Study | Disorder | Association between Valproate Use and Features of PCOS[a] | Study Design |
|---|---|---|---|
| Isojarvi *et al.*, 1993[19] | Epilepsy | + | Cross-sectional |
| Bilo *et al.*, 2001[18] | Epilepsy | + | Cross-sectional and prospective |
| Morrell *et al.*, 2002[31] | Epilepsy | + | Cross-sectional |
| Morrell *et al.*, 2003[32] | Epilepsy | + | Cross-sectional |
| Betts *et al.*, 2003[30] | Epilepsy | + | Cross-sectional |
| Prabhakar *et al.*, 2007[33] | Epilepsy | + | Cross-sectional |
| Hayes *et al.*, 2007[22] | Epilepsy | + | Randomized trial |
| Joffe *et al.*, 2006[29] | Bipolar | + | Cross-sectional[b] |
| Bilo *et al.*, 1988[26] | Epilepsy | − | Cross-sectional |
| Bauer *et al.*, 2000[34] | Epilepsy | − | Cross-sectional |
| Luef *et al.*, 2002[20] | Epilepsy | − | Cross-sectional |
| Rasgon *et al.*, 2005[38] | Bipolar | − | Cross-sectional |

[a]+ means association between valproate and PCOS features found; − means no association between valproate and PCOS features found.

[b]Excludes women with PCOS that developed prior to diagnosis and treatment of bipolar disorder.

Joffe H, Hayes FJ. Menstrual cycle dysfunction associated with neurologic and psychiatric disorders: their treatment in adolescents. Ann N Y Acad Sci. 2008;1135:219-29.

# Valproic acid and PCOS

J Clin Psychiatry. 2002 Apr;63(4):322-30.

## Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder.

O'Donovan C, Kusumakar V, Graves GR, Bird DC.

Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada. mcpar@is.dal.ca

**Abstract**

**BACKGROUND:** Valproate treatment has been associated with high rates of menstrual abnormalities, hyperandrogenism, and polycystic ovaries in women with epilepsy. This pilot study investigated whether valproate treatment had the same associations in women with bipolar disorder.

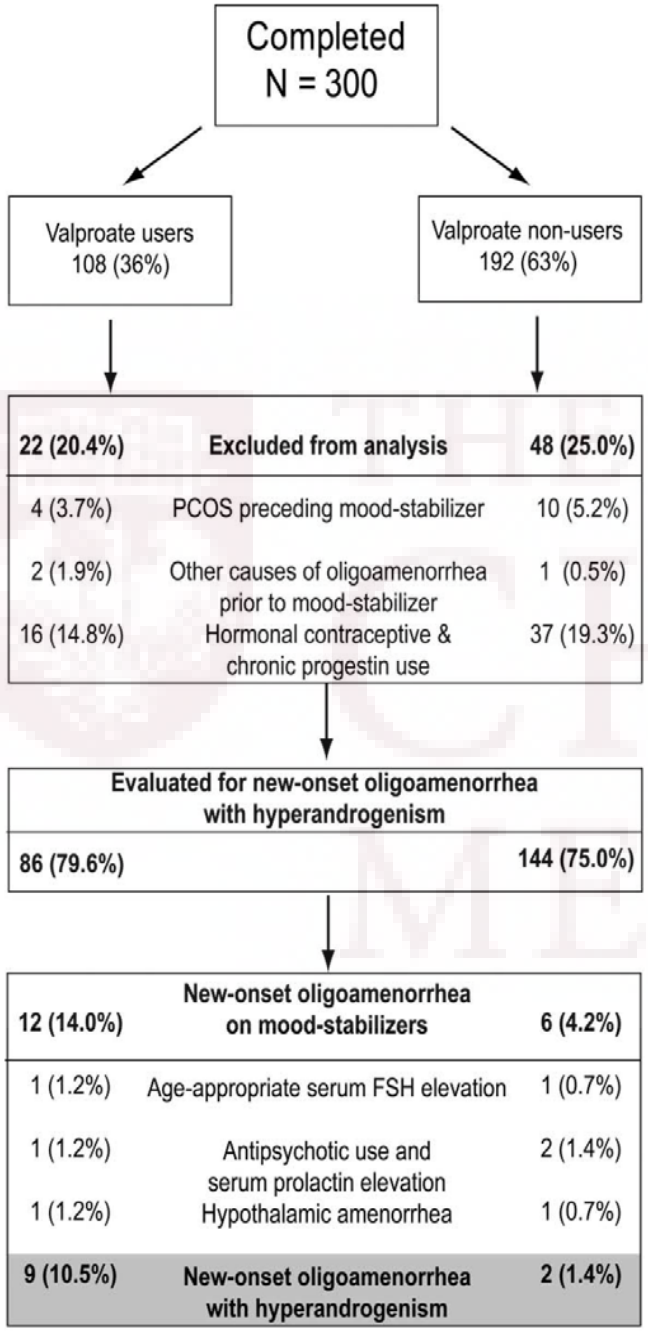
**METHOD:** One hundred forty outpatient women with a DSM-IV diagnosis of bipolar disorder (aged 15-45 years) were surveyed on their medical, psychiatric, and reproductive health history. Thirty-two women met entry criteria for the study and were divided into 2 groups: (1) those currently receiving valproate (valproate, N = 17) and (2) those who were not currently taking valproate (nonvalproate, N = 15). These 2 groups were compared with a normal (never diagnosed with a psychiatric disorder) control group of 22 women. Women in the valproate group with current menstrual problems (N = 7) underwent further assessment for the presence of polycystic ovaries and hyperandrogenism.

**RESULTS:** The age at onset of menses, mean length of menstrual cycle, and mean length of menses were not significantly different between the groups. Significantly more women reported menstrual abnormalities in the valproate group (47%) than women not receiving valproate (13%) and controls (0%). Forty-one percent of women with bipolar disorder taking valproate had polycystic ovary syndrome.

**CONCLUSION:** These results suggest high rates of menstrual disturbances and polycystic ovary syndrome in women with bipolar disorder currently receiving valproate.

PMID: 12000206 [PubMed - indexed for MEDLINE]

O'Donovan C, Kusumakar V, Graves GR, Bird DC. Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder. J Clin Psychiatry. 2002 Apr;63(4):322-30.



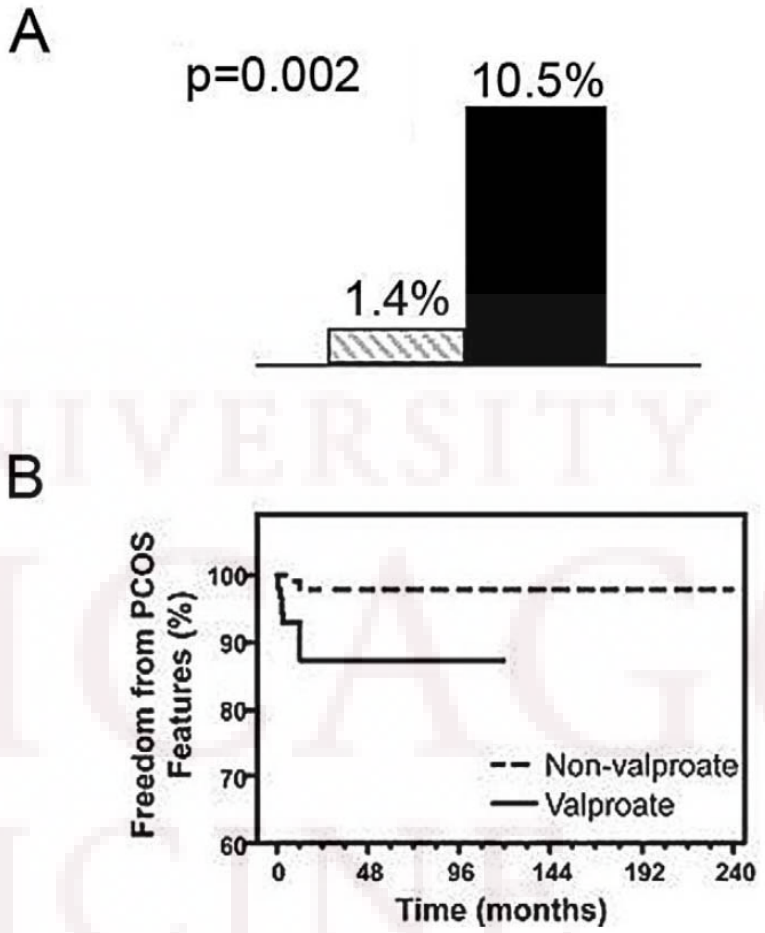




**Figure 2. (A)** Proportion of 86 valproate users (dark bar) and 144 valproate nonusers (striped bar) who developed new-onset oligoamenorrhea with hyperandrogenism and **(B)** Kaplan-Meier survival curve indicating the number of months until onset of new-onset oligoamenorrhea with hyperandrogenism developing on valproate (solid line) and nonvalproate (dashed line) mood stabilizers (log-rank $\chi^2 = 108.1$, $p < .001$).

Joffe H, Cohen LS, Suppes T, McLaughlin WL, Lavori P, Adams JM, Hwang CH, Hall JE, Sachs GS. Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. Biol Psychiatry. 2006 Jun 1;59(11):1078-86. Epub 2006 Jan 31.

# PCOS features in adolescents taking valproic acid

- PCOS features develop more commonly among those who are younger when valproate treatment is begun.
- Among adolescents and adult women (13–40 years) with epilepsy who were randomized to valproate, **hyperandrogenemia and ovulatory dysfunction developed in 44% of women 13–25 years old, but only in 24% of those who were over 25 years** old when they started valproate treatment.[1]
- Other studies in epilepsy have found **polycystic ovarian morphology and/or an elevated testosterone level in 80% of women who started taken valproate before age 20**.[2]

[1] Morrell MJ, Hayes FJ, Sluss PM, Adams JM, Bhatt M, Ozkara C, Warnock CR, Isojärvi J. Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. Ann Neurol. 2008 Aug;64(2):200-11.

[2] Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med. 1993 Nov 4;329(19):1383-8.

# PCOS features in adolescents taking valproic acid

**TABLE 2. Valproate use in girls with epilepsy during the pubertal transition**

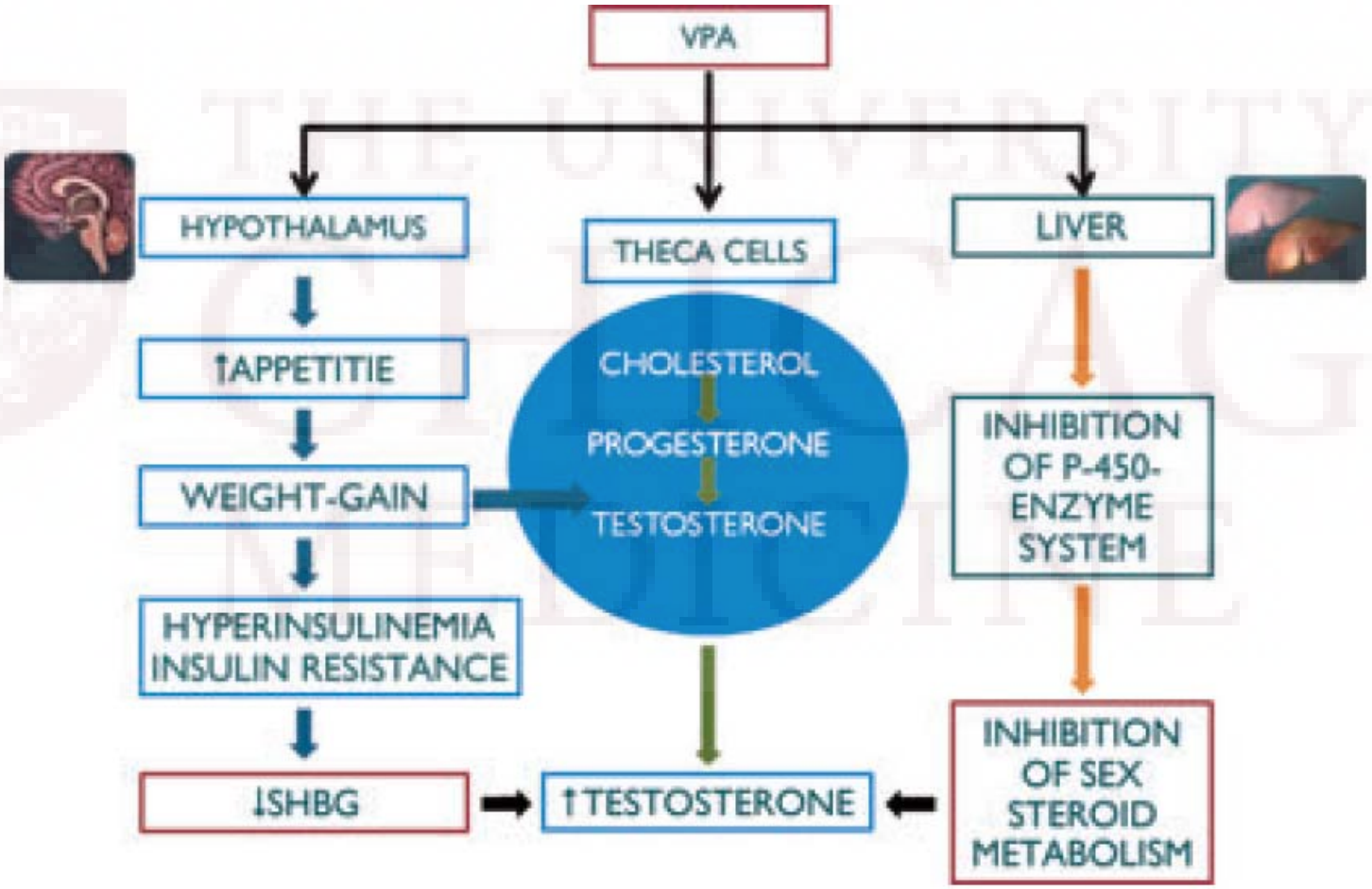
| | No. of Girls with Epilepsy | Age (yr) | Menstrual Irregularities[a] | Androgen Levels | Obesity/ Weight Gain | Insulin | PCOS |
|---|---|---|---|---|---|---|---|
| Rattya *et al.*, 1999[44] | 77 | 8–18 | NR | NR | ↑ | ~ | NR |
| Vainionpaa *et al.*, 1999[43] | 41 | 8–18 | ~ | ↑ (all pubertal stages) | ↑ | ~ | NR |
| El-Khayat *et al.*, 2004[41] | 66 | 8–18 | NR | ↑ (post-pubertal) | ↑ (post-pubertal) | ~ | ~ |
| Mikkonen *et al.*, 2004[24] | 69 | 8–18 | NR | ↑ | NR | NR | ↑ |
| de Vries *et al.*, 2007[40] | 88 | 6–20 | ~ | ↑ (post-pubertal) | ~ | ~ | ~ |

[a]Among postpubertal girls only. NR = not reported; ~ means no abnormality found.

- Given that postpubescent girls have a high incidence of anovulation, it is possible that the relative immaturity of the HPG axis at this time period makes it more vulnerable to perturbation.

Joffe H, Hayes FJ. Menstrual cycle dysfunction associated with neurologic and psychiatric disorders: their treatment in adolescents. Ann N Y Acad Sci. 2008;1135:219-29.

# Mechanisms of proposed hyperandrogenism by valproic acid

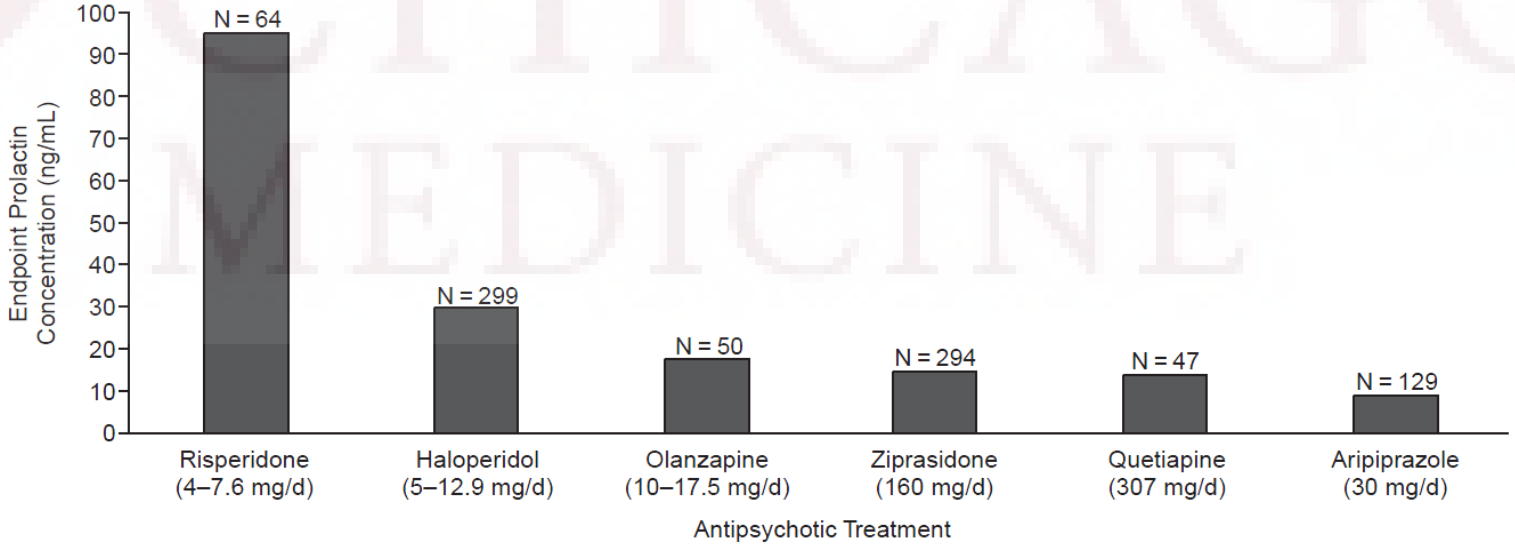



Verrotti A, D'Egidio C, Mohn A, Coppola G, Parisi P, Chiarelli F. Antiepileptic drugs, sex hormones, and PCOS. Epilepsia. 2011 Feb;52(2):199-211.

# Antipsychotic medications and hyperprolactinemia

- Antipsychotic medications, that work as D2 dopamine receptor antagonists, are associated with hyperprolactenemia secondary to reduced dopaminergic inhibition of prolactin secretion.

Figure 1. Mean Plasma Prolactin Levels After 4 to 8 Weeks of Antipsychotic Treatment[a]




[a]Reprinted with permission from Perkins.[3]

Henderson DC, Doraiswamy PM. Prolactin-related and metabolic adverse effects of atypical antipsychotic agents. J Clin Psychiatry. 2008;69 Suppl 1:32-44.

# Antipsychotic medications and adverse events

Table 1. Frequency of Adverse Event Reports by Antipsychotic[a]

| Drug | Pituitary Tumor[b] | Hyperprolactinemia[b] | Galactorrhea | Amenorrhea | Gynecomastia[b] | Total[c] |
|---|---|---|---|---|---|---|
| Risperidone | 54 | 702 | 530 | 445 | 118 | 1247 |
| Olanzapine | 11 | 37 | 17 | 21 | 23 | 93 |
| Haloperidol | 9 | 32 | 49 | 24 | 28 | 104 |
| Ziprasidone | 6 | 12 | 13 | 2 | 4 | 30 |
| Clozapine | 4 | 15 | 16 | 17 | 7 | 46 |
| Quetiapine | 1 | 13 | 12 | 3 | 5 | 28 |
| Aripiprazole | 0 | 5 | 5 | 2 | 4 | 16 |
| Total[c] | 77 | 796 | 630 | 503 | 186 | 1530 |

[a]Reprinted with permission from Szarfman et al.[29]
[b]Adverse events were studied by combining several event codes.
[c]Totals are not the sum of the preceding columns or rows; a single report may mention > 1 event and/or > 1 antipsychotic drug.

Henderson DC, Doraiswamy PM. Prolactin-related and metabolic adverse effects of atypical antipsychotic agents. J Clin Psychiatry. 2008;69 Suppl 1:32-44.

# Antipsychotic medications and metabolic effects

**Table 2. Atypical Antipsychotics and Metabolic Abnormalities[a]**

| Drug | Weight Gain | Risk for Diabetes | Worsening Lipid Profile |
|---|---|---|---|
| Clozapine | +++ | + | + |
| Olanzapine | +++ | + | + |
| Risperidone | ++ | D | D |
| Quetiapine | ++ | D | D |
| Aripiprazole[b] | +/– | – | – |
| Ziprasidone[b] | +/– | – | – |

[a]Reprinted with permission from American Diabetes Association.[36]
[b]Newer drugs with limited long-term data.
Abbreviations: + = increase effect; – = no effect; D = discrepant results.

**Table 3. ADA Monitoring Protocol for Patients Given Atypical Antipsychotics[a,b]**

| Clinical Parameter | Baseline | 4 Weeks | 8 Weeks | 12 Weeks | Quarterly | Annually | Every 5 Years |
|---|---|---|---|---|---|---|---|
| Personal/family history | ✓ | | | | | ✓ | |
| Weight (BMI) | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Waist circumference | ✓ | | | | | ✓ | |
| Blood pressure | ✓ | | | ✓ | | ✓ | |
| Fasting plasma glucose | ✓ | | | ✓ | | ✓ | |
| Fasting lipid profile | ✓ | | | ✓ | | | ✓ |

[a]Reprinted with permission from American Diabetes Association.[36]
[b]More frequent assessments may be warranted based on clinical status.
Abbreviations: ADA = American Diabetes Association, BMI = body mass index.

Henderson DC, Doraiswamy PM. Prolactin-related and metabolic adverse effects of atypical antipsychotic agents. J Clin Psychiatry. 2008;69 Suppl 1:32-44.

# Take home points:

- PCOS is more prevalent in patients with bipolar disorder that in general population
- PCOS-like symptoms in patients with bipolar disorder could be related to use of antiseziure medications and antipsychotics
- There is little data exist about the management of PCOS-like symptoms in this population, tapering or switching the offending medication should be attempted when possible

# References


- Joffe H, Kim DR, Foris JM, Baldassano CF, Gyulai L, Hwang CH, McLaughlin WL, Sachs GS, Thase ME, Harlow BL, Cohen LS. Menstrual dysfunction prior to onset of psychiatric illness is reported more commonly by women with bipolar disorder than by women with unipolar depression and healthy controls. J Clin Psychiatry. 2006 Feb;67(2):297-304.

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