Polycystic Ovarian Syndrome is Associated with Valproate Use in Bipolar Women

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BACKGROUND

- **Does valproate (VPA) predispose to polycystic ovarian syndrome (PCOS)?**
  - Contradictory findings in epilepsy and bipolar disorder
  - HPG abnormalities in epilepsy: Confounder? Predisposing factor?
- **PCOS occurs in 4–7% of women**
  - Infrequent ovulation (oligomenorrhea, amenorrhea) and hyperandrogenism (hirsutism, acne, male-pattern alopecia, or elevated serum androgen levels)
  - Obesity and insulin resistance in majority
  - PCO morphology in most PCOS cases but also independent of PCOS
  - Health consequences: infertility, diabetes, ?cardiovascular disease, ?endometrial cancer

Hypotheses: **(1)** VPA exposure predisposes to PCOS
(2) Association seen in women with bipolar disorder, independent of epilepsy

METHODS

Subjects

- Women age 18–45 years with bipolar disorder
- 16 STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) sites
- Taking ≥ one established or putative "mood-stabilizer" (valproate, lithium, lamotrigine, gabapentin, topiramate, carbamazepine, oxcarbazepine) for ≥ 3 months

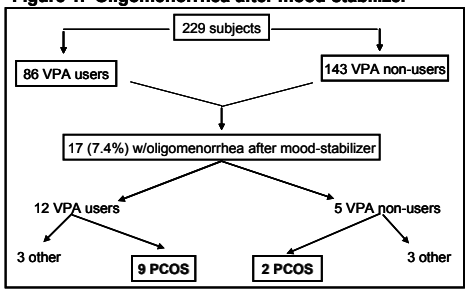
Study Design

- **Cohort study**: current VPA use = "exposed"; use of mood-stabilizers other than VPA = "non-exposed"
  - Retrospective assessment of menstrual-cycle patterns
  - Cross-sectional collection of menstrually timed serum hormone assays and skin examinations
- **Primary outcome measure:** treatment-emergent PCOS after initiation of mood-stabilizer
  - Oligomenorrhea: <10 menstrual cycles in the past year developing after mood-stabilizer AND
  - Hyperandrogenism: ≥ one of hirsutism (Ferriman-Gallwey >5), acne, male-pattern alopecia, elevated serum androgen levels (testosterone, calculated free testosterone, DHEAS)
- **Analytic plan:** compare incidence of treatment-emergent PCOS after VPA *vs.* non-VPA mood-stabilizers

RESULTS

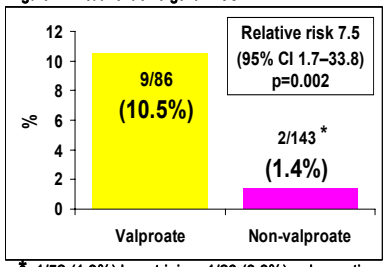
- **300 completed assessment**
  - Excluded if: PCOS prior to mood-stabilizer (n=14); BCP use (n=54); progestin use (n=2); PCOS with elevated prolactin (n=1), TSH (n=0), FSH (n=0)
- **229 evaluated for treatment-emergent PCOS**
  - 86 (37.6%) VPA users *vs.* 143 (62.4%) VPA non-users
  - 45 (52.35%) of 86 VPA users on VPA as only mood-stabilizer
  - Age 33.5 ± 7.1 yrs
  - 89.5% Caucasian
  - Bipolar disorder I (57.6%), II (34.1%), NOS (8.3%)

Figure 1. Oligomenorrhea after mood-stabilizer



RESULTS (cont.)

Figure 2. Treatment-emergent PCOS

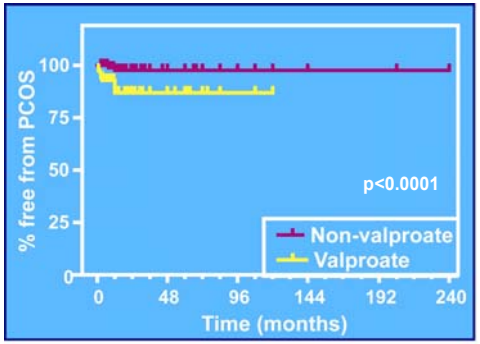


* 1/52 (1.9%) lamotrigine, 1/26 (3.8%) gabapentin

Treatment-emergent PCOS after VPA started

- **9/86 (10.5%) VPA users *vs.* 2/143 (1.4%) of VPA non-users developed treatment-emergent PCOS (p=0.002)**
  - Rapid onset of oligomenorrhea
    Median 3 mo, range 1–12 mo
  - Associated with obesity (p<0.01)
    VPA + PCOS: median BMI 36.0, range 25.8–47.5 kg/m²
    VPA – PCOS: median BMI 26.3, range 17.7–52.9 kg/m²
  - Associated with insulin resistance (p=0.04)
    VPA + PCOS: HOMA-IR 3.1, range 0.6–8.1
    VPA – PCOS: HOMA-IR 1.7, range 0.4–12.2
  - Developed in 3/45 (6.7%) with VPA as only mood-stabilizer *vs.* 6/41 (14.6%) using VPA + other mood-stabilizers (p=0.23)
  - Developed with first VPA trial in 7/9 (78%)
  - Younger age at first VPA use is risk factor (p=0.03)
    Median 23, range 13–40 yrs *vs.* 31, range 11-44 yrs

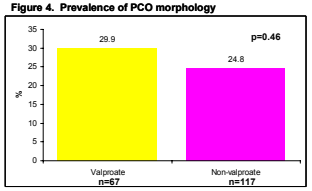
Figure 3. Kaplan-Meier curve of time to PCOS



PCO morphology

- Optional pelvic ultrasound
- VPA use not associated with PCO morphology (p=0.46)

Figure 4. Prevalence of PCO morphology



CONCLUSION

- Valproate use predisposes to PCOS in women with bipolar disorder, with 1 in 10 women developing PCOS after initiation of valproate
- Treatment-emergent PCOS develops rapidly with valproate use and is associated with obesity and insulin resistance
- Reversibility of treatment-emergent PCOS warrants further study
- Risk of PCOS should be conveyed to women with bipolar disorder taking valproate and PCOS symptoms should be monitored, especially in the first year of valproate use

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