# CURRENT LITERATURE

## WHAT VALPROATE DOES AND DOESN'T DO

### Higher Androgens and Weight Gain with Valproate Compared with Lamotrigine for Epilepsy

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PURPOSE: Valproate (VPA) is used widely for the treatment of epilepsy but has been associated with hyperandrogenism, hyperinsulinemia, and dyslipidemia. The mechanism for these associations is unknown, but they have been hypothesized to be secondary to VPA-associated weight gain. This study was conducted to test the hypothesis that the antiepileptic drug (AED) lamotrigine (LTG), which also has a broad spectrum of antiseizure efficacy, would not be associated with endocrine abnormalities and would not cause weight gain.

METHODS: This open-label, cross-sectional study compared (a) endocrine and lipid measures during the early follicular phase of the menstrual cycle; (b) prevalence of menstrual disorders (from patient diaries recorded over three cycles); and (c) body weight of women with epilepsy receiving LTG monotherapy ($n = 119$) with those receiving VPA monotherapy ($n = 103$) for <5 years.

RESULTS: Mean total serum testosterone and androstenedione levels were higher ($P < 0.02$) in the VPA group compared with the LTG group. More LTG patients (87%) than VPA patients (77%) reported regular menstrual cycles at the screening visit. The prevalence of anovulation did not differ between LTG and VPA. Mean high-density lipoprotein cholesterol levels were higher ($P < 0.01$) with LTG compared with VPA as were low-density lipoprotein and total cholesterol levels ($P < 0.05$). Mean total insulin levels did not significantly differ between the groups. Whereas mean body weight in LTG patients did not differ between the time LTG treatment was initiated and the study visit, mean weight in VPA patients increased by 3.7 kg.

CONCLUSIONS: Compared with LTG monotherapy, VPA monotherapy was associated with weight gain and higher androgen levels in women with epilepsy. These data suggest that the hyperandrogenism observed in some women using VPA for epilepsy may be secondary to drug therapy. LTG monotherapy may be more appropriate than VPA therapy for women in whom reproductive endocrine or metabolic abnormalities are potential concerns (i.e., women with concerns about weight gain, diabetes, hirsutism, polycystic ovary syndrome, menstrual dysfunction, or infertility).

### COMMENTARY

The recent report by Morrell and colleagues is as significant for what it does not show as for what it does reveal regarding the differences in metabolic parameters with lamotrigine (LTG) use compared with valproate (VPA) use. In this study, ~100 women of reproductive age, taking either long-term VPA or LTG monotherapy for epilepsy, were monitored prospectively for menstrual cycle length and variability as well as for the occurrence of ovulation over three menstrual cycles. Additionally, total testosterone levels and levels of its interconvertible metabolite, androstenedione, were measured, along with insulin and lipid levels.

This cross-sectional study showed that serum testosterone and androstenedione were significantly higher in the VPA group compared with the LTG group, but the mean levels for both groups were within the normal reference ranges for both androgens. The ranges of androgen levels for each drug were not provided; therefore it is unclear whether any individual levels were outside the reference ranges with either treatment.

Insulin levels and all lipid levels, adjusted for body weight, were slightly, but not significantly, higher in the LTG group compared with the VPA group. No significant differences were found in menstrual cycle length or variability or in the prevalence of anovulation between treatment groups. The groups were nearly identical for these parameters.

If at any time subjects in either group had used VPA, they reported weight gain. Weight was not prospectively monitored in this study. Neither LTG nor VPA was initiated during the study; therefore monitoring weight changes after starting these medications was not part of the study design.

Increased androgen levels and weight gain are associated with VPA use. The data from the study of Morrell et al. document that the increase in androgen levels for women of

reproductive age taking VPA will likely not be outside the expected range for age and gender. The increase in androgen levels may be expected from the cytochrome P450 enzyme–inhibiting action of VPA. Cytochrome P450 2C19, and to a lesser extent, P450 2C9, catalyze the reversible 17-position oxidation of testosterone to form androstenedione (1). Inhibition of this pathway by VPA therefore could increase the levels of testosterone. Another antiseizure medication that inhibits P450 2C19, oxcarbazepine, also produces increased testosterone levels (2) in men, but does not cause significant weight gain. Topiramate, which also is a P450 2C19 inhibitor, has not been evaluated for its effect on androgen levels. The effect of these antiseizure medications on androgen levels could be predicted by their cytochrome P450 enzyme–inhibiting activity. However, the clinical importance of the elevations documented thus far, in terms of sexuality, androgenization, and occurrence of polycystic ovarian syndrome (PCOS), is unclear.

A recent study of metabolic and endocrine functioning in nonepileptic rhesus monkeys exposed to VPA for 12–15 months, at serum levels similar to patient levels, also revealed no alteration in any endocrine markers (3). Endocrine abnormalities that characterize PCOS, such as increased androgen levels and an increase in the ratio of follicular luteinizing hormone/follicular stimulating hormone, did not occur after VPA treatment. Histologic examination of all animals' ovaries showed no features of PCOS but did show evidence of normal ovulation. The occurrence of regular, ovulatory menses was not altered by VPA treatment, although the animals did gain weight. The insulin response to a glucose tolerance test also was unchanged by VPA treatment. This study is probably a good approximation of what might occur in nonepileptic women with VPA use, because rhesus monkeys have a menstrual cycle very similar to that of humans. Epilepsy itself, known to be a contributing issue to the increased risk of ovarian cysts in women with epilepsy, may be the key, important factor. The data also are consistent with the observations of Morrell et al., reinforcing the view that, at least in the short term, VPA induces relatively minor perturbations in endocrine physiology.

These reports are extremely valuable to clearing up the cloudy picture of what VPA does and does not do. It does cause weight gain and mild increases in androgen levels. It does not per se cause irregular or anovulatory menstrual cycles, increased lipid levels, or insulin resistance. The increased risk of ovarian cysts reported in women with epilepsy taking VPA may reflect synergism between the effects of the drug and changes in the reproductive neuroendocrine system associated with epilepsy.

Caution regarding VPA use in women of reproductive age must be observed, because of the clear-cut increased risk in neural tube defects to the exposed fetus. Unwanted weight gain from a medication is never welcomed and must be factored into the risk-to-benefit ratio when prescribing it. However, at least in the short term, other reproductive endocrine risks do not appear to be significantly increased with VPA use.

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## References

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