Sex Differences in the Efficacy and Side Effects of Lamotrigine and Levetiracetam

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BACKGROUND

Sex differences in epilepsy are well understood, but their mechanisms and treatments remain unclear. Research on **genes**, **sex hormones**, and **neurosteroids** influences epilepsy development and seizure characteristics. Considering sex as a biological variable could lead to more effective, sex-specific treatment strategies. Additionally, sex influences the pharmacokinetics of antiepileptic drugs, with estrogen levels significantly affecting women's metabolism.

- LEVETIRACETAM (LEV) - broad-spectrum anticonvulsant with a unique mechanism of action that modulates neurotransmitter release and inhibits N-type calcium channels, contributing to reduced neuronal excitability.
- LAMOTRIGINE (LTG) - primary mechanism of action is thought to involve the blockade of voltage-sensitive sodium channels, which stabilizes neuronal membranes and inhibits the release of excitatory neurotransmitters like glutamate. It may also affect calcium channels.

OBJECTIVES

The aim of the study was to conduct a comprehensive review of studies published over the last two decades that investigate sex-related variations in the effectiveness, metabolism, and tolerability of lamotrigine and levetiracetam in epilepsy management.

RESULTS

Women treated with levetiracetam were 27 % more likely to develop **treatment resistant epilepsy** than men.

PD cause:
1. **Estrogen and progesterone fluctuations**: E2 has pro-epileptic effects enhancing glutamate activity, P has anti-epileptic effects enhancing GABA-ergic activity [1]
2. Women show hormone-driven fluctuations in GABA_AR subunits, particularly α4, δ, and γ2 [2]

PK cause:
1. Women receiving on average higher medication doses, since women in general have a lower body weight than males.
2. Women on average receive more medications that can affect the metabolism of levetiracetam.

Combined oral contraceptives (OC) and **lamotrigine** can interact bi-directionally, resulting in possible therapeutic failure of either treatment, which may lead to **unintended pregnancy** and/or **increased seizure activity**. It is important to mention that OC failure was the cause of one in four unplanned pregnancies in women with epilepsy. [3]

PD cause:
The estrogen compound used is 17-a-ethinyl estradiol (EE). EE is metabolized by cytochrome P450, uridine disphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 and SULT.
EE may induce UGT enzymes, thereby affecting the metabolism of drugs principally metabolized by this route such as lamotrigine and inhibit CYP enzymes. The clinical relevance came to be that the serum concentrations of lamotrigine were found to be decreased by 50%, and therapeutic failure in the form of increased seizure frequency has been reported. [3]

Men treated with levetiracetam can also progress to treatment resistant epilepsy due to various factors:

PD cause:
1. Men don't experience the same hormonal fluctuations as women do. [1]
2. Men have more stable expression of GABA-AR subunit γ2 and α1. [2]

PK cause:
1. Since LEV is eliminated through the kidneys, renal function differences in the 2 sexes may affect their efficacy.
2. Men have a higher creatinine clearance and so a more stable LEV elimination than women.
3. And don't experience the drastic increases of renal clearance in pregnancy that women do.

Adrostenedione levels of men treated with LEV and LTG were also significantly lower and testosterone levels of men treated with LTG were also lower.

PD cause:
1. Lamotrigine induces the UGT1A4 enzyme (as mentioned previously), therefore enhances androgen metabolism. [4]
2. Androstenedione and testosterone are metabolized via glucuronidation in the liver, meaning LTG increases their breakdown and reduces circulating levels. [4]

PK cause:
1. LTG is primarily eliminated through renal excretion, and its metabolites can increase renal clearance of steroid hormones.
2. Testosterone and androstenedione metabolites may be excreted more rapidly than in control patients.

CONCLUSIONS

- Women experience **more therapy-resistant epilepsy** due to hormonal fluctuations affecting GABA_AR expression.
- Men generally have **more stable drug responses**.
- The personalized antiepileptic therapy treatment should include hormone-based adjustments for women (e.g., progesterone therapy) and sex-specific dosing strategies for antiepileptic drugs.
- Practically: If using hormonal contraception, lamotrigine doses **need to be increased**.
- If stopping contraception, the lamotrigine dose should **be reduced** gradually to prevent toxicity.
- Men have more stable lamotrigine levels, requiring fewer dose adjustments.
- Unlike lamotrigine, levetiracetam is not metabolized by liver enzymes making it less affected by estrogen and pregnancy.

Bibliography: [1] M. Soledad Cepeda, Rachel E. Teneralli, David M. Kern et al., "Differences between men and women in response to antiseizure medication use and the likelihood of developing treatment resistant epilepsy", 2022, Epilepsia Open. 2022; 7:598-607 [2] Pandya, Madhavi, Thulani H. Palpagama, Clinton Turner, Henry J. Waldvogel, Richard L. Faull, and Andrea Kwakowsky. 2019. "Sex- and Age-related Changes in GABA Signaling Components in the Human Cortex". *Biology of Sex Differences* 10 (1), [3] Arne Reimers, Eylert Brodtkorb, Anne Sabers et al., "Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations", 2014, Seizure, [4] Sigrid Svalheim, Erik Taubøll, Gerhard Luef et al., "Differetial effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults", 2009, Epilepsy and Behaviour