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Review

# Gender issues in antiepileptic drug treatment

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ABSTRACT

The purpose of this review is to discuss gender-related aspects in the, pharmacokinetics, effects, selection and use of antiepileptic drugs (AED). In general, there are few known gender related differences in pharmacokinetics or efficacy of AEDs. Conversely, gender has a significant influence on the susceptibility to certain adverse effects, not the least those involving alterations in sex hormone metabolism. Particularly relevant are the teratogenic effects of AEDs, with important differences among AEDs in their potential to cause adverse effects on the fetus when used during pregnancy. Pregnancy can also markedly affect the pharmacokinetics of several AEDs, and dose adjustments are often needed during pregnancy to maintain seizure control. Some treatments that are used only by women, such as contraceptive steroids and hormone replacement therapy, can also interact with AEDs to an extent that may affect the utilization of both the AEDs and the other drug.



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## Introduction

With the exception of a few epilepsy syndromes, there are no major gender differences in the incidence or prevalence of epilepsy (Beghi and Beghi, 2013), and the response to antiepileptic drug (AED) treatment in general appears to be similar for men and women. Nevertheless gender

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can impact on antiepileptic treatment in many ways. This is mainly related to either the physiological phases of life that are unique to women, such as the menstrual cycle, pregnancy, and menopause, or to pharmacokinetic interactions between AEDs and other drugs that are used preferentially in only one gender, such as contraceptives or hormone replacement therapies. This may have a major gender specific influence on drug selection as well as on dose optimization and monitoring of treatment, as discussed further in this review.

## Gender and pharmacokinetics

### *Gender differences in pharmacokinetics*

Potential gender-related differences in the pharmacokinetics of AEDs have not been systematically explored. While modest differences have been reported for a few AEDs in occasional studies (Bockbrader et al., 2011; Greenblatt et al., 1981; Ibarra et al., 2013; Marino et al., 2012; Markoula et al., 2014; Perucca et al., 2008; Smith et al., 1979), a review of available evidence does not suggest that gender influences the absorption, distribution or elimination of AEDs in a consistent and clinically relevant manner (Johannessen Landmark et al., 2012),

### *Effects of menstrual cycle on AED pharmacokinetics*

Given the ability of exogenous estrogens to accelerate the rate of metabolism of AEDs that are glucuronidated, in particular lamotrigine (Reimers et al., 2005), one might expect that the natural fluctuations in estradiol levels over the menstrual cycle could have similar effects. However, data on variations in serum AED levels with the menstrual cycle phase are scarce, limited to a few of all AEDs, and partly contradictory. In one study, 12 women on lamotrigine and 12 on valproic acid were studied at two time points, corresponding to high and low reproductive estrogen level phases, respectively. A non-significant 31% decline in lamotrigine levels was observed during the mid-luteal (high estrogen) phase compared to early-mid follicular phase. Valproic acid levels declined by only 8% (Herzog et al., 2009). Another study sampled more frequently during the menstrual cycle in 7 women with lamotrigine monotherapy. No significant fluctuation in lamotrigine clearance was observed during the cycle (Wegner et al., 2009), similar to findings in an earlier report based on two young women on lamotrigine (Reimers et al., 2006). Hence, there is no evidence from the limited available data that fluctuations in endogenous hormones have a significant impact on serum concentrations of AEDs cleared extensively by glucuronidation, such as lamotrigine or valproic acid. Data are also limited and partly conflicting regarding drugs metabolized by cytochrome 450 (CYP). A small study of seven patients found no correlation between serum concentrations of phenytoin, phenobarbital, or carbamazepine and plasma estradiol or progesterone concentrations over the menstrual cycle (Bäckström and Jorpes, 1979). In contrast, a study comprising 37 women with epilepsy with increase in seizure frequency during the premenstrual or menstrual phase (catamenial epilepsy), reported a significant decline in plasma concentrations of phenytoin between days 27 and 28 of the menstrual cycle, while phenobarbital levels remained relatively stable (Rosciszewska et al., 1986).

### *Effects of pregnancy on AED pharmacokinetics*

The physiological changes that take place during pregnancy can significantly affect the pharmacokinetics of AEDs. The most important mechanisms are increased metabolic rate for AEDs that are metabolized and increased renal clearance for drugs eliminated by the kidneys, both leading to declining serum drug concentrations as pregnancy progresses (Tomson et al., 2013). Information on gestational effects on pharmacokinetics is very limited for many of the newer or newest AEDs, such as felbamate, eslicarbazepine acetate, gabapentin, lacosamide, perampanel, retigabine, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide (Tomson et al., 2013). The most pronounced effects seem to occur with lamotrigine. Serum lamotrigine concentrations begin to fall already during the first trimester but the decline is most pronounced in weeks 32–35 (Öhman et al., 2000; Tran et al., 2002; Pennell et al., 2004; Petrenaite et al., 2005; de Haan et al., 2004; Reimers et al., 2011). The extent of this effect is variable but on average serum lamotrigine concentrations decrease by 50–70% to return to pre-pregnancy levels within days after delivery (Tomson et al, 2013). Serum concentrations of oxcarbazepine's mono-hydroxy-derivative (MHD), which like lamotrigine is cleared extensively by glucuronidation, decline slightly less, on average by 30%–40% (Christensen et al., 2006; Mazzucchelli et al., 2006; Petrenaite and Sabers, 2009). AEDs cleared by other routes can also be affected significantly by pregnancy. Serum concentrations of levetiracetam have been reported to fall from pre-pregnancy levels by 40% to 60% at the end of pregnancy (Tomson et al., 2007; Westin et al., 2008). Topiramate levels decline by 30–40% (Ohman et al., 2009, Westin et al., 2009) and phenobarbital by 50–55% (Battino et al., 1984). In contrast, serum carbamazepine concentrations generally remain fairly stable throughout pregnancy (Tomson et al., 1994). The decline in total serum valproic acid concentrations during pregnancy appears to be due to a reduction in serum protein binding, without any significant change in the pharmacologically active, unbound concentrations (Yerby et al., 1992). A more complete review of changes in AED disposition during pregnancy has been published recently (Tomson et al., 2013).

Clinical observations from in particular lamotrigine- and oxcarbazepine-exposed pregnancies indicate that the decline in serum concentrations is associated with an increased risk of seizures (Tran et al., 2002, Pennell et al., 2004, de Haan et al., 2004, Petrenaite et al., 2004, Mazzucchelli et al., 2006; Petrenaite and Sabers, 2009). In a prospective study of pregnancies with lamotrigine monotherapy, the risk of deterioration in seizure control was significantly increased when serum lamotrigine concentrations declined by more than 35% from the individual optimal serum concentration before pregnancy (Pennell et al., 2008). In the prospective observational EURAP study, pregnancies with lamotrigine were less likely to be seizure-free and were at greater risk of deterioration in seizure control from the first to second or third trimester compared with other monotherapies, which could be a reflection of insufficient dose adjustments during pregnancy (Battino et al., 2013). Because the effects of pregnancy on AED disposition can be difficult to predict in the individual patient, monitoring of serum concentrations of AEDs such as lamotrigine, MHD (for oxcarbazepine-treated patients) and levetiracetam, is frequently recommended during pregnancy. Dose adjustments to maintain the individual optimal pre-pregnancy serum level should be considered.

### *Menopause and pharmacokinetics*

Menopause is another phase in a woman's life with profound changes in hormone levels. Whether such changes can affect AED levels has been addressed to a very limited extent. A retrospective analysis of data from a therapeutic monitoring service looked at dose/plasma concentration ratios for lamotrigine and carbamazepine by age groups and gender. While the dose/concentration ratios of carbamazepine were similar for men and women in all age groups, there was a decline in this ratio for lamotrigine in women 51–55 years of age, which was not seen in men (Tomson et al., 2010). Another study applied population kinetics to a different therapeutic monitoring database and found no support for an effect of perimenopausal age on clearance of lamotrigine, MHD or carbamazepine (Wegner et al., 2013a). Other AEDs have not been investigated in this regard.

### *Gender-specific pharmacokinetic interactions*

The mechanisms underlying pharmacokinetic drug interactions (e.g., formation of insoluble complexes in the gastrointestinal tract,