



Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit

A unit funded by the FSRH and supported by NHS Greater Glasgow & Clyde to provide guidance on evidence-based practice

CEU Statement (January 2010)

Antiepileptic Drugs and Contraception

SUMMARY

What We Already Know

- Epilepsy itself is a condition for which there are no restrictions on the use of contraceptive methods, but restrictions may apply if certain antiepileptic drugs (AEDs) are used.
- AEDs that induce liver enzymes may reduce the contraceptive efficacy of combined contraceptive methods, progestogen-only pills and progestogen-only implants.
- AEDs that induce liver enzymes do not reduce the efficacy of depot medroxyprogesterone acetate (DMPA), the levonorgestrel-releasing intrauterine system or non-hormonal methods
- Combined hormonal contraception (CHC) increases the clearance of lamotrigine and reduces serum lamotrigine levels.
- Women using lamotrigine should be advised that seizure frequency may increase when initiating CHC, and that lamotrigine side effects may increase in the pill-free interval or when discontinuing CHC.

What This Statement Adds

- There is evidence that progestogen-only methods do not affect lamotrigine levels.
- Lamotrigine levels are not reduced by CHC when lamotrigine is given in conjunction with sodium valproate.
- CHC may increase the clearance of sodium valproate. The clinical significance of this interaction is unknown.
- Long-term treatment with carbamazepine, phenytoin, primidone and sodium valproate is associated with loss of bone mineral density (BMD) and fracture. Whether concomitant use of DMPA leads to further loss of BMD or increases the risk of fracture is unclear.

Background

Interactions between antiepileptic drugs (AEDs) and contraceptive hormones are clinically important due to the risk of contraceptive failure, teratogenicity or reduced seizure control. Understanding of these interactions continues to change as new evidence emerges and new AEDs and contraceptive products become available.

This statement provides updated information based on current pharmacological and epidemiological data. It is intended to supplement previously published guidance from the Faculty of Sexual and Reproductive Healthcare (FSRH) on Drug Interactions with Hormonal Contraception (2005)¹ and to supersede the FRSFH statement on Changes to Prescribing Information for Lamotrigine (2005).² The statement includes reference to newly updated versions of the *UK Medical Eligibility Criteria for Contraceptive Use*³ (Table 1) and the Summary of Product Characteristics (SPC) for lamotrigine.⁴

Current Evidence

Effect of enzyme-inducing AEDs on hormonal contraception

The metabolism of estrogen and progestogen is increased by AEDs that induce cytochrome P450.^{1,5} AEDs may be strong inducers (e.g. carbamazepine and phenytoin) or weaker inducers (e.g. topiramate) (Table 2). There is a lack of good quality evidence on the effect of liver enzyme-inducing AEDs on the efficacy of hormonal contraception. Available evidence suggests that the magnitude of any effect on contraceptive efficacy depends on the dose of hormone(s) and route of administration. These differences are reflected in the 2009 UKMEC categories³ for enzyme-inducing AEDs and different methods (Table 1).

The efficacy of the progestogen-only injectable, depot medroxyprogesterone acetate (DMPA), is not reduced. Guidance relating to epilepsy from the Scottish Intercollegiate Guideline Network (SIGN)¹⁰ and the National Institute for Health and Clinical Excellence (NICE)¹¹ suggests that a reduced dosing interval is necessary. NICE guidance on long-acting

Table 1 2009 United Kingdom Medical Eligibility Criteria for Contraceptive Use (UKMEC) categories for anticonvulsant therapy and contraception³

Anticonvulsant	Combined hormonal methods	Progestogen-only pill	Progestogen-only implant	Progestogen-only injectable	Levonorgestrel-releasing intrauterine system	Copper-bearing intrauterine device
Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	3*	3*	2*	DMPA - 1 NET-EN - 2*	1	1
Lamotrigine	3	1	1	1	1	1

*The consistent use of condoms is recommended.
 UKMEC Category 1: A condition for which there is no restriction for the use of the contraceptive method with the condition or in that circumstance.
 UKMEC Category 2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
 UKMEC Category 3: A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist provider, since use of the method is not usually recommended unless other methods are not available or not acceptable.
 UKMEC Category 4: A condition which represents unacceptable health risk if the method is used.
 DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate.

Table 2 Effect of antiepileptic drugs on cytochrome P450 enzymes⁶⁻⁹

Strong inducers	Less potent inducers	No significant effect
Carbamazepine Eslicarbazepine Oxcarbazepine Phenobarbital Phenytoin Primidone	Rufinamide Topiramate	Benzodiazepines Ethosuximide Gabapentin Lacosamide Levetiracetam Pregabalin Sodium valproate Tiagabine Vigabatrin Zonisamide

reversible contraception suggests no alteration is required¹² and CEU guidance advises the standard dosing interval of 12 weeks.¹ The SPC for Depo-provera[®] states that:

*The clearance of medroxyprogesterone acetate is approximately equal to the rate of hepatic blood flow. Because of this fact, it is unlikely that drugs which induce hepatic enzymes will significantly affect the kinetics of medroxyprogesterone acetate. Therefore, no dose adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.*¹³

Whilst no specific interaction studies have been performed with the etonogestrel-only implant,¹⁴ true failures have been reported in women using AEDs^{15,16} and the SPC for Implanon[®] advises that efficacy may be affected.¹⁴

There is evidence that interactions with the AED topiramate may be dose dependent. In a study of women using a combined oral contraceptive pill (COC) containing 35 µg ethinylestradiol (EE) and norethisterone enanthate (NET-EN), clearance of just EE was slightly to modestly increased with topiramate doses of 200 to 800 mg daily.¹⁷ However, there was no apparent interaction at daily doses of 50 to 200 mg of topiramate in another randomised study using the same COC.¹⁸ This suggests that topiramate has low enzyme induction potential at usual therapeutic doses.

Although certain combinations of enzyme-inducing AED and contraceptive method appear less likely to affect efficacy, the consequences of contraceptive failure are potentially serious. The CEU therefore advises the consistent use of condoms in women using any enzyme-inducing AED with combined hormonal contraception (CHC) (ie, COC, vaginal ring, patch), the progestogen-only pill (POP) or progestogen implant (Implanon). If a COC is chosen, CEU guidance on drug interactions recommends a minimum dose of 50 µg EE (UKMEC 2009 suggests a minimum dose of 30 µg EE) in addition to the consistent use of condoms. For women on long-term enzyme-inducing AEDs, alternative reliable contraceptive methods should be recommended (e.g. DMPA or intrauterine methods).

Effect of enzyme-inducing AEDs on emergency contraception

Women who require emergency contraception while using liver enzyme-inducing AEDs should be advised that an intrauterine device is the preferred option.¹⁹ Those who prefer to use oral progestogen-only emergency contraception (POEC) may be advised to double the dose of levonorgestrel (LNG) [i.e. take a total of 3 mg LNG (two tablets) as a single dose as soon as possible and within the first 72 hours of unprotected sexual intercourse (UPS)]. There is no

evidence to confirm that this increase in dose is actually required. The emergency contraceptive, ulipristal acetate, is metabolised by cytochrome P450 and its efficacy may be reduced by enzyme-inducing AEDs. Increasing the dose of ulipristal is not currently recommended as there is no evidence that this is effective. The SPC for POEC (Levonelle®)²⁰ and ulipristal acetate (ellaOne®)²¹ do not recommend use in women using enzyme-inducing AEDs.

Effect of lamotrigine on hormonal contraception

Lamotrigine is not thought to induce liver enzymes and thus would not be expected to have any effect on contraceptive efficacy. However, a pharmacokinetic and pharmacodynamic study examining the co-administration of lamotrigine and a COC found that EE pharmacokinetics were unaffected by lamotrigine (titrated up to 300 mg/day), but there was a slight decrease of LNG levels.²² The clinical significance of this interaction with progestogen and the corresponding increase in follicle-stimulating hormone and luteinising hormone levels is unknown, as suppression of ovulation appeared to be maintained.²²

Effect of hormonal contraception on lamotrigine

Lamotrigine's major route of elimination is by conjugation with glucuronic acid (glucuronidation). EE is thought to induce lamotrigine glucuronidation,²³ which explains the reduction in lamotrigine levels found in users of CHC.^{22–29} The SPC suggests a two-fold increased clearance of lamotrigine in users of an EE/LNG (30 µg/150 µg) pill.⁴ A case series reported increased frequency of seizures in four women with reduced lamotrigine levels following the initiation of COC.²⁹ Conversely, an increase in lamotrigine levels has been observed during the pill-free week²⁷ and following cessation of oral contraceptives.²³ Lamotrigine side effects have been reported on discontinuation of COC, suggesting that the rise in lamotrigine levels may be clinically significant.³⁰

Due to the risk of drug interactions, the use of lamotrigine monotherapy with CHC is a UKMEC Category 3 (risks generally outweigh the benefits). The SPC for lamotrigine⁴ indicates that consideration should be given to using contraception without a pill-free week. No such products are licensed in the UK [apart from every day (ED) preparations, which are not suitable]. Therefore continuous use of CHC would be outside the product licence, although it is often carried out.

More complex interactions may come into play when lamotrigine and CHC are used in combination with other AEDs that affect glucuronidation. For example, when lamotrigine is taken together with an enzyme-inducing AED, lamotrigine glucuronidation is maximally induced and initiation of CHC makes no difference to lamotrigine levels. However, this combination of drugs would not be ideal because of the effects of the enzyme-inducing AED on CHC efficacy.

Lamotrigine glucuronidation is inhibited by the non-cytochrome P450 enzyme-inducing AED, sodium valproate, resulting in reduced lamotrigine metabolism and an increase in its mean half-life.³¹ A very small study looking at the kinetics of lamotrigine in COC users and pregnant women demonstrated that combined lamotrigine and valproate therapy was associated with similar plasma concentrations of lamotrigine in COC users and women using no oral contraception.³² This suggests that valproate lessens the effect of estrogen on lamotrigine metabolism. The World Health Organization (WHO) and UKMEC therefore advise that anticonvulsant regimens that combine lamotrigine and sodium valproate do not interact with COC.^{3,33}

There is evidence to suggest that progestogen-only methods are not affected by lamotrigine and thus the use of progestogen-only methods is not restricted with lamotrigine (UKMEC Category 1). A small trial²⁶ investigated any interaction between lamotrigine and combined (COC or vaginal ring) or progestogen-only contraception (i.e. POP, implant, DMPA or the LNG-releasing intrauterine system). Mean plasma concentrations of lamotrigine were significantly lower in CHC users (2.0 ± 1.3 mg/L) than controls (5.6 ± 3.1 mg/L) [$p < 0.001$], but there was no statistically significant difference between levels in progestogen-only contraception users (5.4 ± 2.1 mg/L) and controls.

The SPC for lamotrigine contains dosing recommendations for lamotrigine monotherapy and combination therapy in CHC users who are starting lamotrigine or stopping CHC use.⁴

Effect of non-enzyme inducing AEDs on hormonal contraception

Studies suggest that sodium valproate, levetiracetam, vigabatrin, pregabalin, zonisamide, tiagabine and gabapentin do not affect the pharmacokinetics of oral contraceptives.^{7,34–39}

Effect of hormonal contraception on sodium valproate

There is a small amount of evidence that suggests sodium valproate levels may be affected by hormonal contraception. A small prospective pharmacokinetic cohort study⁴⁰ ($n = 9$) found that the total and unbound valproic acid concentrations were higher during the COC-free interval than during COC intake in all nine subjects. The authors note that the study was limited by small numbers and by only assessing levels on the last day of hormonal contraception intake and on Day 6 or 7 after hormonal contraception interruption.⁴⁰

Similarly a recent prospective cross-sectional observational cohort²⁴ to determine whether COC use affects serum

levels of valproate or lamotrigine found that both valproate and lamotrigine levels were lower when taking active COC than when taking inactive pills. There was a 23.4% decline in the valproate-COC group and a 32.6% median decline for the lamotrigine-COC group. The clinical significance of the interaction with valproate is not known and there is no mention of such an interaction in the SPC for Epilim®.³¹

Effect of AEDs and hormonal contraception on bone

A recent drug safety update⁴¹ from the Medicines and Healthcare products Regulatory Agency (MHRA) has suggested that: *Long-term treatment with carbamazepine, phenytoin, and primidone, and in addition long-term treatment with sodium valproate, is associated with decreased bone mineral density that results in an increased risk of developing osteopenia, osteoporosis, and fractures in the following at-risk patients: those who are immobilised for long periods, those who have inadequate sun exposure and those with inadequate dietary calcium intake.*

The MHRA advises vitamin D supplementation for at-risk patients on long-term treatment with carbamazepine, phenytoin, primidone, phenobarbital or sodium valproate.

As DMPA has been associated with loss of bone mineral density (BMD),⁴² the CEU has been asked whether use of DMPA is appropriate in those being treated with the above listed AEDs. One study sought to evaluate any association between the incidence of osteoporotic fractures and use of DMPA and/or AEDs among woman and girls with developmental disabilities.⁴³ Compared to those who did not take DMPA or AEDs, those who received one or other or both had a significantly increased incidence of fracture. The authors concluded that women with developmental disabilities may be poor candidates for use of DMPA but that more research is needed. The CEU found no other evidence as to whether or not use of DMPA with these AEDs would increase the risk of users developing osteopenia, osteoporosis or fractures. The CEU would suggest that women are informed about the potential effect of both drugs on BMD and about strategies that can help to protect against BMD loss such as diet and exercise. Women should be assessed for other osteoporosis risk factors and a decision should be taken on an individual basis, weighing up the potential risks of DMPA use against the risks of unwanted pregnancy.

Further information

Guidance on the management of epilepsy has been produced by SIGN¹⁰ and NICE.¹¹ Health professionals should check the SPC and *British National Formulary* for up-to-date information on drug interactions.

Acknowledgements

The CEU would like to thank Professor Pamela Crawford, Consultant Neurologist, York District Hospital, York, UK and Dr Rhoda Lee, Staff Editor, *Stockley's Drug Interactions*, for peer reviewing this statement.

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