

Lamotrigine interactions with oral contraceptives

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Ms. A, age 20, presents to the clinic after experiencing difficulty sleeping, depressed mood, fatigue, and difficulty concentrating. Her psychiatric history includes bipolar II disorder (BD II), predominantly with depressive episodes. Ms. A's current medications include a combination of lamotrigine 200 mg/d and bupropion extended-release 450 mg/d, and her symptoms were well maintained until 2 weeks ago. When her psychiatrist performs a medication reconciliation at her medication management appointment, Ms. A indicates she started taking an oral contraceptive, ethinyl estradiol and norgestimate, approximately 1 month ago for management of endometriosis symptoms. She is not currently taking any other medications or supplements.

Lamotrigine is indicated for epilepsy and as maintenance treatment for BD I. It is also used off-label to treat other mood disorders. After oral administration, lamotrigine is rapidly and fully absorbed with a high bioavailability (98%). The principal metabolic pathway is via glucuronic acid

conjugation, leading to the major inactive metabolite 2-N-glucuronide. Minor metabolites include 5-N-glucuronide and a 2-N-glucuronide metabolite.¹

Combined oral contraceptives contain an estrogen component, typically ethinyl estradiol, and a progestin component, which varies based on the specific formulation. The metabolism of ethinyl estradiol occurs through cytochrome P450 (CYP)3A4, CYP2C9, sulfation, and glucuronidation. For progestin—the second component of combined oral contraceptives and the lone component of progestin-only oral contraceptives—metabolism occurs via CYP3A4 and conjugation reactions.² This article focuses on lamotrigine interactions specifically with oral contraceptives, but it is important to note that other formulations of combined hormonal contraceptives, such as the combined contraceptive patch

Combined oral contraceptives may reduce lamotrigine levels, and high doses of lamotrigine may interact with certain oral contraceptives

Practice Points

- **Combined oral contraceptives may reduce lamotrigine concentrations,** necessitating increased monitoring and a potential dose increase of lamotrigine.
- **Lamotrigine doses \geq 300 mg/d may lower concentrations of progestin-based hormonal contraceptives,** but the clinical significance of this is unknown.
- **Alternative contraceptive options that may be considered for patients taking lamotrigine include depot medroxyprogesterone acetate, levonorgestrel subdermal implants, intrauterine devices (IUDs) containing levonorgestrel, and the copper IUD.**

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Disclosures

Dr. Maroney served on the advisory board for Biogen and Sage Therapeutics, served as a consultant for Novus Medical Education, and received honoraria from Pharmacy Times Office of Continuing Education. Ms. Perumpail reports no financial relationships with any companies whose products are mentioned in this article, or manufacturers of competing products.

doi: 10.12788/cp.0373

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Clinical Point

Combined oral contraceptives cause increased lamotrigine metabolism and decreased lamotrigine levels

Table 1

Antiseizure mood stabilizers' effects on hormonal contraceptives

Antiseizure mood stabilizer	Proposed mechanism of interaction	Clinical impact on oral contraceptives	Clinical recommendations
Carbamazepine	Dose-dependent induction of CYP3A4 Increase in sex hormone-binding globulin	Decreased effectiveness Reduced free plasma concentrations of progestins	Use alternatives: depot medroxyprogesterone acetate (possibly with a shorter dosing interval of every 10 weeks), or IUD (levonorgestrel or copper) Consider continuous (no hormone-free interval) use of high-dose estrogen combined oral contraceptives ^a Consider doubling the dose of levonorgestrel emergency contraceptive or using copper IUD as an alternative form of emergency contraceptive
Gabapentin ^b	NA	No effect	None
Lamotrigine ≥300 mg/d	Possible induction of glucuronidation, hydroxylation or sulfation of levonorgestrel	Modest reductions (approximately 20%) in levonorgestrel levels with oral contraceptives; clinical significance is unclear	Consider alternatives: depot medroxyprogesterone, etonogestrel subdermal implant, or IUD (levonorgestrel or copper)
Oxcarbazepine ^b	Induction of CYP3A4	Decreased effectiveness	Same as carbamazepine
Topiramate ^b >200 mg/d	Induction of CYP3A4	Decreased effectiveness	Same as carbamazepine ^c
Valproic acid/divalproex sodium ^d	NA	No effect	None

^aOnly select products containing 50 mcg/d of estrogen are FDA-approved; use of higher doses is considered off-label and may increase the risk of thrombosis without guaranteeing increased efficacy
^bNot FDA-approved for the treatment of bipolar disorder and may not be recommended in clinical practice guidelines
^cGiven topiramate's teratogenic potential, some recommend using contraceptive alternatives with topiramate regardless of dose
^dGiven valproate's teratogenic potential, it should generally be avoided in women of childbearing age; if use is necessary in this population, a reliable method of contraception (hormonal or nonhormonal) should be employed
 CYP: cytochrome P450; IUD: intrauterine device; NA: not applicable
Source: References 3-6

(Ortho Evra) and vaginal ring (NuvaRing), would be expected to interact in the same way as oral formulations.³

Bidirectional interaction

While many antiseizure medications are known to interact with and potentially decrease the efficacy of oral contraceptives (Table 1³⁻⁶), the interactions between lamotrigine and oral contraceptives is uniquely bidirectional. Combined oral contraceptives are thought to interact with lamotrigine primarily via the estrogen component, which

causes increased metabolism of lamotrigine through induction of glucuronidation. This drug interaction decreases the plasma concentrations of lamotrigine in the body by up to 2-fold, resulting in an increased risk of seizures or inadequate mood stabilization.¹ This effect on metabolism is very rapid, resulting in decreases in lamotrigine concentrations within 1 week.^{4,7} A recent study suggested that certain progestins may also contribute to decreased plasma levels of lamotrigine, but the mechanism for this is unknown (Table 2,³⁻⁷ page 45).⁸



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Table 2

Oral contraceptives' effects on antiseizure mood stabilizers

Antiseizure mood stabilizer	Proposed mechanism of interaction	Clinical impact on antiseizure medication	Clinical recommendations
Carbamazepine	NA	No effect	None
Gabapentin ^a	NA	No effect	None
Lamotrigine	Estrogen induces the metabolism of lamotrigine via induction of UGT1A4	May decrease lamotrigine plasma levels by 41% to 64%, resulting in potential breakthrough symptoms (unless also taking valproic acid)	Consider monitoring plasma levels Titrate lamotrigine dose by 50 to 100 mg/d weekly until efficacy is achieved, consider limiting hormone-free interval, and reduce dose if estrogen is discontinued
	Unknown	Certain progestins (drospirenone and levonorgestrel) may decrease lamotrigine levels	Consider alternatives: depot medroxyprogesterone, etonogestrel subdermal implant, or IUD (levonorgestrel or copper)
	Unknown	Desogestrel (progestin-only pill) may increase lamotrigine levels	Monitor for increased adverse effects with lamotrigine when used with progestin-only contraceptives
Oxcarbazepine ^a	NA	No effect	None
Topiramate ^a	NA	No effect	None
Valproic acid/divalproex sodium ^b	Estrogen may induce the metabolism of valproic acid via induction of UGT1A4	May decrease valproic acid levels by 21.5% to 23.4%	Consider monitoring valproic acid levels upon initiation, discontinuation, and during hormone-free intervals

^aNot FDA-approved for the treatment of bipolar disorder and may not be recommended in clinical practice guidelines

^bGiven valproate's teratogenic potential, it should generally be avoided in women of childbearing age; if use is necessary in this population, a reliable method of contraception (hormonal or nonhormonal) should be employed

IUD: intrauterine device; NA: not applicable; UGT1A4: UDP-glucuronosyltransferase 1A4

Source: References 3-7

Clinical Point

Consider increasing the lamotrigine dose by up to 2-fold in a patient who starts taking a combined hormonal contraceptive

Clinicians should consider increasing the lamotrigine dose (potentially as much as 2-fold) in a patient who initiates treatment with a combined hormonal contraceptive. Dose increases should not be >50 to 100 mg/d every week.¹ Collect lamotrigine blood levels before starting a hormonal contraceptive and during dose titration. While there is not a well-established therapeutic range for lamotrigine in BD, expert consensus recommends a range of 1 to 6 mcg/mL.⁸

The lamotrigine dose should be decreased if combined hormonal contraceptives are discontinued. Dose decreases should not exceed 25% of the total daily dose per week.¹ Desogestrel, a progestin-only medication,

may increase exposure to lamotrigine, but this has not been observed in research with other progestins.^{5,9} When starting a progestin-only pill, monitor patients for signs of lamotrigine toxicity (ataxia, diplopia, dizziness) and consider monitoring their blood levels.

An important consideration to note with combined oral contraceptives is the hormone-free interval, also known as the pill-free week. Due to the rapid effect of estrogens, the lamotrigine concentrations have been shown to rise, even double, during this hormone-free interval, so patients should be closely monitored for adverse effects.³ Some recommend use of

Clinical Point

For patients taking lamotrigine and valproate, oral contraceptives may not cause reductions in lamotrigine concentrations

Related Resources

- Makino KK, Hatters Friedman S, Amin J. Emergency contraception for psychiatric patients. *Current Psychiatry*. 2022;21(11):34-39,44-45. doi:10.12788/cp.0300
- MGH Center for Women's Mental Health. You asked: is there an interaction between lamotrigine and oral contraceptives? September 29, 2015. <https://womensmentalhealth.org/posts/you-asked-is-there-an-interaction-between-lamotrigine-and-oral-contraceptives/>

Drug Brand Names

Bupropion extended-release • Wellbutrin XL	Etonogestrel • Implanon, Nexplanon
Carbamazepine • Equetro, Tegretol	Gabapentin • Neurontin
Desogestrel • Cerazette	Lamotrigine • Lamictal
Divalproex sodium • Depakote	Levonorgestrel emergency contraceptive pill • AfterPill, Plan B
Ethinyl estradiol and etonogestrel • NuvaRing	Levonorgestrel intrauterine device • Mirena, Skyla
Ethinyl estradiol and norelgestromin • Ortho Evra	Medroxyprogesterone acetate • Depo-Provera
Ethinyl estradiol and norgestimate • Ortho	Oxcarbazepine • Trileptal
Tri-Cyclen, TriNessa, others	Topiramate • Topamax
	Valproic acid • Depakene

an extended cycle regimen (with a limited hormone-free interval), or continuous cycle regimen (with no hormone-free interval) to avoid fluctuations in lamotrigine levels.^{3,5} Additionally, data suggest that in patients taking lamotrigine and valproate, which inhibits glucuronidation, oral contraceptives do not cause reductions in lamotrigine concentrations.^{2,5} In these instances, dose increases of lamotrigine are not needed.

The metabolism of ethinyl estradiol and progestin are susceptible to CYP3A4 induction and increased glucuronidation. Serum concentrations may be reduced by $\geq 50\%$ when used concomitantly with CYP enzyme-inducing medications, which could possibly result in subtherapeutic levels and unplanned pregnancy.³ CYP3A4 induction occurs for up to 4 weeks after discontinuation of an enzyme-inducing agent, pointing to the need for alternative or backup contraception during this time.³ Lamotrigine is not a CYP enzyme-inducing medication; it is unlikely to affect the efficacy of oral contraceptives in the same manner as other antiseizure medications. However, a study of lamotrigine and the combined hormonal contraceptive ethinyl estradiol

and levonorgestrel demonstrated reduced exposure to levonorgestrel, resulting in breakthrough bleeding.⁵

In a study on the coadministration of lamotrigine and combined oral contraceptives, Sidhu et al⁴ observed a small mean reduction (20%) in progestin concentrations when lamotrigine was used at a dose of 300 mg/d. Although there is no research suggesting decreased effectiveness in preventing pregnancy when lamotrigine is used with combined oral contraceptives, progestin-only oral contraceptives, or progestin implants, additional or alternative contraceptive methods may be considered based on this pharmacokinetic data, particularly in patients who require lamotrigine doses ≥ 300 mg/d.⁵

CASE CONTINUED

Given when Ms. A started the oral contraceptive, the treatment team determines it is likely that an interaction with lamotrigine is causing her resurgence of depressive symptoms. Her care team decides to titrate the lamotrigine gradually to 300 mg/d, then 400 mg/d if needed, while carefully monitoring for signs of a serious rash. This dosage increase may help Ms. A achieve symptom remission. Monitoring plasma levels may be considered, although it is unknown what plasma level was effective for Ms. A before she started the oral contraceptive. Ms. A would need to be counseled regarding the effect of higher doses of lamotrigine on the effectiveness of the oral contraceptive.

Although it does not appear Ms. A is using the oral contraceptive specifically to prevent pregnancy, the team informs her about the possibility of unintended pregnancy with this medication combination. If Ms. A was also using the medication for this indication, alternative contraceptive options would include medroxyprogesterone acetate, levonorgestrel implants, or an intrauterine device (levonorgestrel or copper, though copper would not be effective for endometriosis symptom management). Ms. A should consult with her gynecologist regarding the most appropriate option for her endometriosis. If the decision

is made to discontinue her oral contraceptive in the future, the lamotrigine dose should be decreased to her previously effective dose of 200 mg/d.

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Lamotrigine is unlikely to affect the efficacy of oral contraceptives in the same manner as other antiseizure medications