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CLINICAL CONUNDRUM

WILEY BIPOLAR DISORDERS

Combined oral anticonceptives and the pill-free week in two bipolar patients treated with lamotrigine

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1 | BACKGROUND

Lamotrigine (LTG) is a level 1 treatment option for bipolar disorder, as both treatment and prophylaxis of depressive symptoms. It is generally safe and well tolerated, with the rare but serious side effect of Stevens-Johnsons syndrome. This occurs when dose titration is done too fast; hence, a titration phase of 5-6 weeks is recommended. Since valproic acid is no longer recommended as a first-line mood stabilizer in fertile women, LTG is often used in these patients. For birth control, these women often use combined oral anticonceptives (COC) containing ethinyl estradiol and progestins. However, estrogens interact with LTG and potentially lower the plasma concentration up to 60%.[1] Estrogen-induced glucuronidation is responsible for the drop in lamotrigine levels during active COC use. This drug interaction is well documented and is also seen with other ethinyl estradiol containing anticonceptives (eg, vaginal ring), hormonal replacement therapy, and during pregnancy.[1,2] For use as an anticonvulsant in epilepsy, guidelines recommend the use of a different anticonceptive strategy or to skip the pill-free week. Often, women do not prefer to continuously skip the pill-free week, since this can lead to more breakthrough bleeding (spotting).

When used as a mood stabilizer, it is unclear what effect a pill-free week (and thus variable LTG-concentrations) may have on mood symptoms. Some evidence exists for a plasma concentration-response association, with a therapeutic range between 1-6 μg/mL.[3] The evidence for a clinically relevant therapeutic window is sparse, and therefore, therapeutic drug monitoring is not recommended. However, in theory, patients have a higher LTG blood level during the pill-free week, which could improve mood or induce more side effects/toxicity, which was reported in a case-report series.[4] On starting with a new COC strip, lowering of the plasma concentration might induce depressive symptoms. Although no randomized controlled trials have been done to confirm or reject these hypotheses, our clinical experience is that Dutch pharmacies may advise bipolar patients to skip the pill-free week.

We present two euthymic patients who completed daily mood monitoring (LifeChart method). No other medication adjustments were made in this period. Plasma concentrations were evaluated three times. The first test was done in the last week of the COC strip. The second test was done on day 6 or 7 of the pill-free week, since the LTG-concentration increases daily with a peak level on day 6 or 7. The third test was done in the first week of the COC strip.

2 | CASE 1

A 31-year-old consultant was treated for bipolar I disorder at our outpatient clinic since 2016. Her history mentions one manic episode without psychotic symptoms, for which she was admitted in 2015 when living abroad. This episode was possibly induced by the use of monotherapy citalopram. Before and after this episode, she mainly suffered from depression, which was now adequately treated with cariprazine 3 mg once a day, fluoxetine 10 mg once a day, and zolpidem 10 mg for the night, when needed. The last year she was euthymic and functioning well; she had a job, was socially active, and lived together with her partner. She had no family history of bipolar disorder. Since the start of cariprazine she reported symptoms of restless legs, an inability to sit still and mild anxiety. This was assessed as akathisia, a common side effect of cariprazine. Shared decision-making leads to the conclusion to add lamotrigine as a mood stabilizer, in order to replace the cariprazine and the fluoxetine. For anticonception, she used

a combined ethinylestradiol/levonorgestrel (30 μg/150 μg) pill. Soon after starting lamotrigine, she contacted us for consultation. The pharmacy had advised her to skip her pill-free week, as this could influence the efficacy of her lamotrigine. With consent of the patient, we decided to do therapeutic drug monitoring after reaching a stabilizing dose of lamotrigine 200 mg once a day, while she kept a daily record of her mood for a month.

3 | CASE 2

A 35-year-old designer was recently referred to our outpatient clinic for continuing treatment for her bipolar II disorder. She recently immigrated to the Netherlands, and was already treated successfully with a combination of quetiapine 200 mg once a day, lamotrigine 200 mg twice a day, and fluoxetine 30 mg once a day. The age of onset of her first mood symptoms was at the age of 19, with mainly depressive and anxiety symptoms. Her family history mentions no bipolar disorders, only anxiety disorders (mother). She was admitted once for 3 days, due to severe anxiety and insomnia, when she was 20 years old. When referred to our clinic, she was euthymic for more than a year. She was socially functioning well, recently started an ambitious job and lived with her husband, with whom she had a long and healthy relationship. She used an ethinylestradiol/levonorgestrel (30 μg/150 μg) combination for years, but was not aware of the interaction with lamotrigine. When discussing her mood during her pill-free week, she did not recognize a pattern of mood instability linked to this week. We decided to continue her pill-free week, keep a daily life chart and start therapeutic drug monitoring for a month.

Key message

Fluctuations of plasma concentrations of lamotrigine due to combined oral anticonceptives did not affect mood stability or reported side effects in two euthymic patients during prophylactic treatment. A pill-free week may be safe during prophylactic treatment, as opposed to pill-free weeks during treatment in epilepsy. This hypothesis needs confirmation by further research.

Learning points

- Lamotrigine plasma concentrations are potentially lowered up to 60% due to interaction with combined oral anticonceptives containing ethinyl estradiol.
- Our clinical experience is that this variability does not influence mood stability or side effects. A pill-free week may be safe when treating stable bipolar disorder, but there is no evidence for this claim.
- A pill-free week during dose escalation may hypothetically lead to a rapid increase of lamotrigine plasma concentration and thus the risk to induce rare but serious side effects.

4 | DISCUSSION

In both patients, a strong variability was shown in the lamotrigine concentrations, probably due to interaction with their COC. The

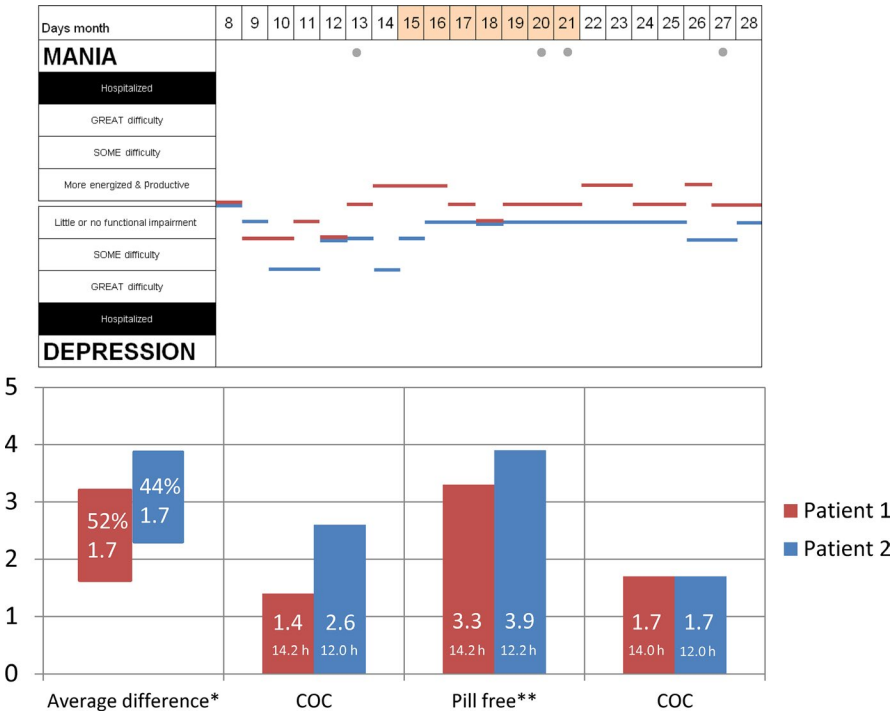

FIGURE 1 Lamotrigine plasma concentrations and corresponding life charts. Lamotrigine plasma concentrations are in milligram/liter and intervals in hours after last lamotrigine dosage. *Average difference: difference between the average of the two concentrations during COC use and the concentration on day 6 or 7 without COC. **Day 6 (patient 1) and day 7 (patient 2) of the pill-free week [Colour figure can be viewed at wileyonlinelibrary.com]

LTG-concentrations increased with 52% and 44%, respectively. There was no effect on mood (Figure 1) and no new side effects (such as headache, irritability or sleeping problems) were reported. This is consistent with the current literature that indicates a wide therapeutic range. However, the European Medication Agency (EMA) and the Dutch protocol for treatment for bipolar disorders do recommend changing to continuous hormonal contraceptives or nonhormonal methods for birth control.[5] In our experience, pharmacies may recommend this to patients as well. This seems based on the experience and evidence for a plasma concentration-response association in treatment of epilepsy with lamotrigine, with a possible loss of seizure control during a pill-free week. However, such fluctuations in efficacy may not occur in the treatment of bipolar disorder despite fluctuations in plasma levels. This insight could result in fewer patients having to change their contraceptive regime of preference, or experiencing less breakthrough bleeding when skipping the pill free-week. Also, in patients who do not wish to change COC or undergo cyclic hormone replacement therapy for menopausal symptoms, lamotrigine remains a possible treatment option.

Another potential problem due to this interaction is whether to advise a pill-free week during dose escalation of lamotrigine. Slow-dose escalation is crucial to reduce the risk of Stevens-Johnsons syndrome within the first 8 weeks. When patients do have a pill-free week during escalation, hypothetically the plasma concentration may rapidly double which could increase the risk of a rash. There is no evidence that this occurs and a recommendation concerning a pill-free week during escalation is not mentioned by the EMA or in literature. After a skin reaction during escalation, protocols advise against restarting lamotrigine, with a potential loss of a level 1 treatment option. These clinical dilemmas ask for further research by instigation of a naturalistic study or double-blind randomized controlled trial in a large sample, to monitor the effect of variable LTG-concentrations on mood stability.

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REFERENCES

1. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduceslamotrigineserumconcentrations.*Epilepsia*.2005;46(9):1414-1417. https://doi.org/10.1111/j.1528-1167.2005.10105.x.
2. Reimers A. Hormone replacement therapy with estrogens may reduce lamotrigine serum concentrations: A matched case–control study. *Epilepsia*. 2017;58(1):e6-e9. https://doi.org/10.1111/epi.13597.
3. Unholzer S, Haen E. Retrospective Analysis of Therapeutic Drug Monitoring Data for Treatment of Bipolar Disorder with Lamotrigine. *Pharmacopsychiatry*. 2015;48(06):211-214. https://doi.org/10.1055/s-0035-1559635.
4. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res*. 2001;47(1-2):151-154. https://doi.org/10.1016/S0920-1211(01)00305-9.
5. European Medicines Agency. Opinion following an Article 30 referral for Lamictal and associated names International Non-Proprietary Name (INN): lamotrigine: background information. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Lamictal_30/WC500008824.pdf. Published 2008. Accessed August 3, 2018.