

Contraception for women with epilepsy: counseling, choices, and concerns

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Abstract: Approximately 50% of all pregnancies in women with epilepsy (WWE) occur unplanned. This is worrying, given the increased occurrence of obstetrical complications in WWE, including the risk of seizures and their possible consequences for both the mother and the unborn child. Hormonal contraception is usually regarded as highly effective, but it is subject to numerous bidirectional drug interactions with several antiepileptic drugs. These interactions may lead to loss of seizure control or contraceptive failure. Further concerns are loss of bone mineral density and increased seizure activity due to hormonal effects. Many physicians lack sufficient knowledge regarding these issues, and most WWE have never received adequate counseling. Moreover, several studies show that a large proportion of WWE do not take their medicines regularly. This article reviews all of these issues and offers practical recommendations for the management of contraception in WWE.

Keywords: ethinyl estradiol, progestins, epilepsy, antiepileptic drugs, interactions, pregnancy, seizure aggravation, bone mineral density

Introduction

With an estimated prevalence of 0.3%–0.7%, epilepsy is one of the most frequent neurological diseases.¹ Women with epilepsy (WWE), like healthy women, use different kinds of contraceptive methods, ie, hormonal contraception (HC), intrauterine devices (IUDs), barrier methods, or combinations of them. HC includes combined oral contraceptives (COCs), progestin-only pills, intramuscular injections, subdermal implants, skin patches, hormone-releasing IUDs, and vaginal rings. However, most WWE also use antiepileptic drugs (AEDs). Many of these drugs do interact with HC, which may lead to contraceptive failure or impaired seizure control.^{2,3} Either of these complications may have serious social, psychological, professional, and economic consequences. Additionally, many AEDs possess teratogenic potential and/or may exert a negative impact on cognitive and psychomotor skills of children exposed to these AEDs in the womb.⁴⁻⁶

Given the above, it is deeply concerning that ~50% of all pregnancies among WWE occur unintended.^{7,8} This is about the same proportion as found in the general population.^{9,10} Risk factors for unintended pregnancy include low socioeconomic status, low education, and ethnicity.⁸ Also, only half of all WWE using contraception do so with a highly effective method (HC, IUDs, or surgery). Moreover, many WWE use enzyme-inducing AEDs that may impair the efficacy of highly effective HC.⁸

It might be speculated whether better education of WWE could reduce the proportion of unplanned pregnancies. However, several studies show that a large proportion

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of doctors, including neurologists and gynecologists, lack sufficient knowledge about reproductive health issues of WWE and how these may be affected by AEDs.^{11–13} Hence, the current treatment guidelines may not be followed.¹⁴ More recent surveys found a trend from prescribing older AEDs toward newer AEDs with a more favorable interaction and safety profile, which may indicate a growing awareness among doctors.^{15–18} However, most WWE do not receive necessary information.^{19,20} A 2015 survey found that <7% of women received contraceptive counseling.²¹ Even when information is provided, many WWE do not recall the information they were given.²² Consequently, most WWE have only limited knowledge about interactions between HC and AEDs and potentially harmful effects of AEDs on the child.^{23,24}

Apart from drug interactions between HC and AEDs, contraception for WWE comprises further questions. Does HC aggravate seizures? Is there an increased risk of osteoporosis? Is adherence an issue? The answers to these questions affect treatment options and need to be discussed with the patient. Hence, the attending physician should have thorough knowledge.

Epilepsy, AEDs, and female fertility

While many WWE will have normal sex lives and normal pregnancies, they in general have lower fertility rates than healthy women. Also, anovulatory cycles, irregular menstrual bleedings, or oligo-/amenorrhea occur more frequently in WWE than in women without epilepsy.²⁵ This is more common with antiepileptic polytherapy than with monotherapy, which suggests a causal role of AEDs. However, available data also suggest that seizures and epileptic discharges, especially temporal lobe epilepsy, may negatively affect ovarian function and ovulation via disturbances in the hypothalamic–pituitary axis.^{25–27}

It is well established that enzyme-inducing AEDs may increase sex hormone-binding globulin and induce the metabolism of sex steroid hormones, thus reducing the serum concentration of free and total sex hormones.^{28,29}

Valproate, one of the most frequently used AEDs, can induce polycystic ovary syndrome.³⁰ This syndrome consists of polycystic ovaries, hyperandrogenism, menstrual disturbances, and anovulatory cycles. The underlying mechanisms are not completely understood, but an interaction of valproate with sex steroid synthesis and metabolism in the ovary is presumed.²⁵

WWE also have a higher risk for complications during pregnancy and delivery, eg, hypertension, preeclampsia,

bleedings, preterm birth, or small for gestational age. The frequency of cesarean section is also higher.³¹

In conclusion, current evidence suggests that both epilepsy itself as well as drug treatment with AEDs may affect female fertility and cause complications during pregnancy and delivery. These findings underline the importance of pregnancy planning, which includes contraception.

What AEDs do to HC

Many of the “old” or “first-generation” AEDs (phenytoin, phenobarbital, primidone, carbamazepine) and several of the “new” or “second-generation” AEDs (oxcarbazepine, eslicarbazepine, topiramate, felbamate, rufinamide, perampamil) have more or less pronounced enzyme-inducing effects. They may induce either cytochrome P450 (CYP) enzymes, uridine-diphosphate-glucuronosyltransferase (UGT) enzymes, or both, thereby accelerating the metabolism of steroid hormones. Contraceptive failure provoked by enzyme-inducing AEDs is common and may affect both oral and nonoral HC.^{32–34} The estrogen compound used in combined HC usually is ethinyl estradiol (EE), which has been used for decades. EE has a well-known pharmacokinetic and interaction profile. It is mainly metabolized by CYP 3A4, but conjugation by UGT also plays a role.³⁵ Besides EE, there is a plethora of older and newer progestins used for HC.^{36,37} Their metabolism and possible interactions with AEDs are much less studied. In general, their metabolism is inducible like that of EE. Thus, their contraceptive effect may fail when they are coadministered with carbamazepine or other enzyme-inducing AEDs. Examples for this include oral levonorgestrel, oral norethindrone, and the subdermal etonogestrel implant.^{32,33,38,39} The interaction potential of depot medroxyprogesterone acetate (DMPA) intramuscular injection has not been specifically studied. However, if an AED has been found to induce the metabolism of one specific progestin, it appears reasonable to assume that other progestins may be affected as well.

On the other hand, there are many different HC preparations available, and they may contain not only different hormones, but also different doses of EE and different doses of the same progestin. The conclusions drawn from one study investigating one HC preparation may not necessarily apply to another HC preparation with the same active substances but different doses. Hence, even if the available data suggest that an interaction is unlikely to occur in a specific HC–AED combination, the attending physician and the patient should take any irregular bleeding as a sign of possible contraceptive failure.

As a consequence of the pharmacokinetic interaction between enzyme-inducing AEDs and HC, the “classic” recommendation has been to use high-dose HC, ie, a daily EE dose of at least 50 µg.^{40–42} However, this advice is theoretically derived, has not been clinically proven, and has considerable conceptual weaknesses, one of them being that the ovulation-suppressing dose of EE is ~100 µg.⁴³ Given the ever decreasing dose of EE in COCs, it may also be hard to find a contraceptive pill with such a high estrogen content. Moreover, despite this decades-old recommendation, a recent study from the Netherlands reported that 43.5% of WWE taking enzyme-inducing AEDs used a low dose of EE.⁴⁴ A similar study performed in the UK found even a figure of 56%.¹²

More recent recommendations take into account the mechanism of action of modern HC and focus on a high progestin dose instead, since in modern HC preparations, ovulation inhibition is mediated via the progestin, not EE.⁴³ Modern HC contains EE mainly for the purpose of creating a hormonal balance with the progestin component. Indeed, modern oral HC preparations typically contain ~1.5–2 times the ovulation-inhibiting progestin dose.⁴³ However, as enzyme induction affects not only EE but also progestins,⁴⁵ even the contraceptive effect of a “high” progestin dose may be impaired by enzyme-inducing AEDs, and clinical evidence for the “high progestin” concept is lacking. Consequently, neither high-dose EE nor high-dose progestin guarantees safe contraception in WWE taking enzyme-inducing AEDs, and additional contraceptive measures, eg, barrier methods, should be considered. This applies to combined (EE plus progestin) as well as progestin-only HC (oral or depot-formulations).

Hormone-releasing IUDs release a progestin and act locally on the endometrium. In contrast to systemic HC (oral, patch, vaginal ring, or implants), their contraceptive effect may not – at least in theory – be impaired by hepatic enzyme induction. Preliminary data from one study indeed suggest that this method is not affected by AEDs, which would make them a suitable alternative to systemic HC.⁴⁶ However, this study has not been confirmed. There is also one case report on contraceptive failure with a progestin-releasing intracervical device, presumably due to simultaneous use of carbamazepine.⁴⁷ However, there are no further such reports. Nevertheless, caution is advisable until possible interactions of locally acting HC with enzyme-inducing AEDs have been studied more systematically.

The most obvious solution to this drug interaction problem would be to not use enzyme-inducing AEDs together with HC. With today’s spectrum of available AEDs (>20 in most Western countries), chances for the neurologist to avoid enzyme-

inducing AEDs in fertile WWE are good. Indeed, recent surveys indicate that more and more WWE are prescribed newer, nonenzyme-inducing AEDs.^{15–18} In many countries however, these new AEDs may either not be available or just be too expensive. One of the “old”, nonenzyme-inducing AEDs is valproate. It is very effective in a large variety of epileptic seizures and syndromes, usually well-tolerated, inexpensive, and a first-line drug for the treatment of epilepsy. It is one of the most used AEDs worldwide. Alas, it has considerable teratogenic potential and may negatively affect the cognitive outcome of children exposed in utero.^{5,6} This is a substantial risk, especially because half of all pregnancies in WWE occur unplanned. Moreover, typical side effects of valproate include hair loss and weight gain. Valproate may also cause polycystic ovary syndrome and metabolic disturbances. It is therefore prescribed less frequently for WWE,^{15–18} and the European Medicines Agency has advised physicians to not prescribe valproate to fertile women unless other treatments are ineffective or not tolerated.⁴⁸ If valproate is prescribed to fertile women, highly effective contraception and adequate adherence should be ensured.

When enzyme-inducing AEDs cannot be avoided, HC should be combined with barrier methods. Recently, it has also been recommended to use HC in an extended-cycle pattern when enzyme-inducing AEDs are used simultaneously.⁴³ Without the pill-free week, gonadotropin secretion and ovarian function will be continuously suppressed, which will enhance contraceptive efficacy compared to the usual pattern of use (3 weeks “on”, 1 week “off”). Whether this alone provides reliable contraception despite enzyme induction remains to be proven. Until then, HC should be regarded as non-safe when combined with enzyme-inducing AEDs, and additional contraceptive methods (barrier methods) be employed.

In any case, WWE using enzyme-inducing AEDs and HC must be informed of this problem and possible solutions be presented, so that they can make an informed decision on which contraceptive method (and/or which AED) to choose. It may also be helpful to discuss this issue directly with the patient’s neurologist.

What HC does to AEDs

While it has been known for over 40 years that enzyme-inducing AEDs may impair the contraceptive effect of HC,^{49,50} the possibility of the opposite had practically been ignored until 2001, when it was demonstrated that COCs may reduce the serum levels of lamotrigine by >60% and lead to loss of seizure control.⁵¹ Later studies confirmed these findings and showed that it is the estrogen component (EE)

that is responsible for this interaction.^{52,53} In fact, it has been known long before 2001 that EE may affect the metabolism of quite many other drugs.^{54,55} Interestingly, EE has a unique dual effect on drug-metabolizing enzymes: while the activity of several CYP enzymes may be reduced, the activity of some UGTs may be increased.⁵⁴ Thus, the clinical efficacy of AEDs that undergo elimination by glucuronidation may be reduced. Surprisingly, studies on the possible effects of EE on the metabolism of AEDs are still sparse.

So far, an effect of EE on the metabolism of AEDs has been demonstrated only for lamotrigine (discussed in Lamotrigine section) and, to a lesser degree, for valproate. In contrast to lamotrigine, the effect on valproate is only moderate and much less well documented (only two small studies).^{56,57} However, as with lamotrigine, there is large interindividual variation, and in some patients this interaction may gain clinical relevance, ie, lead to increased seizure activity.⁵⁷ Oxcarbazepine and its derivative eslicarbazepine, as well as retigabine/ezogabine, are also subject to glucuronidation, but a possible effect of EE on their metabolism has not been examined so far.

It must be emphasized that, according to the current knowledge, only EE affects the metabolism of AEDs. There is no convincing data suggesting any clinically relevant effect of progestins (“mini-pill”, implants, depot injections, hormonal IUDs, emergency pill) on the metabolism of lamotrigine or any other AED. In one small study, a desogestrel-only pill

caused a 20%–100% increase in lamotrigine concentrations, but only in seven out of ten women.⁵⁸ However, this study from the year 2004 still exists only in an abstract form and it has not been confirmed by others.

It should also be noted that EE is used not only in oral preparations (COCs) but also in skin patches and the vaginal ring. Accordingly, it has been found that the EE-releasing vaginal ring may reduce lamotrigine serum concentrations in a similar manner as COCs.^{52,59} Although not specifically studied, such an effect should also be anticipated for the EE-releasing skin patch.

Lamotrigine

Lamotrigine is metabolized by UGT enzymes that are inducible by EE. The use of EE together with lamotrigine may become challenging. First, lamotrigine concentrations fall by ~50%–60% and seizure aggravation may occur when EE is added.^{51–53} This usually requires a considerable increase, and often a doubling, of the lamotrigine dose, in order to avoid seizure breakthrough. Second, lamotrigine levels rise (with considerable interindividual variation) and may even double within the pill-free week.^{53,59,60} This may provoke or aggravate adverse effects if the dose is not reduced during this period (Figure 1). In clinical practice though, most WWE will not experience relevant problems with side effects in the pill-free week. Finally, lamotrigine has a

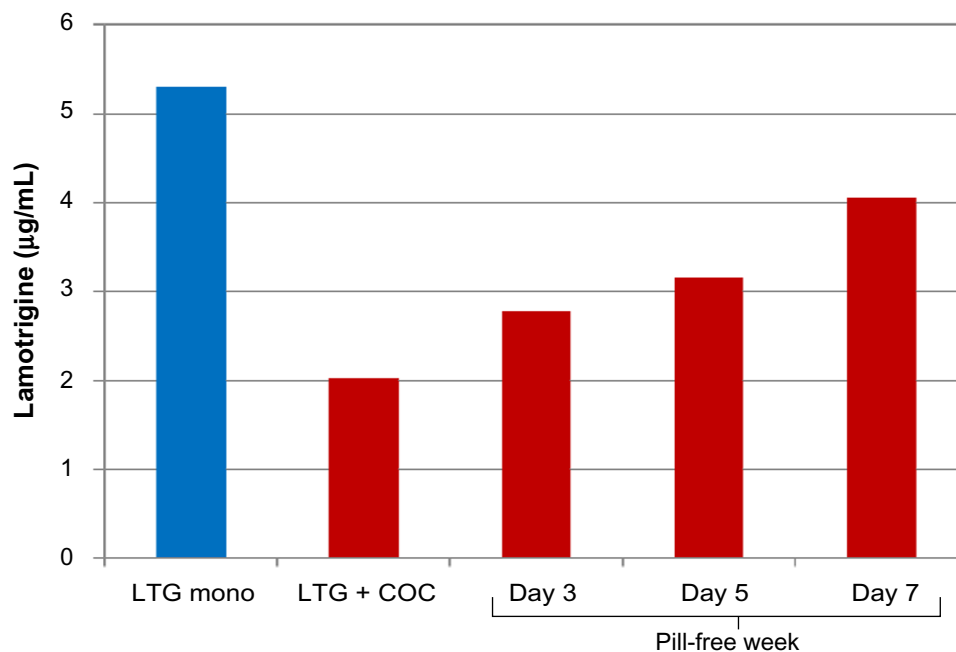


Figure 1 Impact of addition and withdrawal of combined oral contraception on lamotrigine (LTG) serum concentration.

Note: Permission is kindly granted by John Wiley & Sons Ltd to adapt data from Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol.* 2006;61(2):191–199.⁵³ (c) 2005 Blackwell Publishing Ltd.

Abbreviation: COC, combined oral contraceptive; mono, monotherapy.

comparatively long half-life of 20–30 hours, which means that the pharmacokinetic steady state after dose changes or addition/removal of interacting comedication will be achieved first after 4–5 days.

Together, all this means that COC users may have large fluctuations of the lamotrigine serum concentration during the menstrual cycle, with the possibility of both subtherapeutic and toxic levels, if the dose remains unchanged all the time. Likewise, because of the large fluctuations, serum-level measurements of lamotrigine may be considerably misleading if not always taken exactly at the same time relative to the menstrual cycle.

If active measures become necessary, dynamic dose adjustments (increase while EE is taken, decrease in the pill-free week) might prevent the loss of seizure control or the occurrence of adverse effects, but such a strategy is unrealistic as it would require great efforts from the attending neurologist and the patient, including tight clinical follow-up and regular measurement of the lamotrigine serum level over a long period of time.

All in all, the combination of lamotrigine with EE (COCs, patch, or vaginal ring) appears unfavorable. When this combination cannot be avoided, a practical solution would be to omit the pill-free week, ie, to use EE continuously. This would require only one initial dose adjustment of lamotrigine. Such “long-cycle” or “extended-cycle” regimens have been proven safe and convenient, and are becoming increasingly popular among fertile women.^{61,62} Recently, a COC designed for an 84-day regimen that results in bleeding only four times a year has been introduced. HC preparations for even longer cycles, 6 and 12 months, are currently being developed.⁶²

As stated earlier, progestins apparently do not affect lamotrigine metabolism. These preparations may therefore be preferred over EE-containing HC when the patient uses lamotrigine. One caveat exists though. It has been found in one study that lamotrigine reduced the area under the curve of levonorgestrel by 19%. This is a comparatively small effect, and the authors conclude from low progesterone serum concentrations that suppression of ovulation still was maintained.⁵³ No case of contraceptive failure due to lamotrigine has been published so far. However, it cannot be ruled out that in some patients, the contraceptive effect may become uncertain. Caution is therefore advisable, especially with low-dose progestin preparations (Table 1).

Does HC affect epilepsy?

The complex interaction between sexual hormones and epileptic brain activity has recently been reviewed.²⁷ In general, neuronal excitability is increased by estrogens and reduced

Table 1 Pharmacokinetic interactions between HC and AEDs

	AED reduced by EE	EE reduced by AED	Progestin reduced by AED
Old AEDs			
Carbamazepine	NA	Yes	Yes
Phenobarbital	NA	Yes	Yes
Phenytoin	NA	Yes	Yes
Valproate	Yes	No	No
New AEDs			
Eslicarbazepine	NA	Yes	Yes
Felbamate	NA	Yes	Yes
Gabapentin	NA	No	No
Lacosamide	No	No	No
Lamotrigine	Yes	No	Yes
Levetiracetam	No	No	No
Oxcarbazepine	NA	Yes	Yes
Perampanel	NA	No	Yes ^a
Pregabalin	NA	NA	NA
Retigabine/Ezogabine	No	No	No
Rufinamide	No	Yes	Yes
Stiripentol	NA	NA	NA
Topiramate	NA	Yes ^a	No
Zonisamide	No	No	No

Note: ^aDose dependent.

Abbreviations: HC, hormonal contraception; AED, antiepileptic drug; EE, ethinyl estradiol; NA, no data available.

by progesterone. There are certain exceptions to this rule,²⁷ but estrogens are mainly regarded as proconvulsants while progesterone is ascribed to anticonvulsant effects. This is also illustrated by the phenomenon of catamenial epilepsy, ie, epileptic seizures that occur predominantly in certain phases of the menstrual cycle.⁶³ Neuroactive, progesterone-derived steroids, such as allopregnanolone and ganaxolone, are being clinically studied for their potential as AEDs.⁶⁴ So far, although HC has been used for ~50 years now, there is no conclusive evidence supporting the idea that EE or HC in general may aggravate epileptic seizures.^{65–67}

Osteoporosis and bone fracture risk

It has long been known that patients taking enzyme-inducing AEDs (phenytoin, phenobarbital, carbamazepine, topiramate, and others) are at a significantly higher risk for developing osteoporosis.^{68,69} HC has also been associated with decreased bone mineral density and increased risk of fractures. This is best documented for DMPA, particularly when used for more than 2 years. Regarding the effects of other contraceptive progestins or EE, recent meta-analyses conclude that data still are conflicting despite a large number of published studies.^{70–72} Some, but not all, studies show that EE may reduce bone mineral density, although this effect may depend on dose and/or treatment duration. Patients must be informed about this issue. Most importantly, the effects

of HC (especially DMPA) and enzyme-inducing AEDs on bone mineral density may add up, which is another reason to avoid this problematic combination.

Adherence

Even the best drug treatment regimen will not work properly if the drug is not used as prescribed. Adherence to long-term therapy for chronic illnesses averages as low as 50% in developed countries. This includes potentially life-threatening conditions such as diabetes, asthma, or epilepsy. In developing countries, the rate is even lower.^{73,74} Irregular drug intake is also very common among HC users. Different studies found that up to 71% of women using COCs were taking their pills irregularly.^{75,76} These numbers match well with population studies demonstrating that approximately half of all pregnancies occur unintended.⁹ Once a woman becomes pregnant, marked physiologic changes occur, including increased metabolic capacity, increased renal blood flow, and increased volume of distribution. Accordingly, it has been shown for several AEDs that their serum levels decrease by half during pregnancy, often leading to breakthrough seizures. Moreover, many patients may fear harmful effects to their unborn child and stop taking their antiepileptic medication once they discover that they are pregnant. Given the serious and potentially fatal consequences of uncontrolled epilepsy for both the mother and the unborn child, as well as the significant risk of harmful pre- and postnatal effects that several AEDs may have on the child, unplanned pregnancy in WWE should be avoided and adherence be improved.

Many factors are negatively correlated with adherence; some of them are difficult to change, such as socioeconomic status, low education, ethnicity, or co-payments.⁷⁷ Apart from such factors, it may seem obvious that better patient education is a key factor to improve patient adherence. However, a large proportion of doctors lack the necessary knowledge, and many patients never receive adequate information.^{11–14,19–24} Also, although knowledge among doctors and patient education may have improved somewhat during recent years, still only half of WWE are able to recall the information they have been given.¹⁴ A recent study in WWE showed that an educational intervention using an informational handout led to increased knowledge on HC and drug interactions with AEDs, compared to standard information without the handout, although this effect was time limited.⁷⁸ However, sufficient knowledge alone may not guarantee a high degree of adherence, as it has been found in a recent study that the level of knowledge was the same among adherent and non-adherent patients with epilepsy (Samsonsen C, Trondheim, Norway, unpublished data). It might therefore be speculated

that many patients simply forget to take their medication. Indeed, it has been demonstrated that regular reminders such as an alarm app on the smartphone, text messages, or a digital pill dispenser improve regular pill intake significantly.^{79,80}

Thus, in addition to purely educative measures, continuous follow-up of the patient, behavioral interventions, and systematic reminders (in the office, via telephone or mail/e-mail, smartphone apps, or digital pill dispensers) may be useful to improve adherence and regular drug intake.^{81,82}

Practical recommendations:

- In patients taking AEDs that interact with HC (phenytoin, phenobarbital, primidone, carbamazepine, topiramate, oxcarbazepine, eslicarbazepine, felbamate, rufinamide, perampanel): add other form for contraception (eg, barrier method, IUD, or a combination of them) or alternatively, discuss with the patient's neurologist if switching to a nonenzyme-inducing AED is possible.
- In patients taking lamotrigine: avoid HC that contains EE (COCs, patch, vaginal ring) or alternatively, omit EE-free week (extended-cycle regimen).
- Inform and educate patient well on: available contraceptive methods and their strengths and weaknesses; frequency and possible consequences of nonadherence; possible drug interactions between AEDs and HC; and possible pre- and postnatal adverse effects of antiepileptic medication: size and nature of teratogenic risks of AEDs and possible negative cognitive effects of AEDs.
- Advocate for long-acting nonoral contraceptive measures (IUD, implant) to avoid risk of missed pills.
- If the patient prefers oral contraception, suggest to use smartphone app (pill-reminder), digital tablet dispenser, or other measures to minimize number of missed pills.
- Schedule frequent follow-ups (in the office, via phone, or via mail/e-mail) and repeat given information (may be done by trained nurses).
- Establish regular communication with the patient's neurologist.
- Keep yourself updated on drug interactions with HC.

Disclosure

The author reports no conflicts of interest in this work.

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