

## Chapter 2

# New Onset Partial Epilepsy in Adolescence

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### Case Scenario

An 18-year-old right-handed neurologically normal woman has new onset focal epilepsy, presenting with a secondary generalized tonic-clonic seizure after a year-long history of episodes of déjà vu associated with mild confusion lasting 1–2 min. She has a normal MRI, no risk factors for epilepsy, and an EEG that shows right temporal spikes. What is your decision pathway in terms of diagnostic and treatment approaches for her?

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## **AUTHOR #1'S RESPONSE**

### ***Evaluation***

#### **Step One**

Review the MRI with a radiologist with experience in epilepsy as well as with an epileptologist.

#### **Step Two**

An overnight EEG should be ordered, either ambulatory or inpatient, to determine the extent of epileptiform abnormalities in sleep and awake and determine risk of future seizures.

#### **Step Three**

Classify the seizures as best as you can! Get a good description of her event including the feelings or auras that the patient experienced before the clinical seizure, the actual presentation, how long it lasted, and how long until it generalized. This will aid in determining the area of seizure onset and help to decide future treatment options including epileptic surgery if the seizures do not respond to treatment with medications.

#### **Step Four: Treatment Options**

1. Wait: Watch to see if more events occur. If this was an isolated incident and the patient had not reported auras, it would be reasonable to wait and see if she had another seizure over the next 6–12 months before initiating treatment.
2. Treat: In this case the patient has auras and an abnormal EEG. There is a risk of recurrent seizures and it is prudent to initiate treatment with medication. When choosing medications for treatment of seizures, the provider must first determine whether the medication is appropriate for the treatment of focal seizures.

### ***Things to Consider***

It is important to get to know your patient—where is she in her life? Starting college, moving out, starting a job, starting a family? The provider needs to consider certain things:

1. Body image issues: Will the medication cause weight loss or weight gain? In adolescent girls, most providers will want to avoid medications that increase appetite and can cause weight gain. However, if the patient is underweight, medications that decrease appetite should be avoided. Weight should be monitored during treatment.
2. Childbearing potential: Will any of the medications cause infertility or are they teratogenic? Pregnancy registries are our best sources of information regarding outcomes. Women with epilepsy are known to be less fertile than other women [1] but there is no evidence to suggest that certain anti-epileptic drugs (AEDs) cause a decrease in fertility. Some medications are teratogenic and should be avoided in pregnancy and in women of childbearing potential, because of a risk of impaired fine motor skills and social skills and major congenital malformations in their offspring [2].
3. Drug-to-drug interactions: It is important to consider the interaction of the anti-seizure medication with medications used for other medical conditions. In this case, the patient has no medical history, but if she had a chronic illness—asthma, cardiac disease, or diabetes, interactions would have to be checked.
4. Contraception: Some contraceptives decrease the efficacy of antiepileptic medications. Some AEDs decrease the efficacy of hormonal contraceptives and therefore alternate birth control options should be explored (see Table 2.1). Contraceptives are sometimes used in catamenial epilepsy to decrease frequency and length of menses, thereby decreasing seizures [3].
5. Neuropsychiatric side effects: Some medications can cause irritability and even psychosis, while others are mood stabilizing. Supplementation with vitamin B6 can prevent this side effect. Often, persons newly diagnosed with epilepsy become depressed and/or anxious. This should be closely monitored.
6. Monitoring: This includes the need for blood levels, CBC, chemistry, liver function tests, and chemistry (all of which are specific to the AED prescribed). The provider should also determine how often the EEG and a prolonged EEG should be repeated and whether or not the neuroimaging study should be repeated, perhaps using an epilepsy surgery protocol. Typically, this would be required if the seizures become intractable.
7. Supplements: All women should be supplemented with Calcium and vitamin D. Women of childbearing age should receive folic acid supplementation to reduce the risk for fetal birth defects.
8. Breast feeding: Recent studies show that antiepileptic medication is safe in breastfeeding [4].
9. Driving: In many states, providers are mandated to report persons with epilepsy to the Department of Motor Vehicles. Laws may restrict driving for a certain period of time after a seizure, although some states make allowances for breakthrough seizures that occur with medication changes.
10. Lifestyles: Alcohol, marijuana, adherence to regimen, late nights, school notification, and marriage notification. The patient in question is 18 years old. In some cultures, she is achieving independence by working. In others, she is in college; and in some she may be preparing for marriage. It is important to choose medications that will provide good seizure control even

**Table 2.1** Medication in focal epilepsy

Generic name	Brand name	Mechanism of action	Teratogenicity	Interaction with hormonal contraceptives	Effect on weight	Comments
Carbamazepine	Carbatrol, tegretol	Blocks sodium channels	Neural tube defects	Decrease efficacy of OCP	Increased	Monitor blood levels—may lower sodium
Oxcarbazepine	Trileptal	Blocks sodium channels	Inadequate data	Decrease efficacy of OCP	Neutral (increased)	May lower sodium
Levetiracetam	Keppra	Inhibits sodium channels	Low rate of defects; no specific type	Weak enzyme inducer/inhibitor	Neutral	Side effect of irritability
Valproic acid	Depakote	Increases GABA, may inhibit glutamate/NMDA	Neural tube defects and lowering of IQ	CYP450	Increased	Not with PCOS or DM—monitor blood levels—may decrease platelets and effect liver
Eslicarbazepine acetate	Aptiom	Inhibits sodium channels	No data	Reduces efficacy of oral contraceptives	Neutral	Monitor sodium
Topiramate	Topamax, Trokendi, Qudexy	Blocks voltage-dependent sodium channels; augments GABA, antagonizes glutamate receptors, and inhibits carbonic anhydrase	Cleft palate	None	Decreased	Can cause renal stones, glaucoma
Lacosamide	Vimpat	Enhances slow inactivation of voltage-sensitive sodium channels	Insufficient data	Prolongs PR interval	Neutral	Contraindicated with cardiac failure
Lamotrigine	Lamictal	Sodium channels	Cleft lip and palate	Decrease efficacy of OCP	Neutral	Risk of Stevens-Johnson sx

if she is using recreational drugs, like alcohol and marijuana and even when she is sleep-deprived. The provider needs to discuss the fact that alcohol, marijuana with a high THC content, and sleep deprivation lower the seizure threshold. She should be encouraged to abstain from the use of recreational drugs, get adequate sleep each night (no pulling all-nighters to study) and that the medication **MUST** be taken as prescribed and at approximately the same time every day. Patients are more compliant when medications are dosed once a day, so the use of extended release medications is encouraged. However, we have found that in some active adolescents, the extended release formulations still need to be taken twice a day. As for marriage, if this girl is about to enter into marriage, it is likely that the other family will require assurance that the epilepsy is not genetically mediated.

11. Menstrual concerns/Catamenial epilepsy refers to epilepsies in which seizures occur more frequently around menses and ovulation, occurring in about 35 % of women with epilepsy, independent of the type of seizure or its etiology [5]. The hypothesis is that cortical excitability varies with hormonal fluctuation in women with epilepsy [6].
12. Other tests: If this patient's seizures become intractable, treatment options include ketogenic diet, non-lesional resective surgery, vagal nerve stimulator, and responsive neurostimulation. Evaluation for surgery would necessitate a repeat MRI, video EEG, neuropsychological testing, functional MRI, and possibly a Wada.

In conclusion, in caring for this adolescent female with a history of auras and new onset of seizures, the decision pathway should include:

- A good evaluation
- Getting to know the patient
- Consideration of side effects when treating with medications
- Education
- Periodic reevaluation of treatment

## **AUTHOR #2'S RESPONSE**

With respect to treatment options, there are several antiepileptic medications that could be considered. It is the responsibility of the physician to inform the patient that AED therapy is important and will, most likely, prevent further seizures. It is also the physician's responsibility to partner with the patient with respect to the available choices of AED therapy. The risks vs. benefits should be described in detail.

The possible AED options include:

1. Oxcarbazepine
2. Carbamazepine
3. Lamotrigine

## 4. Levetiracetam

## 5. Valproate

Levetiracetam is certainly an antiepileptic medication that should be considered. There are no known drug interactions. It does not affect the liver or bone marrow, being excreted primarily through the kidney. It rarely produces an allergic drug rash and does not affect neurocognitive functioning. Its primary side effects include behavioral disinhibition and psychiatric effects, including increased risk of suicidal thoughts. For an adolescent with a tendency for anxiety and/or depression, this might not be the best choice. With respect to reproductive health, the initial pregnancy registry data suggests a low risk for major congenital malformations.

Oxcarbazepine or carbamazepine could be considered for this young woman. These two antiepileptic medications are generally well tolerated at therapeutic dosages and equally effective in the treatment of partial epilepsy [7]. If high dosages are required, there may be cognitive side effects. In addition, weight gain can be seen with both of these medications. Oxcarbazepine does not produce the epoxide metabolite, which is felt to be responsible for the primary side effects of carbamazepine, including nausea, vomiting, diplopia, fatigue, and ataxia.

With respect to reproductive health, carbamazepine does carry a risk of major congenital anomalies, including neural tube defects and oral clefts. The teratogenic effects of oxcarbazepine are yet to be fully defined. If this adolescent chooses to go on oral contraceptives or use Depo-Provera, she should be informed that both carbamazepine and oxcarbazepine are P450 enzyme inducers, but carbamazepine is the more potent inducer. Oral contraceptives and Depo-Provera are metabolized by the P450 enzyme system. Therefore, if an oral contraceptive is chosen, it must contain relatively high-dose estrogen (50 micrograms). The Depo-provera injections need to be given more frequently than in someone who is not taking an enzyme-inducing drug [8, 9].

In summary, both carbamazepine and oxcarbazepine are effective in the treatment of partial epilepsy. However, oxcarbazepine is preferable, given its better safety profile (less risk of idiosyncratic reactions), lack of autoinduction, low protein binding, linear pharmacokinetics, and minimal drug interactions, contraceptives excluded [7, 8].

Lamotrigine is another antiepileptic medication to consider for this young woman. It is well tolerated, with few side effects. It does not change a patient's neurocognitive profile, is a mood stabilizer, and can function as an antidepressant. Most patients like the fact that lamotrigine does not affect their cognitive abilities and improves their mood. There are a few patients who become more anxious on lamotrigine, and some may experience sleep disturbance. If this patient has obsessive compulsive tendencies, lamotrigine might exacerbate them.

One drawback of lamotrigine is that it requires a slow titration in order to avoid the risk of a serious allergic rash. In an adult patient, this risk (such as Steven's

Johnson syndrome) is approximately 0.3 %. If a patient is having frequent seizures, the lamotrigine titration process may be too risky. However, some physicians will use a bridging medication, such as clonazepam, as the lamotrigine is titrated into the therapeutic range.

With respect to reproductive health, lamotrigine does not affect estradiol metabolism, but does affect the levonorgestrel metabolism. No breakthrough ovulation has been reported, but oral contraceptives alone as a form of birth control may be inadequate. One pregnancy registry has reported an increased risk of cleft palate/cleft lip as a teratogenic side effect of lamotrigine. However, this has not been confirmed in other pregnancy registries [8, 9].

Valproate should not be used as a first choice antiepileptic medication in a young woman in the reproductive age. There are several reasons for this, including:

1. Valproate has been reported to cause menstrual irregularities and anovulatory cycles; hormonal changes such as hyperandrogenism and increased testosterone; hyperinsulinism; and polycystic ovaries. With respect to polycystic ovary syndrome and its association with valproate, the epilepsy itself, hypothalamic dysfunction, and additional factors may be also be contributory [10].
2. Valproate has proven teratogenic effects, including an increased risk of neural tube defects [8, 9].
3. In the NEAD study, children who have been exposed to valproate in utero and who had developmental assessments at age three were found to have significant cognitive impairments compared to children who had fetal exposure to other antiepileptic medications [11].

Phenobarbital would be relatively contraindicated in this young woman, due to its cognitive side effects. Phenytoin would also be relatively contraindicated due to its many side effects (cognitive slowing, coarsening of the facial features, hirsutism, osteoporosis, and teratogenic effects), its pharmacokinetics, and its many drug interactions.

Lacosamide is FDA approved as initial monotherapy or conversion to monotherapy and as adjunctive therapy in partial epilepsy. Lacosamide use in this clinical setting is limited by the lack of evidence for teratogenic risk. This limits the ability to counsel and discuss regarding its use. It does not interact with oral contraceptives however.

The optimal choices for this young woman would include: oxcarbazepine, levetiracetam, or lamotrigine. The choice would depend on the concurrent medical and psychiatric history, as well as the woman's own preferences.

Finally, if this woman's epilepsy is not controlled despite two trials of antiepileptic medication, appropriately chosen, with levels pushed to the high therapeutic range, she should be evaluated for epilepsy surgery. Her seizures appear to emanate from the right temporal lobe, probably nondominant. If the presurgical evaluation confirms this, she would fall into a favorable group for epilepsy surgery.

## Reviewer's Comments

These two responses are very different in their emphasis, but between them, the diagnostic, treatment and counseling approaches for the 18-year-old woman with new onset focal epilepsy are encompassed. The contribution by Author #1 begins with a stepwise approach to understanding the exact epilepsy diagnosis and etiology. This is followed by a comprehensive approach to understanding the individual patient and her specific concerns and risk factors for medication side effects, seizure recurrence, and reproductive vulnerability. They point out that the query, “where are you in your life right now?” in terms of school, working, driving, romantic involvements and activities with friends is key to guiding medication choices. Author #2 accepted the premise that this is a newly diagnosed epilepsy patient and focused on her exact medication choices. These were oxcarbazepine, levetiracetam or lamotrigine, with details regarding the benefits and drawbacks of each choice for this patient. Both responses incorporated the need to tailor the treatment choice to fit the clinical scenario as well as involving the patient in the medication choice. Both responses concluded with consideration of epilepsy surgery if the patient does not respond to medication treatment, specifically stated in Author #2's contribution, “if this woman's epilepsy is not controlled despite two trials of antiepileptic medication, appropriately chosen, with levels pushed to the high therapeutic range, she should be evaluated for epilepsy surgery.” Consideration of an epilepsy surgery evaluation for appropriate patients is always on the “front-burner” for epilepsy doctors. However, recent data show that in the pediatric age group, obstacles to the timely consideration of epilepsy surgery are both systematic and random. For example, the decision to move forward with epilepsy surgery is linked to difficult-to-quantify considerations such as the patient and family's acceptance of the option, the strength of the therapeutic alliance with the healthcare team, and the family's ability to absorb a likely financial setback [12]. While epilepsy surgery may be a consideration as this patient is assessed on an ongoing basis, the chapters here provide an excellent overview of initial management of this young focal epilepsy patient.

## Suggested Management

1. Once the diagnosis of focal epilepsy is established, lamotrigine, oxcarbazepine, and levetiracetam are reasonable treatment options.
2. Current lifestyle and lifestyle goals are important considerations in guiding pharmacologic and non-pharmacologic management.
3. Pregnancy risks must be addressed for young women.
4. Early identification of antiseizure drug-resistant patients who may be candidates for surgical cure is important to mitigate a life trajectory turned downward by seizures.



## References

1. Morrell MJ, Giudice L, Flynn KL, Seale CG, Paulson AJ, Done S, et al. Predictors of ovulatory failure in women with epilepsy. *Ann Neurol*. 2002;52:704–11.
2. Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry*. 2014;85:1029–34.
3. Najafi M, Sadeghi MM, Mehvari J, Zare M, Akbari M. Progesterone therapy in women with intractable catamenial epilepsy. *Adv Biomed Res*. 2013;2:8.
4. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol*. 2013;70:1367–74.
5. El-Khayat HA, Soliman NA, Tomoum HY, Omram MA, El-Wakad AS, Shatla RH. Reproductive hormonal changes and catamenial pattern in adolescent females with epilepsy. *Epilepsia*. 2008;49:1619–26.
6. Badawy RA, Vogrin SJ, Lai A, Cook MJ. Are patterns of cortical hyperexcitability altered in catamenial epilepsy? *Ann Neurol*. 2013;74:743–57.
7. Mintzer S, Mattson RT. Should enzyme-inducing antiepileptic drugs be considered first-line agents? *Epilepsia*. 2009;50 Suppl 8:42–50.
8. Pennell PB. Chapter 45: Treatment of epilepsy during pregnancy. In: Wyllie E, Cascino G, Gidal B, Goodkin H, editors. *Wyllie's treatment of epilepsy: principles and practice*. 5th ed. Philadelphia: Lippincott, Williams and Wilkins; 2011. p. 557–68.
9. Pennell PB. Pregnancy, epilepsy and women's issues. *Continuum*. 2013;19(3):697–714.
10. Harden CL, Pennell PB. Neuroendocrine considerations in the treatment of men and women with epilepsy. *Lancet Neurol*. 2013;12:72–83.
11. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med*. 2009;360:1597–605.
12. Baca CB, Pieters HC, Iwaki TJ, Mathern GW, Vickrey BG. "A journey around the world": parent narratives of the journey to pediatric resective epilepsy surgery and beyond. *Epilepsia*. 2015;56:822–32.

Controversies in Caring for Women with Epilepsy

Sorting Through the Evidence

Sazgar, M.; Harden, C.L. (Eds.)

2016, XIII, 173 p. 18 illus., 10 illus. in color., Hardcover

ISBN: 978-3-319-29168-0