# 16 AED Failures

The 28-year-old schoolteacher (see Chapter 10) returned for follow-up. He was initially started on lamotrigine but developed a rash after the third week of exposure. He was then started on levetiracetam (Keppra) 750 mg BID due to the fast action of onset and given that effects on mood and behavior tend to be notable and reversible. He did well for 6 months but then had another seizure, and the dose was increased to 1,500 mg BID 2 months ago. He reports that he not only feels more anxious than before, but also had one typical seizure and several auras on this dose.

***What do you do now?***

With drug failures, the major question becomes whether to change medications, and if so, whether to institute a cross-taper or to add a second medication to the first. A drug failure may be due to intolerance of adverse effects or to lack of efficacy. In this case, his first drug failure was actually lamotrigine due to the rash risk. In most cases with rash, the likely offending agent must be immediately discontinued (see Chapter 12), eliminating that decision. In fact, in most cases of intolerability, the offending AED should be discontinued or reduced, because side effects can be more disabling than the seizures themselves. We must always aim for the modern goal of "no seizures, no side effects."

In this case, the patient appeared to tolerate a moderate dose of levetiracetam, and it appeared to decrease seizure frequency, but it was only partially effective. The dose was increased until side effects were noted, and yet a seizure still occurred. He was compliant with medications, but if he was having problems with missed or late doses, using the extended-release formulation could be considered.

It is important to specifically screen for side effects, particularly as recommended maximal doses are reached, though the recommended dose range may be exceeded as specific patients may be fast metabolizers or may be on concomitant medications that reduce effects. As doses increase, or when polytherapy begins, drawing peak or trough drug levels may help guide dosing, but the paramount guide is the patient and his or her reported or elicited side effects, including mood, irritability, and cognitive abilities. For instance, if the patient had no side effects at a dose of 3,000 mg/day, he may be part of the small percent that improve on 4,000mg/day, though this is not common practice. Occasionally seizures appear to worsen on very high doses of AEDs, although this is controversial.

Complete seizure freedom is the goal. Another medication can be added to the lower, tolerated dose of levetiracetam or a cross-taper can be designed to attempt monotherapy of another AED. The choice has been debated and studied, and there is no clear right or wrong answer. There are a few factors to consider.

1. Adding a second agent may not increase protection, but it also may not increase the likelihood of new or additive side-effects.

a. A study of 157 patients showed no difference in efficacy or side effects in patients randomized to adjunctive therapy or alternative monotherapy (Beghi et al., 2003).
b. A multicenter study ($n$ = 809) studied similar endpoints and concluded it was instead an individual's susceptibility, the type of AED, and the skill of the practitioner that had the greatest impact on side effects (Canevini et al., 2010).

2. Alternative monotherapy (cross-titration) may be best if:
   a. The first AED failed due to intolerability
   b. The patient is planning a pregnancy in the near future
3. Adding a second agent may be best if:
   a. The patient had at least a partial response and had no adverse effects at a lower dose
   b. The consequences of another seizure in the short term are very high
4. Costs: the total healthcare costs of dual therapy compared to switching to another monotherapy treatment were higher, primarily due to the costs of providing two AEDs (Lee et al, 2005).
5. The fact that this initial AED failure occurred decreases the chances of seizure freedom (see Table 16.1).

5a. (Mohanraj & Brodie, 2006), more patients became seizure-free when the combination involved a sodium channel blocker (considered to include carbamazepine, phenytoin, lamotrigine) and

**TABLE 16-1 Percentage Chance of Remission with Sequential Regimens in Patients with Newly Diagnosed Epilepsy ($n$ = 780) Failing Treatment Because of Lack of Efficacy or Adverse Effects**

| | Lack of efficacy | Adverse effects | All causes |
|---|---|---|---|
| First drug | 21 | 42 | 26 |
| Second schedule | 8 | 17 | 11 |
| Third schedule | 4 | 14 | 9 |

From Mohanraj & Brodie, 2006.

a drug with multiple mechanisms of action (considered gabapentin, topiramate, valproic acid) (36%) compared to other combinations (7%, $p$= 0.05).

**KEY POINTS TO REMEMBER**

- A "drug failure" can be due to side effects, to lack of efficacy, or rarely to misdiagnosis. Formal diagnosis in a monitoring unit may become important to ensure you are actually treating epilepsy, as cardiac disorders such as long-QT syndrome and nonepileptic spells of a psychogenic nature can present similarly.
- The choice is between monotherapy with an alternative AED or dual therapy; there appears to be no difference in efficacy or rate of side effects.
- Rational polytherapy is not yet proven, but there may be combinations that are synergistic (sodium channel blocker plus multiple-mechanism medication), while using multiple sodium channel blockers at high doses may increase the risk for side effects. The combination of valproic acid (Depakote) and lamotrigine may be particularly effective based on human observational studies. Polytherapy should be maintained only when the positive effects outweigh the potential side-effect burden. Slow withdrawal of one medication over weeks to months may be indicated.
- With any change in medications, potential pharmacokinetic interactions should be anticipated (see Chapter 17 on AED-AED interactions). Carbamazepine auto-induction is maximal at 4 to 6 weeks of exposure. De-induction may be as quick as days to weeks. Protein binding is important to consider for phenytoin, valproic acid, phenobarbital, and benzodiazepines.

**Further Reading**

Beghi E, et al. Adjunctive therapy versus alternative monotherapy in patients with partial epilepsy failing on a single drug: a multicentre, randomised, pragmatic controlled trial. *Epilepsy Res.* 2003;57(1):1-13.

Canevini MP, et al. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. *Epilepsia.* 2010;51(5):797-804.

French JA, Faught E. Rational polytherapy. *Epilepsia.* 2009;50(Suppl 8):63-68.

Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? *Seizure.* 2000;9(7):464-468.

Lee WC, et al. A cost comparison of alternative regimens for treatment-refractory partial seizure disorder: an econometric analysis. *Clin Ther.* 2005;27(10): 1629-1638.

Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. *Eur J Neurol.* 2006;13(3):277-282.

# 17 Drug-Drug Interactions: AEDs

A 33-year-old woman presents to your office. She was diagnosed with juvenile myoclonic epilepsy in late adolescence and has been on valproate since that time. She was married last year and is now planning a pregnancy. She and her husband were wondering if she should change to another medication.

*What do you do now?*

There are multiple reasons to make changes to a medication regimen. Most are for medication failures, but occasionally they are initiated to reduce the overall medication burden in well-controlled patients and to reduce the potential for teratogenicity.

This case represents a common but relatively simple situation. There is a need to avoid valproate in pregnancy, and there are several medications that appear to have significantly lower risks of major malformations and cognitive outcomes in the baby (see Chapter 19). In this case, lamotrigine was chosen. Because valproate inhibits glucuronidation, lamotrigine is cleared about half as quickly and thus the initial titration to begin lamotrigine is half as fast, starting with 25 mg every other day for 2 weeks, increasing to 25 mg daily for 2 weeks, then to 25 mg BID for 1 week.

If valproate is added to a patient on a steady dose of lamotrigine, the dose of lamotrigine will eventually need to be reduced, possibly as much as halved. Monitoring for side effects and obtaining levels of both medications during this period are advisable (Table 17.1).

Conversely, it is well known that medications that induce liver enzymes will increase clearance of other liver-metabolized medications. Enzyme-inducing AEDs (EIAED) include phenytoin, phenobarbital, carbamazepine, primidone, and (at doses over 400 mg/day) topiramate. Rufinamide may also induce some enzymes at high doses. Oxcarbazepine has minimal to no interactions with other AEDs though does affect oral contraceptives (see chapter 18). Sometimes rapid metabolism can result in worse neurotoxicity despite similar or lower levels of the AED. Carbamazepine epoxide is considered the cause of neurotoxic side effects, and its level is increased with increased metabolism, despite decreasing carbamazepine levels. This toxic epoxide is also increased with coadministration of valproic acid, which inhibits the metabolism of the epoxide. Primidone is a prodrug that is metabolized to phenobarbital, and increasing this process will lower primidone but increase phenobarbital levels.

Phenytoin induces lamotrigine metabolism to a greater extent than carbamazepine. Thus, lamotrigine dosing should be decreased by 50-75% after stopping phenytoin, whereas the decrease in lamotrigine dose should be 25-50% with carbamazepine discontinuation; essentially complete withdrawal of the EIAED is required prior to the change in lamotrigine levels occurring , showing induction is an all-or-none phenomenon rather

TABLE 17-1 Effects of AEDs on Serum Concentrations of Other AEDs

| What happens to the level of AED below with administration of the AED to the right: | Inducers: PB, PHT | CBZ | OXC | Inhibitor: VPA | FBM | GBP^, TPM*, TGB, LVT, OXC, ZNS, PGB, RFN*, LCM, LTG |
|---|---|---|---|---|---|---|
| Benzodiazepines | ↓ | ↓ | ? | ↑ 100-150% | ? | NC |
| Carbamazepine | ↓, CPZ-E may increase | ↓ | | CBZ-E ↑ 100% | ↓20-30%, but CBZ-E ↑50-60% | NC |
| Ethosuximde | ↓ | ↓ | ? | +/- | | |
| Felbamate | ↓15% | ↓ | | ↑ mild | | |
| Gabapentin | NC | NC | NC | NC | NC | NC |
| Lacosamide | | NC | NC | NC | ? | NC |
| Lamotrigine | ↓50% | ↓50% | ↓mild | ↑ 100-150% | NC | NC |
| Levetiracetam | ↓mild | ↓mild | | NC | NC | NC |
| Oxcarbazepine | | NC | | | | |
| Phenobarbital | +/- | +/- | NC | ↑50-80% | ↑30-50% | NC |
| Phenytoin | +/- | +/- | NC | ↑50-80% | ↑30-50% | NC |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pregabalin | NC | NC | NC | NC | NC | NC |
| Primidone | ↑PB/PRM PEMA/PRM ratios | ↑PB/PRM PEMA/PRM ratios | | +/- | | NC |
| Rufinamide | ↓25-46% | ↓10-30% | | ↑ 15-70% dose-dependent | | |
| Topiramate | ↓50% | ↓50% | | ? | ? | NC |
| Tiagabine | ↓ | ↓ | | | | |
| Valproate | ↓33-50% | ↓33-50% | | | ↑25-60% dose-dependent | |
| Vigabatrin | NC | NC | | NC | NC | NC |
| Zonisamide | ↓ | ↓mild | | ↑ | | |

*Topiramate >400 mg/day and rufinamide 40-50 mg/kg/day appear to have inducing properties.

^Gabapentin may significantly increase the elimination time of felbamate.

***Note:*** Some of these interactions have not been directly studied, but probable effects can be inferred from known drug properties. The effects shown in the table represents the effects on each drug/class in the top row when the AED listed on the left is added. PHT, phenytoin; CBZ, carbamazepine; CBZ-E, carbamazepine epoxide; PB, phenobarbital; VPA, valproic acid; GBP, gabapentin; LCM, lacosamide; LTG, lamotrigine; TGB, tiagabine; LVT, levetiracetam; OXC, oxcarbazepine; RFN, rufinamide; ZNS, zonisamide. +/- = variable, NC = no change, ? = unknown.

than proportional to dose. The timecourse of both induction and de-induction is theoretically related to the half-life of the EIAED, requiring 5 half-lives following discontinuation of the EIAED for de-induction to be complete. Half-lives are shown in Appendix II. Hepatic induction of carbamazepine on it's own clearance is termed autoinduction. It starts within a week and is maximal within 6 weeks. De-autoinduction of carbamazepine has been shown to occur within days.

Other AED–AED interactions are due to protein binding. AEDs that are highly protein-bound include phenytoin, valproic acid, and benzodiazepines. Carbamazepine is moderately protein-bound. When administered simultaneously within a patient, they compete for protein binding sites, thereby increasing each other's free fraction, which is the pharmacologically active portion responsible for both therapeutic and toxic effects. The total level measured will not increase, so a free level must be obtained to determine the degree of the effects.

Pharmacodynamics refers to the effect at the receptor or functional level. Research has been aimed at looking at positive pharmacodynamic interactions—that is, AEDs that appear synergistic when used together. There are preclinical data to support this theory but it has not yet been proven in human epilepsy. The opposite appears to occur, in that AEDs with similar side-effect profiles appear more likely to cause side effects when used together. This has been shown when combining lacosamide with other sodium channel-blocking agents.

**KEY POINTS TO REMEMBER**

- Valproate is an inhibitor and generally will increase the levels of other medications that are metabolized by the liver; this includes lamotrigine and benzodiazepines.
- Enzyme-inducers can cause problems with maintaining the therapeutic window of other AEDs or other medications the patient may be taking.
- Protein binding interactions will elevate the effective doses of phenytoin, valproic acid, and benzodiazepines when used together.
- Sodium channel blockers used together tend to have additive adverse effects, thus making their side effects more likely.

## Further Reading

Díaz RA, Sancho J, Serratosa J. Antiepileptic drug interactions. *Neurologist.* 2008;14(6 Suppl 1):S55-65.

Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol.* 2003;2(6):347-356.

Anderson GD, Gidal BE, Messenheimer JA, Gilliam FG. Time course of lamotrigine de-induction: impact of step-wise withdrawal of carbamazepine or phenytoin. *Epilepsy Res.* 2002;49(3):211-7.

# 18 Drug-Drug Interactions: Other Medications

An 82-year-old right-handed man presented for management regarding recent possible seizures. Three years ago, he passed out in a department store. His wife saw him staring at the ceiling, he appeared to be stiff and then fell over, without tongue bite or incontinence. In the ER, he was found to be in atrial fibrillation and warfarin (Coumadin) was initiated. A repeat episode occurred but with confusion that lasted for an hour, with normal vitals. It was presumed he had a seizure and was started on phenytoin (Phenytoin) 200 mg/day. His physicians increased the dose based on his low therapeutic phenytoin blood levels to 400 mg/day.

Within a few weeks of starting phenytoin, his warfarin requirements increased significantly. He was initially on 5mg/day, but the hematologists found his INR remained below therapeutic at a dose of 10 mg/day.

About the same time, he noted tingling sensations running down the legs. He was worried that the Phenytoin was responsible for the leg sensations and the change in the warfarin dosing, and he was wondering whether this was the best medication for him.

### What do you do now?

This patient has multiple medical issues, the most concerning of them being atrial fibrillation and the need for warfarin. Phenytoin was not the optimal choice due to its significant effects as an enzyme-inducing AED (EIAED). In this case, the haematologists continued to "chase" the INR by increasing his warfarin to over twice the original dose. Once the correct dose is found, it should not significantly change. However, if he were to become de-induced, either through exposure to another medication or by grapefruit juice, for instance, he could become severely supratherapeutic in terms of INR and phenytoin toxicity; the combination of ataxia and a lack of clotting factors could be disastrous. In this case, phenytoin was also contributing to peripheral neuropathic symptoms, which could also increase the risk of falls.

This patient was having flashbacks and frightening nightmares, so AEDS with potential for negative behavioral effects were avoided (levetiracetam, zonisamide, topiramate). Lamotrigine was chosen to replace phenytoin due to its antidepressant and mood-stabilizing effects. Initiation of lamotrigine while on phenytoin requires a titration schedule of EIAED regimens without valproic acid: starting with 25 mg BID for 2 weeks, then 50 mg BID for 2 weeks. The dose can then be increased by 100 mg/day every 1 to 2 weeks. Obtaining a therapeutic lamotrigine level is helpful to check whether a reasonable serum level has been achieved prior to the phenytoin taper. A patient who complains of blurred or double vision, lightheadedness, or tremor is likely lamotrigine toxic; this may be worsened by the phenytoin, which can cause similar side effects.

With the reduction of phenytoin there will be de-induction of the liver, and both the lamotrigine level and the INR will climb. The lamotrigine level will approximately double, typically once the phenytoin is completely discontinued, as the level of induction appears independent of the EIAED level (phenytoin or carbamazepine) serum level. The exact timing of de-induction for phenytoin has not been published, but it may be within days to weeks. Loss of auto-induction to carbamazepine may occur within 4 days.

EIAEDs interact with non–epilepsy-related medications that are also metabolized by the liver. This includes statin medications, whose efficacy may be significantly reduced. Interestingly, enzyme inducers may, on their own, cause elevations in markers of vascular disease. The entire list of interactions is exhaustive and includes antineoplastics, beta blockers, calcium channel blockers, immunosuppressants, some neuroleptics and SSRIs,

acetaminophen, and methadone. The increase in metabolism can be harmful—for instance, acetaminophen levels may be lower than normal but the toxic metabolites will be elevated. Oral contraceptives are decreased by the typical enzyme inducers, in addition to oxcarbazepine, topiramate at doses higher than 400 mg/day, and rufinamide at higher doses, often to the point of ineffectiveness. Women of childbearing age who note spotting should use a second method of contraception. Oral contraceptives with higher concentrations of estrogens are recommended (above 50 ug) but are less common on the market these days.

Commonly used medications may have an impact on AED levels. Ibuprofen, protease inhibitors, omeprazole, and tricyclic antidepressants increase phenytoin levels. Valproate levels will be reduced by carbapenems but increased by macrolides. This may be due to effects in the liver or possibly to effects on other mechanisms, such as P-glycoprotein.

**KEY POINTS TO REMEMBER**

- **EIAEDs and enzyme inhibitors affect and are affected by more than just other AEDs.**
- **Commonly used medications that interact with AEDs include oral contraceptives (significant dose increases are required with EIAEDs to avoid unplanned pregnancies) and Coumadin (careful monitoring of INR is required).**
- **EIAEDs can reduce the efficacy of many medications used for cardiovascular health such as beta blockers, calcium channel blockers, and statins.**
- **Levels of medications may be normal, but their toxic metabolite may be elevated (e.g., acetaminophen, carbamazepine).**

**Further Reading**


Anderson GD, et al. Time course of lamotrigine de-induction: impact of step-wise withdrawal of carbamazepine or phenytoin. *Epilepsy Res.* 2002;49(3):211-217.

Mintzer S. Metabolic consequences of antiepileptic drugs. *Curr Opin Neurol.* 2010;23(2):164-169.

Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol.* 2006;61(3):246-255.

# 19 AEDs in Pregnancy and Lactation

The patient is a 27-year-old woman who has had juvenile myoclonic epilepsy since age 14. She was initially treated with lamotrigine and levetiracetam but continued to have frequent myoclonus in the morning and generalized tonic-clonic seizures once or twice per year. She was subsequently switched to topiramate monotherapy and was seizure-free except for rare periods of myoclonus for 2 years. Seizures, however, returned and continued despite maximally tolerated doses of topiramate (400 mg/day). Valproate was added and her seizures became well controlled. She was subsequently able to transition to valproate monotherapy at 1,000 mg twice daily and has been seizure-free for 2 years. She is recently married and is interested in becoming pregnant and breast-feeding her infant. She is concerned about the risks of AED exposure to her developing infant.

*What do you do now?*

Many women with epilepsy are concerned with their ability to have healthy children. In the past, there were many misconceptions about the risks of epilepsy and AEDs for the infant and the pregnant mother. However, most women with epilepsy will have healthy babies and uncomplicated pregnancies. Recent data have allowed physicians to better counsel women with epilepsy on the risks of teratogenicity of AEDs, the effects of seizures on the developing infant, changes in seizure frequency during pregnancy, and the exposure of the infant to AEDs via breast milk (Table 19.1).

**TABLE 19-1 Antiepileptic Drugs in Pregnancy and Lactation**

| Drug | Risk of major malformations or neurocognitive impairment | Changes in serum levels during pregnancy | Breast milk excretion |
|---|---|---|---|
| Carbamazepine | • | • | • |
| Ethosuximide | - | - | ••• |
| Felbamate | - | - | - |
| Gabapentin | • | - | ••• |
| Lacosamide | - | - | - |
| Lamotrigine | • | ••• | •• |
| Levetiracetam | • | ••• | ••• |
| Oxcarbazepine | • | ••• | •• |
| Phenytoin | •• | •• | • |
| Phenobarbital | •• | •• | • |
| Primidone | •• | • | - |
| Pregabalin | - | - | - |
| Topiramate | •• | •• | ••• |
| Valproate | ••• | ••[1] | • |
| Vigabatrin | - | - | - |
| Zonisamide | - | •• | ••• |

• lowest; •• moderate; ••• highest; - insufficient published data
[1]Free levels likely unchanged.

In addition, neurologists and obstetricians have been able to identify ways to mitigate some of the risks.

Children of women with epilepsy have higher rates of major congenital malformations. These malformations include cardiac defects (tetralogy of Fallot, aortic coarctation, ventricular septal defects, valvular defects), genitourinary defects (hypospadias), gastrointestinal defects (imperforate anus, esophageal atresia), skeletal anomalies (hip dysplasia, polydactyly, club foot, finger hypoplasia), facial anomalies (cleft palate), and neural tube defects (spina bifida). These infants are also more likely to have microcephaly and growth retardation. It is thought that many of these defects are due to in utero exposure to AEDs, as women with epilepsy on these medications are 1.12 to 3.92 times more likely to have such malformations compared to untreated women. As much of organogenesis occurs early in fetal development, it is believed that first-trimester exposure to these drugs carries the greatest risk. As many women are already many weeks along when they realize they are pregnant, attempts to reduce the risks of anticonvulsant exposure to the offspring should ideally occur before conception. As in this case, discussion of these risks should occur when women could potentially become pregnant—that is, when they become sexually active or are interested in starting a family.

There is now sufficient evidence to suggest that some AEDs may be associated with higher rates of malformations than others. Valproate use appears to have the highest rate of malformations for which there exist sufficient pregnancy outcome data—10% in a recent meta-analysis by Meador and colleagues. Valproate use also is associated with a 1% to 2% risk of neural tube defects. Evidence suggests that this may be dose-dependent and less common in doses under 1,000 mg/day. Data from a large U.K. pregnancy registry suggested that other commonly used AEDs have lower rates of malformations when used in monotherapy: carbamazepine 2.2%, lamotrigine 3.2%, phenytoin 3.7%, phenobarbital 4.2%. There are insufficient data for other newer AEDs, but preliminary reports from pregnancy registries suggest monotherapy malformation rates for topiramate of 4.8%, levetiracetam 2.7%, oxcarbazepine 2.4%, and gabapentin 2.0%. There are very limited data for all other AEDs. It should be noted that the rate of fetal malformations ranged from 1.6% to 3% in control groups. There is also evidence that AED polytherapy increases the rate of malformations,

especially if the regimen includes valproate. Malformation rates appear to be dose-dependent for lamotrigine and valproate.

In addition to the risks of malformations, in utero exposure to some AEDs may lead to neurocognitive deficits in childhood. In the NEAD study, Meador and colleagues found that children born to women taking valproate had lower IQs at 3 years than children born to women taking carbamazepine, phenytoin, or lamotrigine.

While some AEDs may pose a risk to the offspring, seizures are likely more dangerous to the mother and offspring. A higher-than-expected rate of maternal death occurs in pregnant women with epilepsy, and generalized tonic-clonic seizures and status epilepticus may lead to fetal injury and death. Therefore, it is always advisable for women with epilepsy to take AEDs.

In this case, the patient's seizures are well controlled on valproate, a medication associated with a high rate of malformations. Therefore, as part of prepregnancy planning, steps should be taken to limit the risks associated with its use. While topiramate, lamotrigine, and levetiracetam – all appropriate AEDs for her epilepsy syndrome - were unable to control her seizures, it is unknown if she requires such high doses of valproate. The evidence suggests that doses below 800 mg/day are less likely to be associated with malformations or neurocognitive changes. Prior to becoming pregnant, her dose of valproate should be lowered to see if her seizures could still be well controlled at a lower dose. If she had not been on other appropriate AEDs in the past, a controlled cross-titration to another agent associated with a low rate of malformations is advisable. In addition, she should take folic acid, 2 to 4 mg daily, as several studies have shown lower rates of neural tube defects in women with epilepsy, and specifically in women taking valproate, who took prenatal folic acid. If the patient is already pregnant and her seizures are well controlled, it is usually not recommended to switch medications, as most of the adverse effects on fetal development have already occurred and the patient risks seizure recurrence during the transition to the unproven medication. It is also recommended that women with epilepsy receive prenatal care from an obstetrician with experience in managing high-risk pregnancies, if one is available. However, most of the current evidence suggests that women with epilepsy are not at a significantly higher risk of developing pregnancy or delivery complications than other healthy women.

During pregnancy, a woman undergoes significant physiological changes in blood volume, renal function, and hepatic function. These changes can affect the pharmacokinetics and metabolism of many anticonvulsant drugs. Changes in hepatic metabolism can affect drugs metabolized by the cytochrome P450 system. Levels of phenytoin and phenobarbital can decrease by 40% to 50% in the third trimester. Pregnancy has an even greater effect on glucuronidation, the main elimination mechanism for lamotrigine and the active metabolite of oxcarbazepine. Reductions in serum levels of both drugs can be up to 30% in later stages of pregnancy for some women. Although they are mainly cleared by the renal system, levetiracetam and topiramate serum levels also decrease, up to 50% in pregnancy. AED serum levels should be monitored frequently during pregnancy and dosage adjustments made to keep levels in a range that was adequate for good seizure control prior to pregnancy. After delivery, drug metabolism returns to normal levels within 2 to 3 weeks, and pregnant women should be given a schedule to reduce their doses after delivery to avoid toxicity.

Once the baby is born, women with epilepsy are typically encouraged to breast-feed their infant due to the cognitive, social, economic, and immunological benefits. Almost all AEDs tested are found in breast milk in some quantity, thus exposing the newborn. However, the AED concentration in the breast milk is inversely proportional to its degree of protein binding. Therefore, drugs such as phenytoin and valproate are found in concentrations significantly lower in breast milk than in the mother's serum. Drugs that do not have significant protein binding such as levetiracetam and gabapentin have similar concentrations in the serum and breast milk. In most infants, there is no clear clinical effect of AED exposure via breast milk, as the total amounts ingested are low and effectively cleared by their metabolic pathways. There is a theoretical concern that in preterm and early term infants some metabolic pathways, such as glucuronidation, are less developed and can lead to accumulation of drugs cleared by these mechanisms, such as lamotrigine and the active metabolite of oxcarbazepine. However, no studies to date have clearly demonstrated clinically important effects of infant exposure to AEDs via breast milk. However, all breast-feeding women with epilepsy should be counseled to monitor their infants for excessive sedation or irritability, potential signs that their infant is intoxicated by AEDs.

**KEY POINTS TO REMEMBER**

- Most women with epilepsy can expect to have uncomplicated pregnancies and healthy children.
- Some AEDs, such as valproate, are associated with higher rates of major congenital malformations and neurocognitive delay in children born to mothers with epilepsy and thus should be avoided as first-line agents in women with childbearing potential.
- AED polytherapy, especially when it includes valproate, is associated with higher rates of malformations.
- The ideal treatment for a woman planning to become pregnant is the lowest effective dose of a single AED. Any adjustments in medication dose should ideally be made well before conception.
- All women with epilepsy of childbearing potential should take folic acid to reduce the risk of neural tube defects.
- Pregnant women taking lamotrigine, levetiracetam, topiramate, and oxcarbazepine should have levels monitored frequently during the pregnancy, as serum levels may fall significantly and put them at risk for seizures.
- Women with epilepsy should be encouraged to breast-feed but should monitor their infants for signs of AED intoxication such as sedation and irritability, especially if they are taking medications that are not highly protein-bound.

**Further Reading**


Harden CL, Meador KJ, Pennell PB, et al. Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society *Neurology.* 2009;73:133-141.

Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med.* 2009;360(16):1597-1605.

Meador KJ, Reynolds M, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res.* 2008;81(1):1-13.

Sabers A, Tomson T. Managing antiepileptic drugs during pregnancy and lactation. *Curr Opin Neurol.* 2009;22(2):157-161.

# 20 Treatment of Epilepsy in the Elderly

An 83-year-old woman presented with her family. Six months ago, she had a right hemispheric ischemic stroke and was left with a dense left hemiparesis. Two months after the stroke, she was seen to have pulling of the head to the left, left body trembling with the eyes rolled backwards, and loss of urinary continence, but medications were not initiated. About 2 weeks ago the patient complained that the paralyzed left leg felt like it was shaking, although it was not visibly moving. Two days later, it progressed to visible clonic activity that spread to the left arm, followed by the head turning to the left and eyes rolling back. She was seen in the ER, where lamotrigine was initiated by the neurology consult service and follow-up arranged in your office. Just this past week, she has noticed complete sloughing of the skin off the palms and dryness of the skin on the face.

You note that she was unable to stand or walk unassisted, and she had a complete spastic left hemiparesis. The right wrist and forearm was rigid and cogwheeling was apparent. The left was unable to be

tested due to pain at the wrist, likely related to contractures.

Prior to the stroke, she was up to date with current events and very well read. Since the stroke she has been unable to read (likely due to left neglect/field cut) and behaviorally and verbally disinhibited. She is sleeping poorly due to the chronic post-stroke pain. Her family reports that she has been irritable and seemed depressed, and they are worried about her poor appetite. They also note that in the year prior to the stroke, she began slowing down, with a bent-over posture and shuffling steps. Her medication list includes metoprolol, amlodipine, lisinopril, simvastatin, ranitidine, zolpidem, baclofen, oxycodone, and aspirin.

## What do you do now?

Seizures in the elderly are common. They can be acute symptomatic—for instance, seizures that occur soon after a stroke are considered provoked and may not recur. One study showed 13% of patients who had a seizure within 1 week of an acute neurological event went on to have another in the next 10 years. Most in this situation will start an AED to prevent recurrence in the recovery period. Long-term AED use is generally not recommended, though, and the early EEG is not reliably predictive of long-term seizure recurrence. Many practitioners opt to treat with an AED short-term and at 3 to 6 months, if the EEG is devoid of epileptiform discharges and the history does not support seizure recurrence, the AED will be discontinued. Others will discontinue AEDs upon discharge from the hospital. There are few clear data to support either choice, but the risk of treatment includes medication interactions and possibly worsened post-stroke recovery due to phenytoin (Dilantin) and phenobarbital.

When seizures occur more remotely after a known neurologic insult, the chance of recurrence is between 50% and 90%, and most clinicians will continue AEDs indefinitely. Other risk factors for seizure recurrence are hemorrhagic or ischemic strokes that involve cortical areas.

Numerous studies have shown that the incidence of recurrent, unprovoked seizures (thus, epilepsy) increases sharply with age over 65 and is greatest in the elderly population compared to all other age groups. This will become even more of a problem as the population ages. Cerebrovascular disease is by far the most common cause, with 15% of survivors developing seizures within the first 5 years of the stroke. Degenerative diseases, head trauma, neoplasms, and CNS infections are far less common antecedents, and about 50% of epilepsy cases in the elderly are cryptogenic (an underlying cause is suspected, but etiology cannot be found).

The choice of medication is particularly important in the elderly and should be tailored to the patient, and in particular tolerability. In general, enzyme inducers should be avoided due to the multiple other medications the patient is likely taking. It is known, for instance, that enzyme-inducing AEDs reduce the effectiveness of statin medications and that on their own they may promote the risk of cardiovascular disease (see Chapter 18). Bone health is another consideration, which appears to be related to enzyme induction (see Chapter 29). Surprisingly, despite numerous guidelines, "sub-optimal AEDs," including Dilantin and phenobarbital, were still

initiated in 70% of elderly veterans with new-onset epilepsy between 2000 and 2004.

In the case presented, the patient likely had undiagnosed idiopathic Parkinson's disease even prior to the stroke. Valproate is known to exacerbate tremor, rigidity, and bradykinesia and should be avoided in this and most other elderly patients as it can bring out parkinsonism in patients who are otherwise asymptomatic. Valproate also has antiplatelet effects, which can exacerbate bruising and bleeds after falls, and it has a relatively high potential for encephalopathy and hyperammonemia. Lamotrigine was initially chosen in hopes of improving her depression. It can also bring out a tremor, although quite rarely. Zonisamide has been shown to improve patients with Parkinson's disease and is a reasonable choice, although the side effect of anorexia could be a problem in this patient. In the end, pregabalin was chosen, as it has multiple potential positive effects: it can improve spasticity and chronic pain, increase the appetite, and consolidate sleep. With its use, the patient was able to discontinue regular oxycodone, and the family reports that her personality has returned and she is now joking with them once again.

Pregabalin clearance is proportional to renal function, which is reduced in the elderly. The glomerular filtration rate decreases with time in most people (by 50% between 30 and 80 years of age) and is not always reflected by an increasing creatinine clearance, as decreased muscle mass with age will limit the amount of creatinine that needs clearing. Without limiting doses in the elderly, many medications can become extremely sedating. Recommended dose adjustments for most AEDs are shown in Table 20.1. While AED levels may not be directly related to effectiveness for many of the newer agents, they will still provide feedback as to the patient's ability to metabolize the medication.

On occasion, the events will be less clear than this patient's hemiconvulsion, particularly if they consist only of paroxysmal mental status changes, which can become extremely difficult to diagnose by history alone in patients with dementing disorders. Nonconvulsive status epilepticus can present with varying degrees of confusion and behavior change. Status epilepticus of all types is more common in the elderly than younger adults. The differential diagnosis of seizures in the elderly includes transient ischemic attacks, transient global amnesia, atypical migraine, drop attacks,

TABLE 20-1 Recommended Dose Adjustments in the Elderly

| | |
|---|---|
| **Carbamazepine** | **25-40%** |
| Felbamate | 10-20% |
| Gabapentin | 30-50% |
| Lacosamide | No data, but likely 20-40% |
| Lamotrigine | 35% |
| Levetiracetam | 20-40% |
| Oxcarbazepine | 25-35% |
| Phenobarbital | 20% |
| Phenytoin | 25% |
| Rufinamide | No data, but likely 10-30% |
| Tiagabine | 30% |
| Topiramate | 20% |
| Valproic acid | 40% |
| Vigabatrin | 50-85% |
| Zonisamide | No data, but likely 20-40% |

From Perucca et al., 2006.

myoclonus, metabolic disturbances, REM sleep behavior disorder, hypoglycemia, medication toxicity, and nonepileptic psychogenic seizures. The use of overnight EEG and long-term monitoring likely increases the yield of diagnosing the event or finding epileptiform discharges compared to routine studies, but the EEG, while a necessary screening tool, is unfortunately often unhelpful; clinical judgment is required.

**KEY POINTS TO REMEMBER**

- **Guidelines for treatment in the elderly advise against using enzyme-inducing AEDs. This is to limit drug interactions, but it also appears that enzyme induction has a negative impact on bone health and increases stroke risk factors.**

*Continued*

- **The elderly are more likely to have problems with ambulation, so clinicians should avoid medications that can worsen them. For patients with looming extrapyramidal symptoms, sometimes even clinical Parkinson's syndrome, avoid valproic acid. For patients with unsteady gait, avoid AEDs that are prone to cause ataxia with narrow therapeutic windows (phenytoin, carbamazepine, oxcarbazepine; lamotrigine is less problematic).**
- **AEDs have essentially similar efficacy but differing side-effect profiles and therapeutic windows; tolerability is the most important factor in choice of medication, particularly for the elderly.**

**Further Reading**


Bergey GK. Initial treatment of epilepsy: Special issues in treating the elderly. *Neurology.* 2004;63:S40-S48.

Perucca E, et al. Pharmacological and clinical aspects of antiepileptic drug use in the elderly. *Epilepsy Res.* 2006;68(Suppl 1):S49-63.

Pugh MJ, et al. Trends in antiepileptic drug prescribing for older patients with new-onset epilepsy: 2000-2004. *Neurology.* 2008;70(22 Pt 2):2171-2178.

Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. *Neurology.* 2004;62:S24-S29.

Ryvlin P, et al. Optimizing therapy of seizures in stroke patients. Neurology. 2006; 67(12 Suppl 4):S3-9.

SECTION III

# Refractory Epilepsy: Diagnosis & Management Issues, Including Surgery and Alternative Therapies

# 21 Refractory Epilepsy: General Approach

Carmen is a 41-year-old woman who came for evaluation of persistent seizures. She reports epilepsy since about age 4, and seizures have been qualitatively similar since that time. Her episodes usually begin with anxiety and a rising sensation in her stomach. Sometimes this stops without further manifestations. At other times, it will proceed to loss of awareness with moaning, rising of the right arm, and stiffening without convulsion. She typically sleeps afterwards. She has no definite speech during the episodes.

Her longest seizure-free interval was about 6 months, while pregnant. At present, she has at least several episodes per week and sometimes several in one day. She has failed adequate trials of levetiracetam, lacosamide, carbamazepine, topiramate, phenytoin, gabapentin, valproate, and oxcarbazepine. She came for recommendations on alternative treatment.

As far as the patient knows, she is the product of a normal pregnancy, labor, and delivery. There is no

significant history of childhood illness, meningitis, encephalitis, or febrile seizures. There is no history of significant head trauma. There is no family history of epilepsy.

## What do you do now?

The definition of refractory epilepsy is subject to some debate. However, most studies suggest that roughly 50% of patients with a new diagnosis will be completely controlled (no seizures) with the first appropriate anticonvulsant prescribed, with another 10% to 15% completely controlled with the second agent. An appropriate anticonvulsant is one that is indicated for the patient's seizure type: all agents except ethosuximide are indicated for partial seizures, while only some would be appropriate for absence or other generalized seizure types (except generalized tonic-clonic; see Table 21.1).

After failing two appropriate anticonvulsants at maximally tolerated concentrations, the chances of complete control with the third, or fourth, or tenth, or a combination of agents is probably less than 10%. For this reason, most epilepsy specialists define refractory epilepsy as any patient having failed two or more appropriate anticonvulsant trials. At this point it is critical to confirm the diagnosis of epilepsy, and if in fact the patient suffers from epilepsy, to confirm the epilepsy syndrome and to determine if alternative therapy, particularly epilepsy surgery, is appropriate.

There are cases where the need for confirming a diagnosis of epilepsy is clear. For instance, the history may be unclear or suggestive of an alternative

**TABLE 21-1 Appropriate Drugs for Various Seizure Types**

| Type of Seizure | Drugs* |
|---|---|
| Simple and complex partial; secondarily generalized | Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin; topiramate, valproate, zonisamide (primidone, phenobarbital, vigabatrin) |
| Primary generalized seizures | |
| Tonic-clonic | Valproate, lamotrigine, topiramate, levetiracetam, zonisamide (carbamazepine, oxcarbazepine, phenytoin) |
| Absence | Valproate, lamotrigine, ethosuximide, zonisamide |
| Myoclonic | Valproate, clonazepam, levetiracetam, rufinamide |
| Tonic | Valproate, felbamate, clonazepam, zonisamide |

*Not all drugs have FDA approval for listed uses.

diagnosis. A patient initially described to have vertigo followed by tonic-clonic movements could sound like epilepsy, but with subsequent events it may become clearer that premonitory symptoms sound more consistent with presyncope. An initial description of tonic-clonic activity could subsequently seem more like irregular or chaotic movements suggestive of psychogenic nonepileptic seizures.

In most cases, however, the history remains consistent with epileptic seizures. This all too often misleads clinicians into certainty regarding the diagnosis, but, further diagnostic testing should usually be performed once the patient is refractory. Inpatient video-EEG monitoring is the gold standard for diagnosis of epilepsy and is nearly always indicated for refractory patients. This procedure allows a prolonged EEG recording with simultaneous video ideally to capture actual "seizure" episode. In a controlled, inpatient setting, it is reasonably safe to carefully withdraw anticonvulsant therapy in order to encourage seizure occurrence. Other provocative measures, such as sleep deprivation, alcohol consumption, or provocation particular to the individual, can also be useful to encourage seizure occurrence and reduce the duration of the hospital stay. In this way, treatment can also be redirected: if epilepsy is confirmed, a previously ineffective medication can be replaced with another appropriate agent that may be more effective.

There are two possible outcomes of video-EEG monitoring. In 25% to 30% of patients sent for this procedure, the diagnosis will be found to be nonepileptic spells, usually psychogenic. This topic is discussed in depth in Chapter 4, but in these cases treatment clearly should be redirected before discharge, keeping in mind that a substantial minority of patients may have both epileptic and nonepileptic seizures.

If epilepsy is confirmed, video-EEG will provide a more complete assessment of the seizure type and, if partial, the site of onset. It may be that the seizure type was incorrect, and that the next choice of drug will therefore be more appropriate. However, if the diagnosis is epilepsy and the patient has failed two appropriate drugs, this serves as a preliminary investigation into possible epilepsy surgery. Whereas many physicians and neurologists consider epilepsy surgery as a "last resort" to be used only in the most severe cases, epilepsy specialists agree that this should be considered early, as soon as the patient is deemed refractory. There are many reasons for this. First,

even rare seizures seriously impair quality of life. Think of this: if someone had a seizure every 6 months, as a physician you might not consider this so bad for your patient, particularly if this is improved from every week or even every month. However, if you yourself had a seizure every 6 months, you could not drive. You would never know when or where this might happen, so you would need to avoid many activities, such as climbing or using heavy machinery. You would have an approximately 1% risk of sudden death (SUDEP) per year. And perhaps most importantly, your attitude about life is altered. Never knowing when a seizure may happen, patients with continued seizures tend to be tentative, less productive, and more prone to anxiety. It is therefore not surprising that studies of quality of life uniformly show that a reduction in seizures has little or no effect, but elimination of seizures results in considerable improvement.

Who is a good candidate for epilepsy surgery? The most common surgery, focal resection, depends on knowing the site of seizure onset and being able to remove that area of the brain without serious deficits. Video-EEG monitoring with scalp electrodes usually establishes the site of onset with reasonable certainty, and also determines whether there may be more than one site (usually making surgery impossible). Imaging of the brain is essential, beginning with an MRI. If a lesion is present at the site of onset, this is an excellent prognostic sign for epilepsy surgery if consistent with EEG onset. Particularly if the MRI is ambiguous or normal, other imaging (PET or SPECT) can yield further information regarding the probable site of onset. Neuropsychological testing will help to determine whether there are cognitive deficits related to a certain site. Finally, the intracarotid amobarbital (Wada) test can yield information about memory and language, which is particularly important in patients with probable temporal lobe epilepsy. Functional MRI is now being used in many centers as an alternative to this procedure.

A surgical evaluation needs to be completed in an epilepsy center. Once basic data are obtained, these centers conduct case conferences where all of the data are evaluated with a team of epileptologists, epilepsy neurosurgeons, radiologists, and neuropsychologists to come to a consensus about whether epilepsy surgery is appropriate, the risks and probable chance of seizure freedom, and further testing that might be required before a final recommendation is made. This information is then presented to the patient.

The patient described was found to have left mesial temporal sclerosis on MRI (Fig. 21.1), a clear marker of mesial temporal onset epilepsy. Interictal EEG (Fig. 21.2) and ictal EEG (Fig. 21.3) were consistent with left temporal onset epilepsy, and neuropsychological testing was also consistent with this. She therefore has a very good chance of cure with surgical resection (about 80% in most cases). There is of course a chance of complications. Bleeding, infection, or perioperative complications can occur with any surgery. With this particular operation there is a risk of visual field deficit, as the fibers carrying contralateral upper visual field information pass nearby. There is a risk of memory deficit with resection of the hippocampus as in this operation. The contralateral hippocampus also supports memory; patients with dominant temporal lobe epilepsy are somewhat more likely to experience a verbal memory loss, which is more noticeable. These concerns, however, must be weighed against the risks not only of continued seizures but of the consequent loss of independence, continued psychological difficulties, and sudden death.

Epilepsy specialists would consider this patient a strong candidate for surgery, but the individual desires of the patient must always be taken into consideration after counseling about risks and benefits. Other patients with

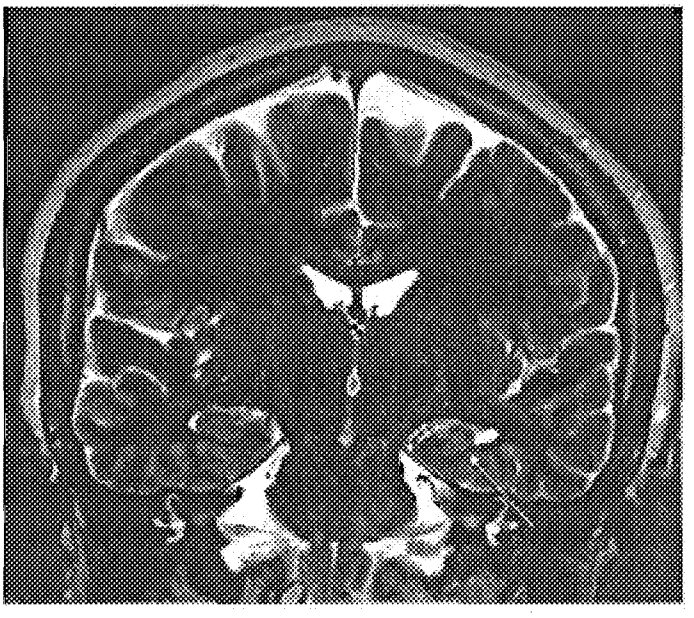


**FIGURE 21-1** Smaller hippocampus with disrupted internal architecture, consistent with mesial temporal sclerosis (*arrow*).

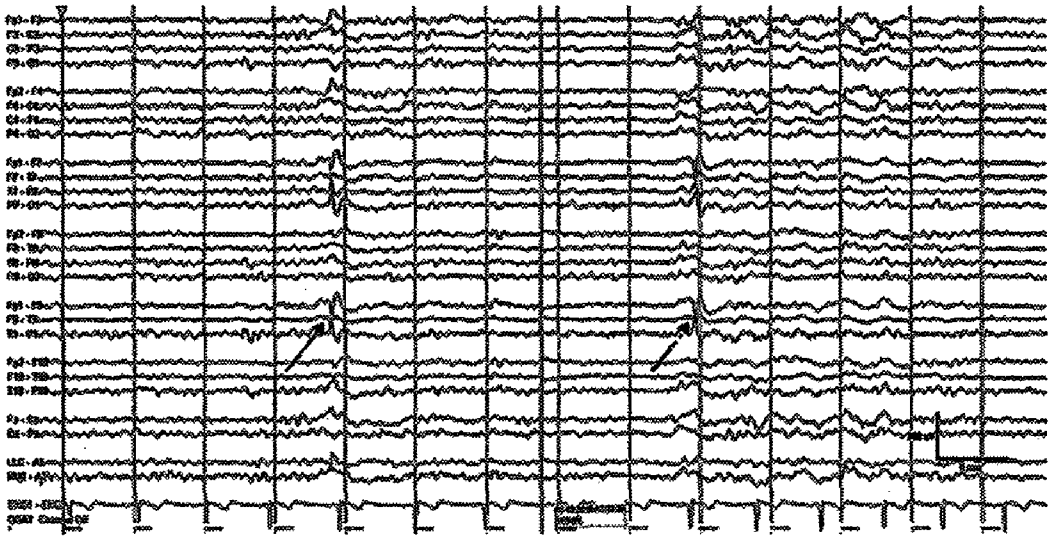


**FIGURE 21-2** Left temporal spikes (*arrows*). These are seen maximally in the anterior to mid-temporal regions. The arrows point to the anterior temporal chain of electrodes.

a structural lesion (arteriovenous malformation, dysplasia, traumatic injury) where seizures are shown to be arising in the same area and resection is not expected to cause a severe neurologic deficit would fall into a similarly good prognostic category. Refractory patients with primary generalized epilepsy are discussed in Chapter 22; more complicated patients with localization related epilepsy are discussed in Chapter 23.

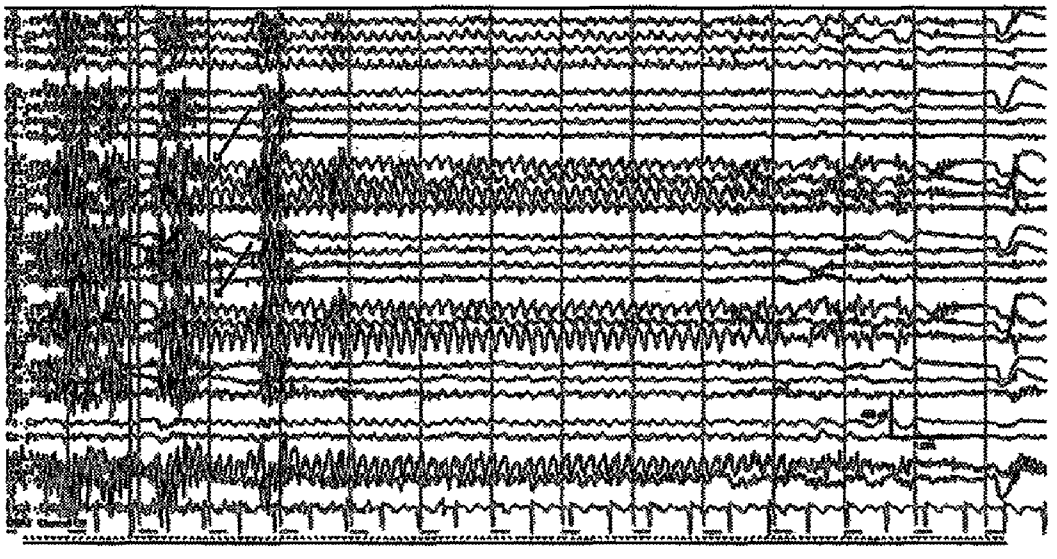


**FIGURE 21-3** Rhythmic theta ictal rhythm maximal in the left anterior temporal region (*arrows*). The seizure onset was somewhat obscured by motor artifact, but this rhythm is clearly seen within 5 seconds of clinical onset.

After successful surgery, medications can often be weaned if the patient is on more than one, which may also improve consequent toxicity. Coming off all anticonvulsants, even after several years of seizure freedom, carries some risk. This risk is not well known but likely is similar to that of any epilepsy patient who is seizure-free on medications for many years (see Chapter 15).

**KEY POINTS TO REMEMBER**

- Patients with a diagnosis of epilepsy who fail two adequate drug trials should, in general, be referred for video-EEG monitoring to confirm the diagnosis and direct future care. Many of these patients will be found to have nonepileptic spells, even with a history strongly suggestive of epilepsy.
- In patients with epilepsy who have failed two or more appropriate drug trials, the chance of complete seizure freedom with additional drug trials is probably less than 10%; alternatives (such as surgical treatment) should be considered.
- In addition to video-EEG monitoring, patients with refractory epilepsy should always be evaluated with a detailed MRI of the brain, and additional information from other imaging studies (PET or SPECT) and neuropsychological testing should be considered.
- Patients with temporal lobe epilepsy and a finding of mesial temporal sclerosis on MRI carry the highest chance of surgical cure; they should be strongly considered for surgery once proven to be refractory.

**Further Reading**


Kwan P, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia.* 2010;51(9):1922.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med.* 2000;342(5):314-319.

Spencer SS, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. *Neurology.* 2005;65(6):912-918.

Wiebe S. Epidemiology of temporal lobe epilepsy. *Can J Neurol Sci.* 2000;27(Suppl 1):S6-10; discussion S20-1.

# 22 Refractory Idiopathic Generalized Epilepsy

The patient is a 53-year-old woman with epilepsy since age 10 that has been refractory to medical therapy. Initially, she had frequent absence seizures. She was treated with ethosuximide but continued to have frequent seizures. An EEG at that time showed generalized 3- to 4-Hz spike-wave discharges. She had her first generalized tonic-clonic seizure at 16. Phenobarbital was added but she continued to have seizures. At 20, she was transitioned to valproate monotherapy without significant improvement in her seizures. At 40, lamotrigine was added and she had an improvement in her seizure frequency. She now has absence seizures every 1 to 2 weeks and generalized tonic-clonic seizures every 2 to 3 months. She also complains of tremor and prominent concentration and memory difficulties.

*What do you do now?*

Based on the above description of absence and generalized seizures starting at age 10 and 3- to 4-Hz spike-wave discharges on EEG, the patient most likely has an idiopathic generalized epilepsy (IGE) syndrome, juvenile absence epilepsy. Her case is unusual, however, because she continues to have seizures despite two appropriate medications at the highest tolerated therapeutic doses. The majority of patients with IGE demonstrate good responses to appropriate AEDs. Some syndromes, such as childhood absence epilepsy, tend to have spontaneous remission of seizures. Other IGE syndromes tend to require lifelong treatment, which is usually effective in keeping patients seizure-free. However, a minority of patients continue to have difficult-to-control seizures. Approximately 10% to 14% of patients with juvenile myoclonic epilepsy continue to have seizures even on valproate, probably the most effective agent for IGE, with or without adjunctive drugs. The proportion of patients who remain refractory to medical therapy in other IGE syndromes such as juvenile absence epilepsy or epilepsy with generalized tonic-clonic seizures upon awakening is unknown.

The initial approach to such a patient is to confirm the diagnosis of IGE. Interictal epileptiform discharges in frontal lobe epilepsies may sometimes be mistaken for generalized spike-wave discharges of IGE due to the extensive interconnectivity of the frontal lobes leading to rapid propagation (secondary bisynchrony). Clues that a generalized-appearing discharge may be due to a single focus include persistent amplitude asymmetries favoring one hemisphere (always higher amplitude on one side) or persistent lead-in from one hemisphere (the discharge always starts on one side). While typically frontally-predominant, true generalized epileptiform activity should generate some field throughout the brain and be seen in all electrodes. Fragmented epileptiform discharges of IGE may not adhere to this general rule. In these patients where there is a suspicion of a focal onset, video-EEG recording of a seizure may confirm the diagnosis of localization-related epilepsy based on EEG or clinical characteristics. Establishing the diagnosis is important for these patients as they can be eligible for other therapeutic options, such as resective epilepsy surgery and narrow-spectrum anticonvulsants.

It is also important to review the medication history. A trial of valproate, if not used previously, should be considered. Nicolson et al. (2004) found that in patients with IGE, treatment with valproate led to remission in 52% of patients as compared to 16% of patients on lamotrigine and 34% of

patients on topiramate. There is also some evidence suggesting that a combination of valproate and lamotrigine may be effective if seizures continue on valproate monotherapy. Other agents that may be effective in IGE include levetiracetam and zonisamide. Clonazepam may be a useful adjunct for treatment of myoclonic seizures. Ethosuximide may be added if absence seizures are difficult to control. Clobazam is not yet FDA-approved for use in the United States, but can also be effective in IGE.

If medical therapy fails or patients are unable to tolerate the doses required to maintain seizure freedom, a vagal nerve stimulator (VNS) may be used to reduce seizure frequency. There are limited data available regarding the efficacy of VNS for IGE, but a small series by Ng and Devinsky (2004) found that 5 of 11 patients had a greater than 50% reduction in seizure and were able to reduce their AED doses. Finally, there is emerging evidence that anterior two-thirds corpus callosotomy, a procedure commonly used to treat refractory drop attacks in some patients with symptomatic generalized epilepsy, may benefit some patients with refractory IGE with generalized tonic-clonic seizures. In a series of nine patients who had corpus callosotomy, Jenssen et al. (2006) reported that four patients had a greater than 80% seizure reduction and four additional patients had 50% to 80% seizure reduction. In another study of 11 patients, Cukiert et al. (2009) noted 75% or greater reduction in seizures in all patients. There was no reported reduction in patient IQ in either study. Further investigation of this option is needed.

**KEY POINTS TO REMEMBER**

- **In a patient with refractory idiopathic generalized epilepsy (IGE), one should:**
  1. **Confirm the diagnosis of IGE. Focal epileptiform discharges with rapid secondary bisynchrony can be mistaken for generalized epileptiform discharges.**
  2. **Consider a trial of valproate if not previously tried, as it appears to be more effective than other agents for IGE.**
  3. **Consider adding ethosuximide for frequent absences or clonazepam for frequent myoclonus.**

*Continued*

- A vagal nerve stimulator may be helpful in reducing seizure frequency and AED dose in patients with IGE.
- There is intriguing preliminary evidence for corpus callosotomy for the treatment of refractory IGE.

**Further Reading**


Cukiert A, Burattini JA, Mariani PP, et al. Outcome after extended callosal section in patients with primary idiopathic generalized epilepsy. *Epilepsia.* 2009;50:1377-1380.

Jenssen S, Sperling MR, Tracy JI, et al. Corpus callosotomy in refractory idiopathic generalized epilepsy. *Seizure.* 2006;15:621-629.

Nicolson, A, Appleton, RE, Chadwick, DW, and Smith, DF. The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalized epilepsies. *J Neurol Neurosurg Psychiatry* 2004; 2004: 75-79

Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalized epilepsy *Seizure.* 2004;13:176-178.

Sullivan JE, Dlugos DJ. Idiopathic generalized epilepsy. *Curr Treatment Options Neurol.* 2004;6:231-242.

# 23 Refractory Localization-Related Epilepsy: Extratemporal Epilepsy and Intracranial EEG Recording

A 28-year-old, right-handed man was referred for refractory epilepsy. He had onset of seizures at age 4. Seizures have always been predominantly nocturnal and consist of lurching of the torso with vocalization lasting approximately 10 seconds. These resolved from about age 15 to 18, then recurred, at which time they were entirely restricted to sleep. At present, however, he has a seizure from wakefulness approximately every 2 weeks, typically within 30 minutes of awakening. When this occurs, it is preceded by a feeling of foreboding followed by loss of consciousness. There is no incontinence and seizures are followed by a brief period of disorientation. Nocturnal episodes occur nearly every night.

There are no risk factors for epilepsy. He has failed treatment with maximally tolerated doses of carbamazepine, valproic acid, pregabalin, and lamotrigine. Previous imaging studies (MRI) of the brain were normal. He works as an administrator in an academic psychology department.

*What do you do now?*

The general approach to a patient with refractory epilepsy is discussed in Chapter 21. This case in particular highlights the issues related to probable extratemporal lobe epilepsy. In general, any patient with refractory epilepsy should be considered for video-EEG monitoring. This serves two purposes: first, to confirm the diagnosis of epilepsy; and second, if the patient does have epilepsy, to clarify the seizure type and to guide further treatment, particularly alternative drug therapy versus device therapy (primarily vagus nerve stimulation) or epilepsy surgery.

In this patient, the clinical characteristics are very suggestive of frontal lobe epilepsy (see Chapter 5). In particular, the episodes, which preferentially or exclusively occur during sleep, and violent motor activity are suggestive of frontal onset. Movements can be quite chaotic, and patients may recall episodes, making the differential from psychogenic nonepileptic seizures difficult without recording. In this patient, as with many others, there is no definite EEG change during seizures (Fig. 23.1). This may be due to a limited discharge with a simple partial seizure, motor artifact, or (in most cases) a combination of both. When this occurs, stereotypy of the events

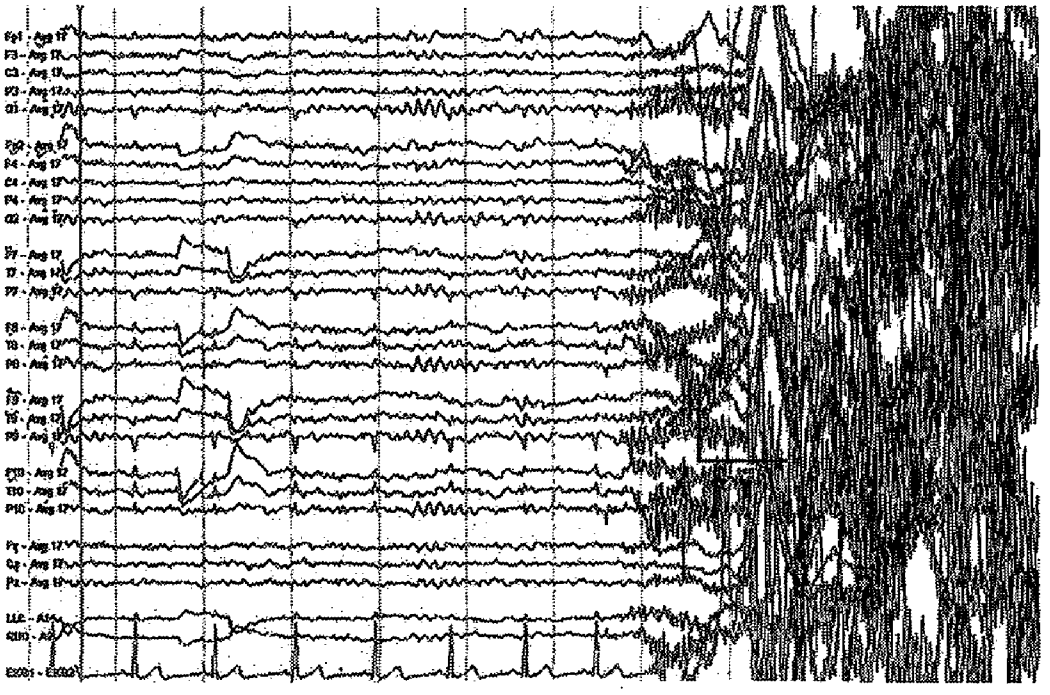


**FIGURE 23-1** Seizure onset in 28-year-old man with refractory frontal lobe epilepsy. Normal background is seen on the left; at seizure onset diffuse muscle artifact obscures the record.

and their onset in sleep help to confirm that the episodes are in fact epileptic. Without EEG, a patient can appear to be asleep at onset but actually have "pseudoseizures from pseudosleep."

Once a patient meets the definition of refractory epilepsy, whether temporal or extratemporal, the chances of complete seizure freedom with additional anticonvulsant trials remain small (less than 10%). The alternatives are surgical resection, if a focus can be found and safely resected, or a device trial. Extratemporal epilepsy carries a lower chance of complete seizure freedom following surgical treatment. Most studies suggest a 40% to 60% chance of seizure freedom, compared with temporal lobe onset with an 80% chance of substantial improvement. Although not as great a response as in temporal lobe epilepsy, this is still substantially greater than with medical management.

Successful surgery is dependent on finding a safely resectable focus, as with temporal lobe epilepsy. The reasons for the somewhat lower success rates are not known. It may be that temporal lobe surgery is more successful due to the more defined anatomic boundaries; extratemporal surgery is also more likely to be limited by eloquent cortex. The approach always includes careful imaging studies. A detailed MRI may show cortical dysplasia, previous trauma, or another possibly epileptogenic lesion. Particularly when the MRI is normal, alternative imaging with PET or SPECT can show regions of abnormality. In this case, the MRI was normal, but hypometabolism was seen in the right frontal region on PET (Fig. 23.2). Additional useful information is obtained from neuropsychological testing, which often yields clues as to possible localization of cognitive deficits corresponding to possible seizure onset zones.

Some patients may benefit from SPECT imaging. Decreased perfusion (interictally) is supportive of a seizure focus. Ictal SPECT injection can show increased perfusion, however the injection must be given as soon as possible after the onset of a seizure. This muct therefore be performed in an epilepsy monitoring unit, and can be logistically difficult as the radioactive tracer must be present a the time of the seizure (most must be injected within 6-10 hours after preparation), the seizure promptly recognized, and the injection performed by trained personel. Practically, this often requires the presence of a physician or nurse practitioner continuously at the bedside, and a spontaneous seizure must occur in the allotted time frame. This might be practical with frequent or stimulus-sensitive seizures, but in many

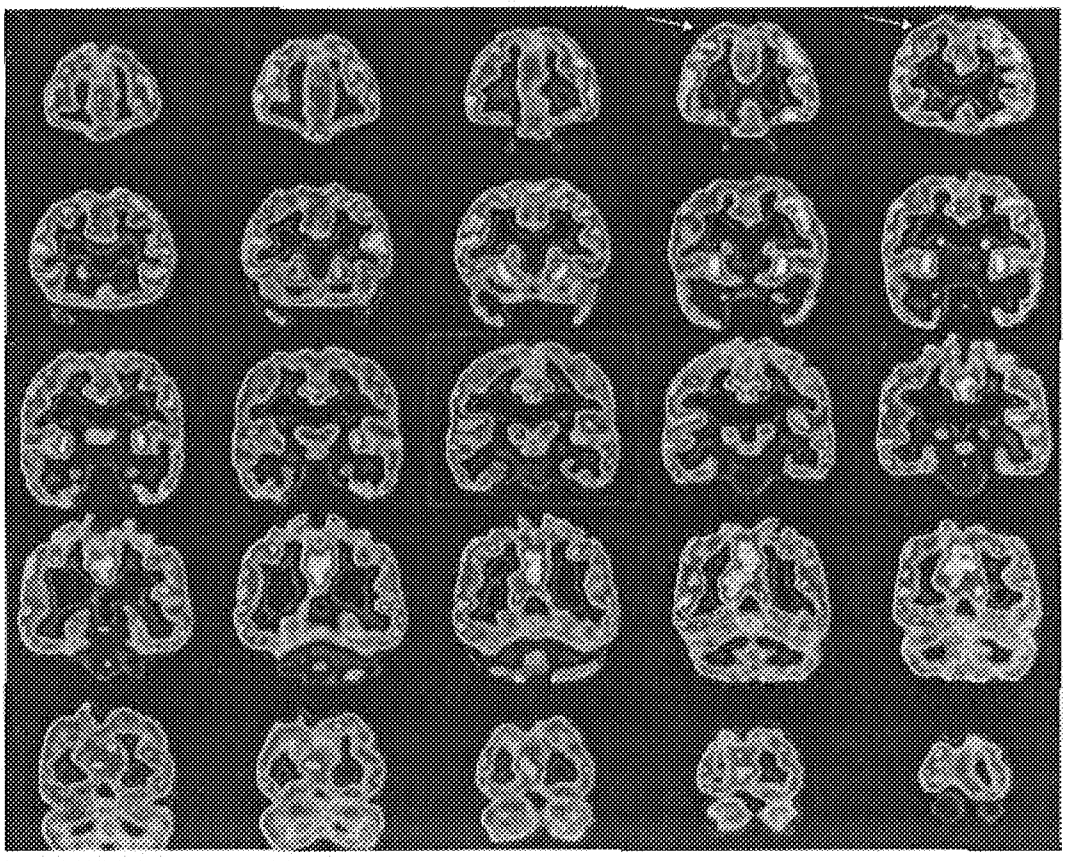


**FIGURE 23-2** PET scan in 28-year-old man with refractory frontal lobe epilepsy. There is hypometabolism in the right frontal region (*arrows*).

patients this is impractical. When obtained, a subtraction of ictal and interictal SPECT yields the clearest illustration of probable onset zone.

Every patient must be individually considered. This should be done at a multidisciplinary conference, ideally in a comprehensive epilepsy center, where all information regarding the patient is reviewed by epileptologists, epilepsy surgeons, radiologists, neuropsychologists, and any others involved in the particular case. A consensus recommendation is then made: Is surgery a reasonable option? If so, is additional testing required? What are the chances of seizure freedom? What are the risks of adverse outcome? This information is then communicated to the patient by the treating epileptologist.

Unless there is a very well-defined lesion corresponding to a clearly defined electrographic seizure focus, most of these patients will require video-EEG monitoring using intracranial electrodes that are surgically implanted. This is also carefully individualized. Electrodes are typically in strips of four to eight electrodes; grids of various sizes (up to 8 × 8 electrodes); and/or depth

electrodes, also with four to eight contact points. In all cases electrodes are spaced about a centimeter apart. Strips and grids lie on the surface of the brain; depth electrodes are placed (often stereotactically) into the brain parenchyma. The broadest possible region should be covered in order to have the best chance of defining the onset area; however, greater electrode numbers increase the risk of infection. A possible map for implantation of electrodes in a case of temporal or parietal onset is shown in Figure 23.3. The patient has an operation for electrode implantation, usually a craniotomy, although for more limited implants of only depth or strip electrodes, burr holes can sometimes be used. Video-EEG monitoring is then performed to record both interictal activity and typical seizures. As the electrodes are directly on the surface of the brain, there is little artifact and the

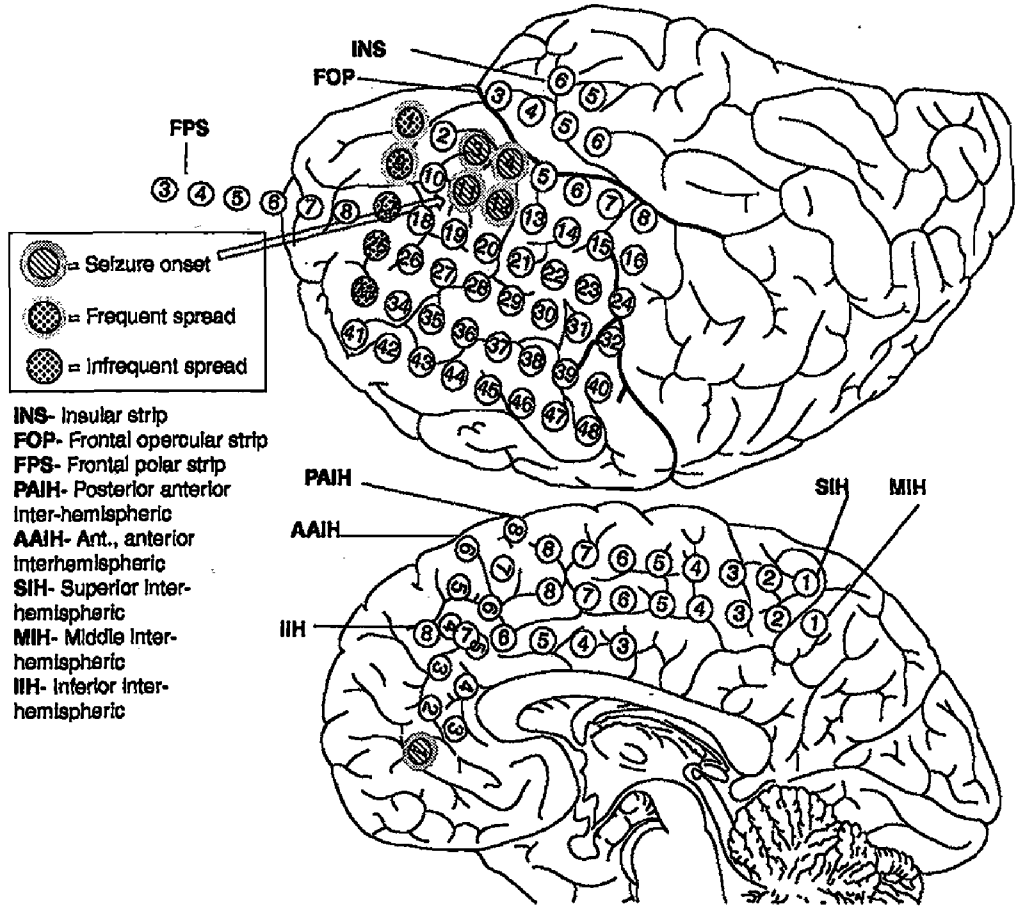



**FIGURE 23-3** Intracranial grid implantation in a 42-year-old man with refractory seizures, probably of right frontal onset by semiology and scalp EEG. The electrodes determined to be onsets and those with early spread are depicted differently from the others (see legend). The arrow points to the major region of onset seen in Figure 23.4.

signal is much stronger (Fig. 23.4). Patients typically also have "mapping" of eloquent cortex during this evaluation. This is performed by external electrical stimulation of the implanted electrodes. Stimulation of an electrode over primary motor cortex, for example, will result in contraction of contralateral muscles. Stimulation of primary visual cortex will result in an experience of colors or lights on the contralateral visual field. In this way, a "map" is created of eloquent cortex so that it is not removed during surgery.

Once all this information is obtained, ideally the ictal onset zone is known, as is its proximity to eloquent cortex. Then a surgical decision must be made. Again, this is very individual: if the entire onset zone can be safely removed, this approach will result in the greatest chance of seizure freedom. While it is rarely in the patient's best interest to remove primary motor cortex with resulting permanent paralysis, it may sometimes be worth a visual field loss to control very refractory seizures. In some cases, an incomplete resection may be performed, or the area that is eloquent might be treated with multiple subpial transections (MSTs), a technique that interrupts cortical connections without removing the actual tissue. Controlled studies of MSTs are lacking, and it is not known how effective these are at improving seizures; however, they are less likely to cause a permanent deficit than resection.

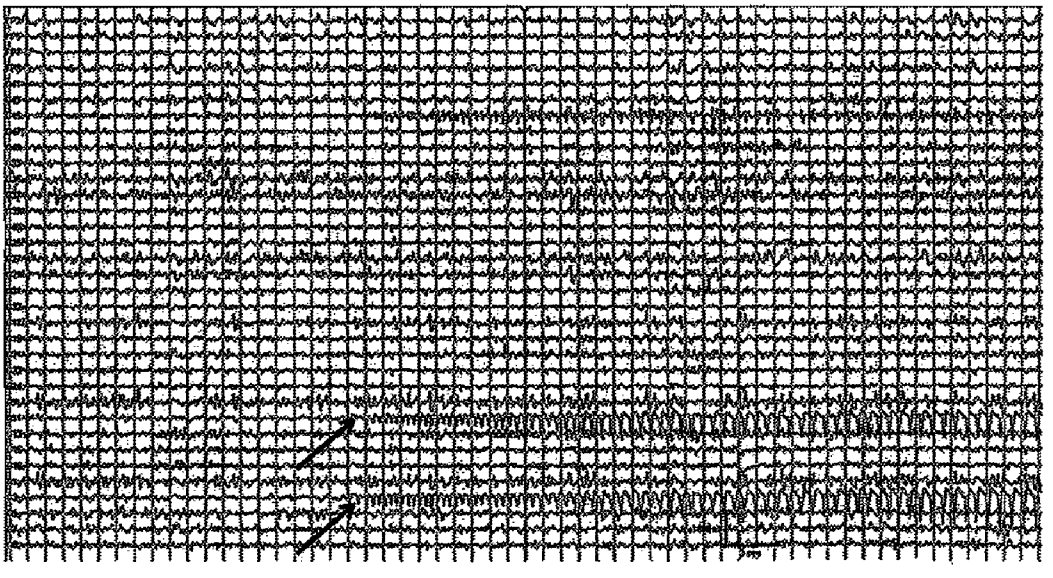


**FIGURE 23-4** Seizure onset in same patient as Figure 23.3. A discrete seizure onset is seen predominantly at the G3 and G11 electrodes in the right lateral frontal lobe. Following resective surgery, this patient has remained seizure free.

**KEY POINTS TO REMEMBER**

- As with temporal lobe epilepsy, patients who fail to respond to two appropriate anticonvulsant drug trials and who are suspected to have extratemporal onset should be considered for video-EEG monitoring to confirm the diagnosis of epilepsy and direct further therapy
- The goal of any treatment should be complete freedom from disruptive seizures. In some patients, simple partial seizures or seizures exclusively occurring during sleep may not appreciably affect lifestyle.
- If refractory extratemporal partial epilepsy is confirmed, patients should be considered for surgical treatment. This is always an individual decision based on the chance of surgical success, the risks of adverse effects, and the degree of disruption caused by seizures to the patient's quality of life.

**Further Reading**


Spencer SS, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. *Neurology.* 2005;65(6):912-918.

Spencer SS, et al. Initial outcomes in the Multicenter Study of Epilepsy Surgery. *Neurology.* 2003;61(12):1680-1685.

Kwan P, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia.* 2010;51(9):1922.

# 24 Complementary and Alternative Therapies

A 19-year-old woman presents with idiopathic generalized epilepsy. She had been on valproate but did not tolerate adverse effects. She has also attempted zonisamide, levetiracetam, and clonazepam, all of which caused significant drowsiness. She was seen for several years in between by a herbal practitioner and an acupuncturist, which seemed to work initially, but she abandoned the idea after she had her first and only generalized tonic-clonic seizure. While considering the options remaining, she questions you about complementary and alternative treatments and specifically the use of marijuana, which, she had read on blogs and Internet posts, may help some people.

*What do you do now?*

There have always been patients interested in nonpharmaceutical treatments for epilepsy, but there has been a recent increase due to distrust of the pharmaceutical industry and a move toward organic and "natural" therapies.

Diet is one of the best-studied alternative therapies for epilepsy, and the ketogenic diet is the best known. It restricts calories to about 75% of the normal diet, and about 90% of those calories must be derived from fat. It essentially tricks the body into believing it is starving to make ketones, the only other fuel source for the brain can utilize besides glucose. Studies on the ketogenic diet vary, but on average 50% of patients have been documented to have at least a 50% reduction in seizures, and about 25% can become seizure-free.

The ketogenic diet is used primarily in children and occasionally in teens and older patients, typically for 1 to 2 years but sometimes longer. Once reserved for those with multiple seizures weekly, sometimes hundreds, it is now more widely used in some centers. It requires the support of an interested nutritionist. It is not easy to make, administer, or tolerate. The portions are small, oily, and often unpalatably thick.

A modified Atkins diet has also been used as a more manageable way of achieving ketogenesis and potentially improving seizures. The number of patients studied has been much smaller (currently less than 200 in the published literature), and most of the studies are unblinded and potentially biased, but they have shown that about 40% of patient reach 50% seizure reduction in the short term, and 20% will continue at that level 6 to 12 months into the protocol. The low glycemic diet has shown similar effects in an even smaller sample size.

When they are successful, the seizure frequency will drop in 2 to 4 weeks from the change in diet. However, sneaking a cookie or other high-carbohydrate snack can result in an abrupt return to the prior baseline. Anecdotal reports of improved behavior and cognitive development and reduction of AEDs are other benefits to consider. In many patients, the ketogenic diet may be discontinued after 2 years with continued seizure control. In fact, some patients have been able to discontinue AEDs following prolonged seizure freedom.

The mechanism by which diets exert their anti-seizure effects has been studied but remains unknown. The ketogenic diet is particularly indicated

for patients with glucose transporter 1 (GLUT-1) and pyruvate dehydrogenase deficiencies, though small studies with infantile spasms and myoclonic-astatic and absence epilepsies have shown that they also respond well. It should not be attempted in those with mitochondrial disorders, porphyria, and beta-oxidation deficiencies. Initiation of the ketogenic diet is typically done in an inpatient setting, as metabolic complications of a yet unknown metabolic disorder rarely may occur. Kidney stones, bone density loss, and growth retardation are possible long-term adverse effects.

Other dietary concerns for patients include food allergies and intolerance. It has been shown that celiac disease is more common in patients with epilepsy, for instance. Anecdotally, patients have reported specific triggers, such as coffee or red meat. Avoidance of triggers, once proven reliable, is common sense.

Hormones are known to exhibit excitatory and inhibitory effects on neuronal firing as well: *E*strogen is *E*xcitatory while *P*rogesterone is *P*rotective from seizures. Stress can bring out nonepileptic events, of course, but is a known instigator for epileptic seizures. Stress releases corticotropin-releasing hormone, which is excitatory, but its downstream effects release hormones that are inhibitory. The peak and half-life of these hormones leave a tendency for seizures to occur with the immediate stress and at the resolution of the stress. Thus, any alternative or complementary therapy that reduces stress may indirectly have an impact on breakthrough seizures.

With respect to herbal remedies and supplements, it is important to be open-minded but with a healthy level of skepticism. Anecdotally, patients exclusively on natural/herbal remedies have been seen in the ER with measurable levels of phenytoin or phenobarbital, which may be why some of them work. However, scientific research is progressing in the field of botanicals, which are probably the most promising non-Western therapy for seizures. Double-blinded clinical evidence may be soon be available: *Passiflora* extracts appear to be anticonvulsant and are currently in phase II trials. Confusion still exists, however, even with the names: omega-3 may help seizures but omega-6 may worsen them; European mistletoe was historically used to treat seizures, but if raw and unprocessed it can be toxic, and American mistletoe can cause seizures and is unsafe for medicinal use. It seems clearer that preparations containing ephedra, evening primrose, and gingko may be pro-epileptic and are to be avoided. Many dietary

supplements have used ephedra or similar agents as "fat-burners" and have increased risks for seizure activity. An excellent reference is the National Center for Complementary and Alternative Medicine, a branch of the NIH, at http://nccam.nih.gov.

The effects of marijuana on seizures are open for discussion. Many patients swear it helps, while for others there is no effect, and it has been reported to worsen juvenile myoclonic epilepsy. There are case reports for both sides, and there is laboratory evidence in animals that it both suppresses seizure activity and is a proconvulsant. It is important for clinicians to know that use is prevalent and to provide appropriate counseling, particularly indicating that there is evidence for both sides and there is at least a theoretical level of toxicity that may promote seizure activity, so patients should limit excessive usage; while patients may report improvement, seizure freedom is not expected.

There are a number of paradigms in EEG biofeedback (also called neurofeedback) for refractory epilepsy, but generally they are aimed at patients learning to increase or decrease specific EEG activity in certain areas of the brain through positive feedback. The results of early studies appear promising, but they are small and some conclusions are conflicting. At present the paradigms and laboratories are far from standardized, making it difficult to confidently refer patients, but this may well change soon.

Other alternative therapies that may come up include yoga (stretching, meditation, breathing), homeopathy (like treated with like in submolecular quantities), aromatherapy with or without hypnosis (scents), acupuncture (stimulating points of energy or meridians on the body), chiropractic (reducing spinal impingements to organs improves their function), Reiki ("healing touch" without touching; energy channels unblocked), and ayurveda (East Indian medicine combining chakras and herbals). Some have been studied, but rigorous clinical trials will be difficult because of "placebo blinding" and the culture of the therapies. It is important to recall that the placebo arms of clinical trials in epilepsy often show a 10% to 30% improvement.

The motto of "it's natural so it can't hurt you" can be easily refuted by many of nature's poisons, and specifically ephedra for seizures. Logically, anything that can help can usually do some harm if administered incorrectly, so the skill of the practitioner may be as important as the method.

Being open-minded but providing a balance and sense of caution to the patient may be the best approach.

**KEY POINTS TO REMEMBER**

- At least 25% of people with epilepsy are using complementary and alternative therapies.
- The ketogenic and modified Atkins diets are the best studied in terms of their effect on seizures, but they are not easy to adhere to.
- Botanicals may be helpful in the long term, but be wary of the many names for the same agent; many herbs can be proconvulsant.
- Marijuana is commonly used by patients, though there are conflicting data on its effect on seizures.
- Biofeedback results are thus far promising, but it has not been fully researched.
- "It's natural so it can't hurt you" is definitely *not* true. Patients need to exercise caution when using complementary and alternative therapies and must also be careful to avoid withdrawing their AEDs without medical guidance.

**Further Reading**


Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. *J Child Neurol.* 2009;24:979.

Monderer RS, et al. Neurofeedback and epilepsy. *Epilepsy Behav.* 2002;3(3):214-218.

National Center for Complementary and Alternative Medicine: http://nccam.nih.gov.

Samuels N, et al. Herbal medicine and epilepsy: proconvulsive effects and interactions with antiepileptic drugs. *Epilepsia.* 2008;49(3):373-380.

Schachter SC. Complementary and alternative medical therapies. *Curr Opin Neurol.* 2008;21(2):184-189.

Sirven JI. Alternative therapies for seizures: promises and dangers. *Semin Neurol.* 2007;27(4):325-330.

Tyagi A, Delanty N. Herbal remedies, dietary supplements, and seizures. *Epilepsia.* 2003;44(2):228-235.

SECTION IV

# Prognostic, Social, and Behavioral Issues

# 25 Depression in Epilepsy

The patient is a 56-year-old right-handed woman with refractory temporal lobe epilepsy since her early 20s. She had four to six complex partial seizures per week and one secondarily generalized tonic-clonic seizure per month. She had right mesial temporal sclerosis on MRI, right anterior temporal discharges on interictal EEG recording, and right temporal seizure onsets during ictal video-EEG monitoring. She underwent a selective right amygdalo-hippocampectomy at age 52. She was initially seizure-free but had a recurrence of her epilepsy 1 year after surgery. She now has one or two seizures per year. However, she and her husband complain of persistent depressed mood, insomnia, and irritability. These symptoms have not improved despite treatment with sertraline (Zoloft) and venlafaxine (Effexor). She has had suicidal thoughts in the past but currently denies any suicidal ideation. She is currently taking zonisamide, 500 mg/day.

*What do you do now?*

This patient has refractory temporal lobe epilepsy that is significantly improved but not cured after resective surgery. However, it is her treatment-resistant depression that has the biggest negative impact on her quality of life. Interictal depressive symptoms due to major depression, dysthymia, and bipolar disorder are the most common psychiatric comorbidity in patients with epilepsy, occurring in 11% to 60%. The prevalence of depression is much higher in patients with epilepsy than in the general population and these symptoms often go unrecognized. In addition, patients with depression have a four- to seven-fold increased risk of developing epilepsy. This bidirectional relationship between the disorders suggests a shared neurobiological substrate. In addition to the disease, some drugs used to treat epilepsy may exacerbate psychiatric symptoms, including depression. Finally, patients with epilepsy have a three-fold increased risk for suicide compared to the general population and higher rates of suicidal ideation and suicide attempts. It is not clear if this risk is due to anticonvulsant use or underlying psychiatric disease. However, in 2008, the FDA issued an alert on the risk of suicidality with all anticonvulsants. Some recent epidemiologic evidence suggests that suicide risk may be limited to drugs that are associated with depressive side effects (see below). While the FDA warning does not suggest that AEDs should not be used in patients who need them, it emphasizes that physicians who care for patients with epilepsy should be able to screen patients for depression and suicidality.

- A *major depressive episode*, according to DSM-IV criteria, includes symptoms of depressed mood or anhedonia and four or more of the following symptoms: weight loss/gain, insomnia/hypersomnia, psychomotor agitation/retardation, daily fatigue, feelings of worthlessness or excessive guilt, difficulty concentrating, or suicidality. To qualify for the diagnosis, the symptoms have to be present near daily for over 2 weeks. A depressive episode typically lasts 6 to 24 months.
- A patient has *major depressive disorder* if the episodes are recurrent and there is no evidence for any other psychiatric condition such as schizophrenia or bipolar disorder.
- *Dysthymia* is a chronic state of depressed mood occurring for the majority of days for at least 2 years. In addition, the patient must

frequently experience at least two of the symptoms listed above (excluding suicidality).

It should be noted that these diagnostic criteria were developed for patients with primarily psychiatric disorders. Patients with epilepsy may experience depressive symptoms that do not fit into one of the typical diagnostic categories. Typically, these patients have prominent anhedonia, fatigue, irritability, appetite changes, and sleep abnormalities with a waxing and waning course. Sadness is a less common finding in patients with epilepsy. Several studies have shown that measures of depressed mood are inversely correlated with healthcare quality of life in patients with epilepsy. Furthermore, in one study, mood was found to be a predictor of a patient's negative self-assessment of health status after anterior temporal lobectomy. Many patients with epilepsy also have coexisting anxiety disorders, and some evidence suggests that the coexistence of anxiety and depression has a worse impact on quality of life.

In some patients, depressive symptoms may be due to side effects of AEDs. All drugs may be associated with mood changes, but the drugs that are more likely to have negative effects on mood are levetiracetam, primidone, phenobarbital, zonisamide, ethosuximide, topiramate, and felbamate (see appendix I). A temporal relationship between initiation of the drug or increases in the dose is a clue to the iatrogenic nature of the depressive symptoms. These patients typically show an improvement in mood when changing to an alternative agent or lowering the dose. When selecting another anticonvulsant in such patients, it may be useful to try an agent that has positive effects on mood, such as lamotrigine, carbamazepine, pregabalin, gabapentin, or valproate, if appropriate.

While in most patients depressive symptoms are an interictal phenomenon, some patients have postictal depression. This is typically a self-limited episode that occurs within several days of a seizure and can be quite severe in rare cases, with suicidal ideation. Seizures can also exacerbate existing depression.

Neurologists treating patients with epilepsy are instrumental in identifying mood disorders, initiating first-line therapies, and assessing suicidality. Patients with epilepsy should be asked about mood symptoms during routine follow-up. Self-rated screening questionnaires may be additional tools

to screen patients. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E, shown in Table 25.1) is a six-item questionnaire that patients can fill out while in the waiting room. A score of greater than 15 suggests the presence of depression and should prompt further evaluation during that visit, including assessment of suicidality. Depression with suicidal ideation or with psychotic features should be urgently evaluated by a psychiatrist. Otherwise, it is reasonable that the first attempt at depression pharmacotherapy be made by the neurologist.

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are first-line agents for the treatment of major depression. While not all drugs in this class have been studied in patients with epilepsy, they are generally thought to be safe, with little impact on seizure frequency. Both citalopram (Celexa) and fluoxetine (Prozac) did not exacerbate seizures in open-label studies. In another study, sertraline (Zoloft) worsened seizure frequency in only one refractory epilepsy patient. The rational approach for selecting an antidepressant for a patient with epilepsy is similar to selecting an AED: treatment is tailored to comorbid conditions, the side-effect profile, and interactions with other drugs. Some SSRIs, such as paroxetine (Paxil), escitalopram (Lexapro), and

**TABLE 25-1 The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) Please Circle the Number that Best Describes How You Felt Over the Past 2 Weeks:**

| | Always/Often | Sometimes | Rarely | Never |
|---|---|---|---|---|
| Everything is a struggle | 4 | 3 | 2 | 1 |
| Nothing I do is right | 4 | 3 | 2 | 1 |
| Feel guilty | 4 | 3 | 2 | 1 |
| I'd be better off dead | 4 | 3 | 2 | 1 |
| Frustrated | 4 | 3 | 2 | 1 |
| Difficulty finding pleasure | 4 | 3 | 2 | 1 |

This is a six-item self-assessment tool to identify patients with major depression. A score of >15 has a specificity of 90%, sensitivity of 81%, and positive predictive value of 62% for major depression.

venlafaxine (Effexor), are effective in generalized anxiety disorder, which is a common coexisting psychiatric condition in epilepsy patients. Antidepressants may have similar side-effect profiles to some AEDs and may act synergistically to worsen adverse effects. For instance, sertraline and paroxetine, like valproate, pregabalin, and gabapentin, cause weight gain. These SSRIs also tend to cause more sedation than others and should be avoided in patients already on sedating AEDs. Physicians should also be aware that sexual side effects, including decreased libido, anorgasmia, and impotence, are common in patients taking SSRIs and SNRIs as well as enzyme-inducing AEDs. Antidepressants can also exhibit pharmacokinetic interactions with AEDs. Fluoxetine inhibits several cytochrome P450 isozymes and can elevate levels of phenytoin and carbamazepine. Enzyme-inducing AEDs such as phenytoin, carbamazepine, and phenobarbital can increase the clearance of SSRIs. Patients on these AEDs may require higher doses of antidepressants to achieve a therapeutic effect. While not explicitly studied in patients with epilepsy, psychotherapy, such as cognitive behavioral therapy, can be a useful adjunct to the pharmacologic treatment of depression and anxiety.

While it is reasonable for the neurologist to initiate antidepressant treatment, referral to a psychiatrist is probably indicated if the patient does not respond to a trial of two drugs at reasonable doses. If depression is severe and refractory or has psychotic features, epilepsy is not a contraindication for electroconvulsive therapy. Extra precautions, however, should be taken in patients with a history of status epilepticus.

**KEY POINTS TO REMEMBER**

- **Mood symptoms are very common in patients with epilepsy and have a significant impact on quality of life.**
- **Depression may have atypical features in patients with epilepsy.**
- **Patients with epilepsy have a higher risk of suicidality than the general population.**
- **All patients with epilepsy should be screened for depressive symptoms and suicidality.**

*Continued*

- **Patients with suicidality or depression with psychotic features should be urgently referred for psychiatric evaluation.**
- **Depression in patients with epilepsy usually responds to treatment with SSRIs or SNRIs.**
- **Patients who fail to respond to two first-line antidepressants should be evaluated by a psychiatrist.**

**Further Reading**


Andersohn F, Schade R, Willich SN, Garbe E. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. *Neurology.* 2010;75(4):335-340.

Gilliam FG, Barry JJ, Hermann BP, et al. Rapid detection of major depression in epilepsy: a multicentre study. *Lancet Neurol.* 2006;5(5):399-405.

Harden CL. The co-morbidity of depression and epilepsy. *Neurology.* 2002;59(S4):48S-55.

Kanner AM. Suicidality and epilepsy: a complex relationship that remains misunderstood and underestimated. *Epilepsy Currents.* 2009;9(3):63-66.

Kanner AM, Frey M. Treatment of common co-morbid psychiatric disorders in epilepsy: a review of practical strategies. In: French JA, Delanty N. *Therapeutic Strategies in Epilepsy.* Oxford, UK: Clinical Publishing Services, 2008:281-303.

# 26 Psychosis and Seizures

A 21-year-old, right-handed man had onset of delusional episodes about 2 years previous to this evaluation. His first episode, at age 19, consisted of the belief that he was dehydrated. He drank water to the point of hyponatremia. This lasted about 2 months and resolved without treatment, by his report. About 6 months later, he became convinced that an ex-girlfriend was trying to kill him. This occurred in the setting of considerable cocaine use. He was hospitalized and treated with olanzapine (Zyprexa). Before this episode began, he recalls episodic appearance of memories or perceived memories of traumatic events that did not actually occur. These were sudden in onset, accompanied by fear, and lasted up to several hours.

There is no history of episodic loss of consciousness, and no history of nocturnal tongue biting or incontinence. There are no known risk factors for epilepsy; he had a concussion 9 months previously (a year after the onset of his current episodes) due to an altercation. He had loss of awareness for about 5 minutes and anterograde amnesia for about 30 minutes after the

event. There is no family history of epilepsy. Current medications were quetiapine (Seroquel) 25 mg QID and risperidone (Risperdal) 0.5 mg QD.

He has a history of drug use, including cocaine, marijuana, LSD, and benzodiazepines. At one point, he reports taking up to 30 mg/day lorazepam (Ativan), stopping suddenly, and treating withdrawal symptoms with alcohol. He was referred to determine whether episodic psychosis, with an atypical presentation, could be related to unrecognized seizures.

On physical examination, he was mildly unkempt but alert and attentive and related well. When the possibility that seizures could be causing his psychosis was explained, he inquired, "Why can't I simply begin a seizure drug and see if it works?" The neurologist replied that he didn't like to "throw drugs" at people when he wasn't sure of the diagnosis, to which the patient said, "Well, clearly you aren't a psychiatrist." Neurologic examination was completely normal.

## What do you do now?

The borderline between neurologic and psychiatric disease is often murky, but in the case of epilepsy or possible epilepsy, this is particularly important. Chapter 25 discusses depression and anxiety in patients with epilepsy, but in this case we consider a patient with clear psychosis.

Psychotic symptoms can occur independently in patients with epilepsy who have a concurrent diagnosis of schizophrenia or a related condition, but this is very uncommon. Frank psychosis can also occur in association with some anticonvulsant drugs, particularly levetiracetam, topiramate, felbamate, vigabatrin and (more rarely) lamotrigine, but this is also unusual. Much more often symptoms are associated with either the immediate postictal state or with postictal psychosis, which is a distinct phenomenon and sometimes more confusing.

In the postictal state, particularly following a generalized tonic-clonic seizure, patients are frequently confused and agitated. Memory is quite poor, and they may be unable to recognize even close family members. Onlookers may try to restrain the patient who is wandering about, which can escalate confusion, paranoia, and agitation. This can be particularly problematic when seizures occur in public; police are called or are nearby, and well-meaning law enforcement personnel approach a patient in the postictal state. ***Postictal confusion*** may easily be misinterpreted as intoxication with alcohol or other drugs, and the police may begin questioning. The confused patient will not understand what has happened and why he or she is being approached, and this can increase his or her agitation. Police restrain the patient, the patient fights back, and injury or arrest can occur before the problem is sorted out, usually once the patient recovers and is able to explain. Because this scenario is common, it is always advisable to explain the possibility to patients and family members so that should postictal agitation occur, they can behave appropriately. This generally consists of nothing more than speaking reassuringly to the patient during confusion and preventing him or her from harm, ideally without restraint of any kind. It is also beneficial in such situations to have a medical alert bracelet or necklace so that emergency or law enforcement personnel can be aware of the problem.

Usually the situation is obvious in these cases, if not immediately then once a full history is obtained. A seizure will have occurred immediately

prior to the agitation and will rapidly clear afterward. An isolated event where the initial seizure is unwitnessed can potentially lead to confusion.

*Postictal psychosis* is sometimes more difficult to diagnose, mainly because of a long gap between the seizure and the onset of psychotic symptoms. Typically this is 24 to 72 hours, but it can be longer. In this case, the patient often develops florid psychosis, with delusional thinking and paranoia. It can appear identical to a psychotic break. Such symptoms typically take 1 to 2 weeks to clear. As with the postictal confusion, a witnessed seizure at the appropriate time makes the diagnosis much easier, but this can be unwitnessed and not recalled by the patient.

In patients with known postictal psychosis, the treatment is with antipsychotic drugs. The main difference from schizophrenia is that the drugs can be discontinued once the psychosis clears. In rare patients with uncontrolled seizures and recurrent postictal psychosis, a continuous, low dose of an antipsychotic such as risperidone could be considered.

In the case described above, the patient was atypical for schizophrenia due to the episodic nature of his psychosis and the relative lack of other signs of psychosis. In such patients, at least a routine EEG should be performed to see if there are signs of an underlying seizure disorder. In cases such as this one, where there is a higher suspicion for epilepsy a prolonged ambulatory EEG or inpatient video-EEG monitoring should be considered to ensure that a very treatable cause—unrecognized seizures—is not being missed.

**KEY POINTS TO REMEMBER**

- **Postictal agitation and paranoia commonly occur in the immediate postictal state, but this is usually easy to recognize due to its short duration and close proximity to seizures.**
- **Postictal psychosis typically begins after a delay of 1 to 3 days after a seizure. Manifestations are similar to psychotic behavior in schizophrenia and are treated with short-term antipsychotics.**
- **A chronic low dose of an antipsychotic could be considered for patients with known recurrent postictal psychosis.**

*Continued*

- **In patients with atypical psychosis, particularly if it is episodic, further investigation with EEG or video-EEG should be considered to determine whether the patient has unrecognized seizures and postictal psychosis.**

**Further Reading**

Kanner AM. Psychosis of epilepsy: A neurologist's perspective. *Epilepsy Behav.* 2000;1(4):219-227.

LaFrance WC Jr, Kanner AM, Hermann B. Psychiatric comorbidities in epilepsy. *Int Rev Neurobiol.* 2008;83:347-383.

Nadkarni S, Arnedo V, Devinsky O. Psychosis in epilepsy patients. *Epilepsia.* 2007;48(Suppl 9):17-19.

Tsopelas ND, Saintfort R, Fricchione GL. The relationship of psychiatric illnesses and seizures. *Curr Psychiatry Rep.* 2001;3(3):235-242.

# 27 Cognitive and Behavioral Issues

A 29-year-old man with a history of epilepsy comes for routine follow-up. He had onset of seizures in adolescence and they proved refractory to multiple medications. The workup, including ictal and interictal EEG, MRI, PET scan, and neuropsychological testing, was consistent with a left temporal seizure focus, and he underwent an anteromesial left temporal lobe resection 3 years previously. He had initial improvement postoperatively, but continued to have rare seizures. The seizures resolved 2 years previously with medication adjustment. He came mainly to report cognitive problems that have been persistent since his surgery. Whereas previously he had been able to hold a job as an accountant, since surgery he has been working mainly in the family business. His fiance reports that he is more distractible; he often forgets what she has told him or has no memory of events she considers significant.

This has become a source of stress in their relationship. He has a history of depression and has been treated with antidepressants in the past, but reports that this is not currently an issue.

### What do you do now?

Cognitive problems are a nearly universal complaint in patients with refractory epilepsy, and they are quite common even in patients with well-controlled epilepsy. Patients usually simply report that their "memory is bad" and may have a difficult time giving further details. The typical tests used in an office setting (mini-mental status, serial 7s, and three-word recall) usually yield little additional information, particularly in already high-functioning individuals.

Memory is actually quite complicated and has many components. Also, many aspects of daily cognitive functioning may be perceived as "memory" when in fact they are not. Further history may yield clues: Does he have trouble remembering short-term things like where the keys are or the name of someone he just met? Does she have difficulty with well-known directions, such as finding her way home? Are events of the more distant past forgotten? If the patient has difficulty with naming or following directions, it could be that the actual problem is language (or hearing). Increased difficulty with short-term memory can be part of normal aging or can be a manifestation of decreased concentration due to mood disorders or medication effects. Overall, there are several possible reasons for memory dysfunction in patients with epilepsy: mood disorders (resulting primarily in inattention); sleep disorders; medication adverse effects; seizures themselves (resulting in postictal states that can be prolonged); or the underlying epileptic condition. In this particular patient, removal of the hippocampus could contribute to difficulty with short-term memory as well.

All epilepsy patients with memory difficulty should be evaluated for mood problems. Depression is the most common comorbid condition that affects people with epilepsy, and it occurs 3- to 10-fold more often in those with uncontrolled epilepsy than in the general population. It affects up to 55% of patients with recurrent epilepsy and 3% to 9% of those with well-controlled seizures. This is discussed extensively in Chapter 25, but it may be the most important source of memory complaints in people with epilepsy.

Although frequently a comorbid condition, the relationship between anxiety and epilepsy has been less thoroughly investigated than depression. Estimates of its incidence in patients with epilepsy are crude and range from 3% to 50%, although incidences of up to 66% have been identified. Anxiety can affect cognition through inattention, possibly exacerbated by sleep

disturbances. Children with epilepsy commonly show behavioral symptoms of inattention and hyperactivity, and some of them have attention-deficit/hyperactivity disorder (ADHD). Estimates of the ADHD prevalence in children with epilepsy vary, although studies using standardized diagnostic criteria have documented ADHD in 14% to 40% of children compared with approximately 5% in otherwise normal school-aged children.

Sleep disorders, discussed extensively in Chapter 28, can be a source of perceived memory dysfunction and frequently go unrecognized. Sleep disorders can result in daytime drowsiness and consequent inattention. Sleep itself is now known to be required for many types of learning, and therefore sleep deprivation from any source—nocturnal seizures, coexisting sleep disorders, or insufficient sleep—could affect cognitive performance.

Medications used for epilepsy can certainly result in cognitive dysfunction (see Table 27.1). Some drugs (most notably topiramate) can have a direct effect on a subset of patients, and this can manifest as short-term memory problems or language difficulty. This has also been seen with other agents, particularly at high concentrations. Cognitive dysfunction can also be an indirect result of drowsiness or worsening mood. Felbamate is rarely used but has a relatively high risk of insomnia; lamotrigine and levetiracetam can also cause this in a small number of patients. Gabapentin, pregabalin, and tiagabine tend to deepen sleep and decrease arousals. Mood problems are most commonly exacerbated by levetiracetam, topiramate, or tiagabine; lamotrigine has a mild antidepressant effect and (along with valproate and carbamazepine) is FDA approved for the treatment of bipolar disease. Benzodiazepines such as clonazepam are used to treat anxiety disorders, and there is good evidence that pregabalin is effective in generalized anxiety. In most cases, adverse effects are more likely at higher, and certainly at toxic, levels of the drug. Therefore, anticonvulsant drug levels may be useful in patients with cognitive dysfunction if toxicity is suspected as a cause of cognitive dysfunction.

Seizures themselves can certainly affect cognition. If problems seem always to be transient and to follow a recognized seizure, this is rarely problematic in terms of diagnosis, and more aggressive seizure management is clearly warranted. If the dysfunction is fluctuating, consideration should be given to the possibility of unrecognized seizures, possibly during sleep. Prolonged ambulatory or inpatient EEG may be the only way to

**TABLE 27-1 Influence of Antiepileptic Drugs on Cognitive Function, Depressive Symptoms/Mood, Anxiety, and Sleep**

| Drug | Cognitive function | Depression/Mood | Anxiety | Sleep |
|---|---|---|---|---|
| Carbamazepine | 0 | ++ | 0 | 0 |
| Gabapentin | 0 | +? | + | ++ |
| Lacosamide | ND | ND | ND | ND |
| Lamotrigine | 0 | + | +? | 0 |
| Levetiracetam | 0 | - | - | 0 |
| Oxcarbazepine | 0 | +? | 0 | ND |
| Phenobarbital | -- | -- | 0 | +/- |
| Phenytoin | - | - | 0 | +/- |
| Pregabalin | 0 | +? | + | ++ |
| Rufinamide | ND | ND | ND | ND |
| Topiramate | -- | - | - | ND |
| Tiagabine | 0 | - | ND | ++ |
| Vigabatrin | 0 | - | ND | ND |
| Valproic acid | -? | + | 0 | - |
| Zonisamide | 0 | ND | - | ND |

*Key:* 0 = no effect;? = possible effect; + = mild beneficial effect; ++ = marked beneficial effect; - = mild detrimental effect; -- = marked detrimental effect; ND = no data.

ensure that frequent unrecognized seizures are not occurring when this is suspected.

Finally, the epileptic condition can affect cognition. Although single seizures are not thought to affect neuronal health unless they are prolonged, it may be that repeated seizures over many years take a toll.

When in doubt, most patients require neuropsychological testing. This is the only way to reliably determine whether significant dysfunction exists—after all, we would all like our memory to be better. Careful testing will also reveal the pattern of dysfunction, with clues as to whether this is

likely due to medication toxicity, mood problems, the epileptic condition, or previous epilepsy surgery. Most importantly, appropriate treatment, including cognitive behavioral therapy, can then be recommended when indicated.

**KEY POINTS TO REMEMBER**

- Cognitive dysfunction is common in epilepsy patients and has many possible sources.
- Coincident mood disorders, sleep disorders, and medication adverse effects should all be considered as possible sources of cognitive dysfunction.
- Particularly if cognitive symptoms are episodic or variable, unrecognized seizures should be considered as a possible source of cognitive dysfunction, even in apparently well-controlled patients.
- Formal neuropsychological testing should be strongly considered in any patient with cognitive dysfunction of unclear etiology.

**Further Reading**


Barry JJ. The recognition and management of mood disorders as a comorbidity of epilepsy. *Epilepsia.* 2003; (Suppl 4):30-40.

Edwards KR, Sackellares JC, Vuong A, Hammer AE, Barrett PS. Lamotrigine monotherapy improves depressive symptoms in epilepsy: a double-blind comparison with valproate. *Epilepsy Behav.* 2001;2:28-36.

Gilliam F, Kanner AM. Treatment of depressive disorders in epilepsy patients. *Epilepsy Behav.* 2002;3(5S):2-9.

Goldstein MA, Harden CL. Epilepsy and anxiety. *Epilepsy Behav.* 2000;1:228-234.

Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? *Neurology* 2002;58 (Suppl 5):S27-S39.

Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. *Lancet.* 2001;357:216-222.

Méndez M, Radtke RA. Interactions between sleep and epilepsy. *J Clin Neurophysiol.* 2001;18:106-127.

Maquet P. The role of sleep in learning and memory. *Science.* 2001;294:1048-1052.

Martin R, Kuzniecky R, Ho S, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology.* 1999;52:321-327.

Scicutella A, Ettinger AB. Treatment of anxiety in epilepsy. *Epilepsy Behav.* 2002;3(5S):10-12.

Stickgold R, Hobson JA, Fosse R, Fosse M. Sleep, learning, and dreams: off-line memory reprocessing. *Science.* 2001;294:1052-1057.

# 28 Sleep Disturbances in Epilepsy

A 41-year-old man presents because of recurrent seizures 1 year following successful epilepsy surgery. He had previously undergone an evaluation for refractory epilepsy, including video-EEG monitoring and MRI, which showed right mesial temporal sclerosis, frequent right temporal interictal epileptiform spikes, and right temporal onset seizures. As the workup was consistent with right temporal onset seizures, he then underwent a right temporal lobectomy. Whereas he had up to weekly complex partial seizures before the operation, he had none in 11 months afterward. Two weeks prior to evaluation, he awoke with blood on his pillow and felt diffuse muscle weakness; the event was unwitnessed as his wife had been out of town and he did not seek medical attention. Two nights previous to the evaluation, his wife awoke to chewing noises and found the patient to be unresponsive, with eyes open, for 2 minutes, followed by confusion. These were similar to the episodes that had occurred prior to surgery, when they occasionally had occurred during sleep.

On further questioning, his wife reported increased snoring, and she frequently noted gasping for breath. The patient had become much more tired during the day and reported a 25-pound weight gain following surgery.

### What do you do now?

This patient has recurrent epilepsy, but the history also suggests a high likelihood of obstructive sleep apnea (OSA). In patients with epilepsy, this is one known risk factor for intractability; failure to treat the underlying sleep disorder can result in continued seizures.

Before discussing specific sleep disorders, two aspects of sleep are critical: obtaining sufficient sleep and adequate sleep hygiene. One of the more common reasons for inadequate sleep is perhaps the most obvious: failing to spend enough time in bed. This is common in the general population—perhaps particularly in physicians, who may tend to underemphasize its importance. The demands of modern society, including work, family, and leisure time, often cause people to limit their sleep. Although most believe this to be benign, chronic sleep deprivation can clearly result in neurocognitive deficits. Epilepsy patients are certainly not immune from this; in fact, many studies suggest that epilepsy patients with sleep disruption suffer more than do healthy subjects without epilepsy. This may be the most difficult of sleep disorders to treat; it requires convincing patients that sleep is more important than other activities.

Sleep hygiene is a fairly straightforward concept, but it is one with which many patients and caregivers are unfamiliar. Review of sleep hygiene can also be time-consuming, and in a busy office practice it is easy to overlook. The basic principle of sleep hygiene is optimization of the conditions for sleep. Contrary to many people's beliefs and to the accepted norms of American society, humans do not have full voluntary control over sleep, as with (at least to a greater extent) eating and voiding. Many would like to believe that sleeping and waking are like a switch, on and off, but this is simply not true. Although sleep cannot be fully controlled, it can be encouraged through good sleep habits. Principles of sleep hygiene are summarized in Table 28.1.

Specific sleep disorders most common in the general population, and in epilepsy patients, include OSA, insomnia, periodic limb movements of sleep (PLMS), and restless legs syndrome (RLS). Patients with partial epilepsy have twice the incidence of drowsiness as control subjects, and this significantly worsens their quality of life. OSA occurs in at least 3% of the general population, and this disorder is disproportionately responsible for excessive sleepiness seen in epilepsy patients. In selected epilepsy patients referred for polysomnography, up to 70% are found to have OSA, and

**TABLE 28-1 Principles of Sleep Hygiene**

General

1. Go to sleep at about the same time each night, and awaken at the same time each morning. Wide fluctuations between workdays and days off can further impair your sleep.
2. Try not to nap. If you do, restrict this to about an hour per day, and do it relatively early (before about 4 in the afternoon).
3. If you are not sleepy, either don't go to bed or arise from bed. Do quiet, relaxing activities until you feel sleepy, then return to bed.
4. Avoid doing stimulating, frustrating, or anxiety-provoking activities in bed or in the bedroom (watching television, studying, balancing the checkbook, etc.). Try to reserve the bedroom, and especially the bed, for sleep and sexual activity.

Use of Drugs

1. Avoid coffee, tea, cola, or other caffeinated beverages after about noon. Also avoid chocolate late in the day.
2. If you smoke, avoid this in the hour or two before bedtime.
3. If you drink alcohol, limit this to one or two drinks per day and do not drink immediately before bedtime. Although you may find this relaxing, alcohol actually can interfere with sleep later in the night.
4. If you take prescription drugs or over-the-counter drugs that can be stimulating, discuss dosing times with your doctor.

Exercise

1. Exercise, particularly aerobic exercise, is good for both sleep and overall health and should be encouraged.
2. Avoid stimulating exercise in the evening (ideally at least 5 hours before bedtime).

Bedtime Ritual

1. Perform relaxing activities in the hour before bedtime.
2. Make sure your sleeping environment is as comfortable as possible, paying attention to temperature, noise, and light.
3. Do not eat a heavy meal just before bedtime, although a light snack might help induce drowsiness.
4. It is sometimes helpful to place paper and pen by the bedside. If you find yourself worrying about completing or remembering a task the next day, write it down and let it go.

During the Night

1. If you awaken and find you can't get back to sleep, arise from bed and do quiet, relaxing activities until you are drowsy. Then return to bed.
2. Place clocks so that the time is not visible from the bed.

diagnosis and treatment of OSA can improve seizures in patients with epilepsy. First-line treatment is positive airway pressure; however, mandibular advancement devices or surgery may be helpful in some patients.

Insomnia occurs in more than 10% of the general population and is more frequent in patients with epilepsy. Sleep disturbance occurs in 39% of patients with intractable epilepsy, and most of the additional disturbance compared with controls is due to insomnia. According to the National Health Interview Study, adults with seizures are more than twice as likely to report insomnia and more than three times as likely to report excessive sleepiness as adults without epilepsy. Depression and anxiety are known to be common in epilepsy patients and can be important contributors to insomnia in this population. Insomnia due to depression is best treated by addressing the psychiatric problem. Otherwise, insomnia is treated with cognitive behavioral techniques and/or hypnotics as necessary.

PLMS and RLS are both relatively common in the general population. The incidence of RLS is about 10% and increases with age. PLMS occurs in about 5% of young adults; however, the prevalence may be as high as 44% in patients over age 64. RLS and PLMS often occur together and have many characteristics in common; the main known effect of both is daytime somnolence. Studies of epilepsy patients suggest that RLS is more common in patients with epilepsy than in control subjects. Both conditions are treatable: dopamine agonists, gabapentin and pregabalin, benzodiazepines, and opioids have all been shown to be effective. In epilepsy patients the gabapentinoids may be most reasonable to try first. All patients should have a ferritin level checked, as low iron stores are a treatable cause; some studies suggest that even patients with normal ferritin can benefit from iron supplements.

All of these studies underscore the increased prevalence of sleep disorders (particularly OSA) in the epilepsy population. An evaluation for sleep disorders should be considered not only in cases of recurrent or intractable seizures, but also in patients with unexplained cognitive dysfunction, fatigue, or sleepiness. When in doubt, overnight polysomnography is indicated, particularly for suspected OSA or PLMS.

**KEY POINTS TO REMEMBER**

- Sleep disorders are common in epilepsy patients and can result in daytime drowsiness, problems with concentration, and increased seizures.
- Sleep disorders are commonly overlooked, and an evaluation should be considered in any patient who is intractable or has unexplained problems with memory or daytime somnolence.
- The common sleep disorders are very treatable, but this cannot be done without a diagnosis.
- Polysomnography should be considered for epilepsy patients with suspected sleep disorders.

**Further Reading**


Ancoli-Israel S, et al. Sleep apnea and periodic movements in an aging sample. *J Gerontol.* 1985;40(4):419-425.

Bazil CW. Sleep disturbances in epilepsy patients. *Curr Neurol Neurosci Rep.* 2005;5(4):297-298.

de Weerd A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. *Epilepsia.* 2004;45(11):1397-1404.

Jefferson CD, et al. Sleep hygiene practices in a population-based sample of insomniacs. *Sleep.* 2005;28(5):611-615.

Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. *Sleep.* 1994;17(8):739-743.

Malow BA, et al. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology.* 2000;55(7):1002-1007.

# 29 Bone Health

A 44-year-old African-American man was referred to you. He began having seizures at age 12, shortly after falling down some stairs. He has been on phenytoin ever since, currently at a dose of 200 mg BID. Two years ago he began taking lamotrigine as an adjunct, currently at 200 mg BID. Complex partial seizures and nocturnal convulsions continue, provoked by missed doses and with the moderate use of alcohol. Because of the known association of phenytoin to decreasing bone density, a DEXA/bone density scan was ordered. It showed osteoporosis of the lumbar spine in addition to osteopenia of the left hip.

*What do you do now?*

While seizures are important to treat, the medications we use to treat them often have adverse effects. Bone health has become a well-known problem in the epilepsy population. Phenytoin was a reasonable choice when he was 12, and it still is, as it could have been changed to once-daily dosing, which could help with his tendency to miss evening doses. However, he is a young, healthy, ambulatory African-American man: phenytoin is the only risk factor for osteoporosis, and efforts should be made to reverse the process.

The relationship between chronic AED use and bone loss has not been fully elucidated. Bone homeostasis is a complicated and an active process requiring parathyroid hormones, adequate serum calcium through intestinal absorption and renal reabsorption, and vitamin D. Putative mechanisms of bone loss include liver induction causing increased vitamin D breakdown, calcitonin deficiency, and effects on calcium absorption. Phenytoin is not the only medication to be associated with bone loss: though enzyme-inducing agents are most often cited, there are animal and preclinical studies that hint at decreased bone mineral density or increased bone turnover with the use of most AEDs, though no worsening has yet been reported with lamotrigine, levetiracetam, or topiramate. Bone mineral density testing is now recommended routinely for patients at higher risk for osteoporosis (nonambulatory, elderly and Caucasian patients), but as can be seen in this case, a baseline for any patient is reasonable, particularly if the patient is taking an implicated AED. One study in a pediatric population, showed that half had low bone density, particularly patients with cerebral palsy, severe mental retardation, or gait impairment.

The issues of refractory epilepsy are covered in other chapters; however, as both phenytoin and lamotrigine are metabolized by the liver, an increase in liver metabolism has the potential to decrease levels of both. Tailoring a medication to this specific patient and his lifestyle may have us opt for one with a longer half-life and without liver metabolism. Zonisamide and levetiracetam XR (Keppra XR) are ones to first consider as replacements for phenytoin. Neither drug has clinical data to show chronic bone density losses at this point.

Some neurologists will opt to initiate management and treatment of osteoporosis. Obtaining 25-OH vitamin D levels will provide some initial information and could serve as a marker for improvement. A reasonable

approach would be to supplement with oral vitamin D at 800 to 1,000 IU/day. If the serum 25-OH vitamin D levels do not improve to within the normal range, more aggressive therapy through an endocrinologist may be required. Until recently, calcium with vitamin D was commonly used to treat or prevent osteopenia and osteoporosis, but a longitunial study has associated oral calcium supplementation with increased myocardial infarctions, theorizing that the supplements may cause spikes in serum calcium levels that are detrimental to arterial health. They recommend considering increasing intake of calcium-containing foods (dairy products, dark leafy vegetables and broccoli, tofu, almonds) rather than use tablets. Vitamin D supplementation has not been associated with increased cardiovascular risks, so using it alone appears safer than with oral calcium supplementation. Use of bisphosphonates is the likely next step for bone repletion. However, targeting the likely cause of increased bone loss is most important for this patient. In this case, phenytoin is the offender, and it is presumed that its replacement AEDs will have less negative effects.

**KEY POINTS TO REMEMBER**

- Osteoporosis and osteopenia can occur at any age and in any patient.
- It appears that enzyme-inducing AEDs are more prone to cause accelerated bone loss, and patients taking these medications should have at least one baseline DEXA bone mineral density scan.
- Replacement of vitamin D and calcium may be more complicated than initially thought, and referring patients with osteopenia or osteoporosis to an endocrinologist may be preferred.

**Further Reading**


Coppola G, Fortunato D, Auricchio G, et al. Bone mineral density in children, adolescents, and young adults with epilepsy. *Epilepsia.* 2009;50:2140-2146.

Pack A. Bone health in people with epilepsy: is it impaired and what are the risk factors? *Seizure.* 2008;17(2):181-186.

Verrotti A, Coppola G, Parisi P, et al. Bone and calcium metabolism and antiepileptic drugs. *Clin Neurol Neurosurg.* 2010;112:1-10.

Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ (2010) vol. 341 pp. c3691.

# 30 Sudden Unexpected Death in Epilepsy (SUDEP)

The patient is a 32-year-old woman with refractory cryptogenic multifocal epilepsy since childhood. Her first seizure was at 9 months, when she had a seizure after having a high fever following immunization. She had recurrent seizures associated with fever and was treated with phenobarbital from 18 months to 14 years. Soon after medication was discontinued, she had a generalized tonic-clonic seizure. She was treated with carbamazepine and did well except for occasional seizures in the setting of missed medications or illness until her mid 20s. At 28, she began having more frequent seizures, requiring additional medications. She continued to have two or three complex partial seizures and generalized tonic-clonic seizures per month despite adequate trials of AEDs, including lamotrigine, topiramate, levetiracetam, pregabalin, and felbamate. Her family is concerned about her frequent seizures because they have recently read about sudden death in epilepsy on the Internet.

*What do you do now?*

Patients with epilepsy have a two- to three-fold increased risk of death compared to the general population. While injuries associated with seizures, suicides, adverse effects of medications, and the underlying etiology of the epilepsy contribute to this increased mortality, sudden unexpected death in epilepsy (SUDEP) may be the leading cause of death in patients with refractory epilepsy. SUDEP is defined as a sudden and unexpected nontraumatic or non-drowning-related death in a patient with epilepsy that may or may not be related to recent seizure. On autopsy, there is no evidence of anatomic or toxicologic cause of death. Most often the death is unwitnessed and the patient is found in bed the following morning. SUDEP is a categorical term and may have multiple etiologies (see below). The incidence of SUDEP in the general epilepsy population has been reported to be 0.09 to 1.2/1,000 person-years. This incidence is higher, 1.1 to 5.9/1,000 person-years, in patients with medically refractory epilepsy and even higher, 6.3 to 9.3/1,000 person-years, in patients who have failed resective epilepsy surgery. In several case-control studies, the greatest risk factor for SUDEP was frequent seizures, especially generalized tonic-clonic seizures. Other commonly identified risk factors were young age of epilepsy onset, male sex, variable AED levels, and AED polytherapy (Table 30.1).

**TABLE 30-1 Factors that Increase and Decrease SUDEP Risk**

| Factors associated with increased SUDEP risk | Factors associated with decreased SUDEP risk |
|---|---|
| Poor control of generalized tonic-clonic seizures | Seizure freedom |
| Subtherapeutic AED levels | Sharing bedroom |
| AED polytherapy | Monitoring devices |
| Carbamazepine use (in some but not all studies) | |
| Early age of epilepsy onset | |
| Young adult age | |
| Male sex | |
| Mental retardation | |

The mechanisms underlying SUDEP are unclear and it is likely the common endpoint for a variety of causes. Hypotheses, often generated from observed SUDEP and near-SUDEP in epilepsy monitoring units, include seizure-related respiratory failure, cardiac arrhythmia, or "cerebral electrical shutdown." In the observed cases, ictal obstructive or central postictal apnea preceded cardiac arrest in most cases. In rarer cases, the inciting incident was seizure-associated ventricular arrhythmia. In most cases, the preceding seizure was a secondarily generalized tonic-clonic seizure. Central apnea may be a common feature in many seizures, occurring in 59% of recorded complex partial, tonic, or generalized tonic-clonic seizures in one series. Significant ictal bradycardia or ictal asystole is rarer, occurring in 2 to 4 of 1,000 patients undergoing video-EEG monitoring in several series. However, long-term recordings with an implantable cardiac loop recorder in patients with refractory epilepsy suggest that significant asystole may occur with some but not all seizures in 15% of the patients studied. The frequency of respiratory and cardiac changes during seizures that do not lead to death in patients with epilepsy suggests that SUDEP may result from failure of mechanisms that allow patients to recover from seizure-induced cardiopulmonary derangements.

Currently there are no definitive treatments to prevent SUDEP, but based on identified risk factors, experts recommend several interventions to mitigate the risk. Because of the association of SUDEP with uncontrolled epilepsy, good seizure control is the logical strategy for prevention. This includes ensuring that the patient is on a sufficient dose of an AED that is appropriate for his or her epilepsy syndrome. In addition, epilepsy surgery should be offered to appropriate patients. Nocturnal supervision, especially from someone who is able to provide assistance during a seizure, may also be a simple strategy to limit SUDEP. In addition, patients with refractory epilepsy should undergo cardiac evaluation. Preexisting structural heart abnormalities or arrhythmias may predispose these patients to sudden death. Patients with a history of ictal asystole, even if self-limited, should be considered for pacemaker implantation, especially if asystole is symptomatic. While these interventions make sense, it should be noted that there is no prospective evidence of their effectiveness.

One aspect of SUDEP that is a point of controversy among experts is if and when to discuss the risk of sudden death with epilepsy patients.

Some argue that the knowledge, especially in the absence of clear preventive measures, may cause unnecessary distress in patients. On the other hand, understanding the risks may help patients make informed decisions about treatment, including adhering to medication regimens, pursuing surgery, or making living arrangements. While it may be appropriate to withhold discussions of SUDEP in patients with newly diagnosed epilepsy, we advocate informing patients about their risks when it becomes clear that their epilepsy is difficult to treat.

**KEY POINTS TO REMEMBER**

- **The incidence of sudden death in refractory epilepsy is 1 to 6 per 1,000 person-years.**
- **Risk is related to frequency of seizures, especially generalized tonic-clonic seizures, AED polytherapy, young age of epilepsy onset, and male sex.**
- **Proposed mechanisms include seizure-related hypoventilation, cardiac arrhythmias and cerebral shutdown.**
- **No preventive measures have proven effective, but seizure control and sharing a room may reduce the risk.**
- **Patients with difficult-to-control epilepsy should be counseled on SUDEP risks.**

**Further Reading**


Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain.* 2008;131:3239-3245.

Beran RG. SUDEP—to discuss or not discuss: that is the question. *Lancet Neurol.* 2006;5:464-465.

So EL. What is known about the mechanisms underlying SUDEP? *Epilepsia.* 2008; 49:93-98.

Tomson T, Nashef L, Rivlin P. Sudden unexpected death in epilepsy: Current knowledge and future directions. *Lancet Neurol.* 2008;7:1021-1031.

# 31 Work, Driving, and Epilepsy

A 26-year-old, right-handed man had his first probable seizure in 2005. This occurred about 2 days after excessive alcohol intake and exhaustion due to running in a half-marathon race. He does not have any memory of the seizure, and it began while he was asleep. His family reported hearing choking noises, followed by generalized shaking and unresponsiveness. He was hospitalized for 5 days and the workup was reportedly normal. He was not started on medication. He had no further episodes until October 2008, when he had a similar event in the setting of sleep deprivation. Levetiracetam was started at 750 mg BID. He had a third episode in February 2009, at which time it was increased to 1,000 mg BID. A final episode occurred 4 months prior to presentation, although he reports not taking medicine for about 1.5 days before this. He was also diagnosed with obstructive sleep apnea; this is now successfully treated with positive airway pressure.

He has no risk factors for epilepsy. He works as a firefighter and had been placed on light duty due to seizures. An EEG 2 years previously was normal by report.

## *What do you do now?*

When is it safe for a patient with a seizure disorder to drive? In certain professions, notably those involving heavy machinery or potentially dangerous situations (such as this one), a related problem is when, if ever, a patient may safely return to work.

With regard to driving, there are both legal and medical considerations. From a legal standpoint, the obligations of the physician differ by state. The duration of seizure freedom required before a motor vehicle license can be reinstated varies from 3 to 12 months, depending on state law. Twenty-eight states have a fixed seizure-free interval requirement before a driver's license may be reinstated; the remainder have a more flexible approach, allowing for conditions such as seizure due to inability to obtain medication for a short period of time. Five states still have mandatory physician reporting (California, Nevada, New Jersey, Oregon, Pennsylvania). In a patient who has been seizure-free for over a year, all states allow driving privileges.

The medical recommendation is not always identical to the legal requirement. Medically, the risks that a seizure with impairment of consciousness may occur during driving must be weighed against the practical need for driving in order to carry out a normal life. This also includes the potential risk to passengers or others should a person with epilepsy lose control of a car during driving. There must be some perspective: driving is never 100% safe, and there is always some risk involved. In patients with frequent complex partial seizures (even one every few months), driving should never be recommended. In someone who has been seizure-free for over a year, most would agree the risk is minimal. Less than a year of seizure freedom is more controversial; however, one study showed that the frequency of seizure-related motor vehicle accidents did not change when one state, Arizona, reduced the seizure-free requirement from 12 to 3 months. A minimum of 3 months of seizure freedom therefore seems prudent from a medical standpoint for all patients. Even when allowed (medically or legally), patients should be advised to minimize driving (for example, by having others drive the patient whenever possible) to further reduce risk. It may help to remind the patient that the risk of seizures is never zero. Discretion can be used with patients who have a pattern of seizures exclusively during sleep, or with seizures that are clearly not associated with altered awareness. Keep in mind that with the latter, sometimes further investigation including video-EEG monitoring may be indicated, as patients may not be aware that they are

briefly losing awareness, particularly during temporal lobe onset seizures. Sometimes ambulatory EEG or video-EEG is also warranted to ensure that patients are not having seizures that are completely unrecognized; this may be particularly helpful in cases of absence epilepsy. Counseling is very important: despite the recommendation of physicians, many patients with uncontrolled epilepsy continue to drive. In a study of over 350 patients eligible for epilepsy surgery, all of which had continued seizures with altered awareness, nearly one third continued to drive.

For the seizure-free patient, the question of driving arises during dose or medication changes, and if the decision to withdraw AEDs is made. Any decision to withdraw medications should be accompanied by a recommendation to avoid driving for some period of time, although recurrences can occur up to many years after medication withdrawal. As most recurrences happen in the first 6 months, this is probably a conservative time frame. In any case, patients should certainly be advised not to drive during drug discontinuation, as this has been shown to be a higher-risk time for recurrence.

Recommendations for the work environment may be more difficult. Patients with a diagnosis of epilepsy are generally not able to obtain a license to fly aircraft, although general aviation pilots may sometimes have a license reinstated if they have been seizure-free for at least 10 years. For patients in other high-risk professions, including firefighters, surgeons, and machine operators, it is always prudent to minimize risk whenever possible by restricting duty, or ensuring that someone nearby could always take over in the event of a seizure. The duration of seizure freedom should use the driving guidelines as an absolute minimum time frame; longer periods are often recommended, depending on the individual situation.

Finally, many patients ask about higher-risk recreational activities such as scuba diving, sky diving, and hang gliding. As with driving, the risk must always be minimized whenever possible. However, as these are optional activities, more caution should be used compared with the more important (for most people) activity of driving.

**KEY POINTS TO REMEMBER**

- Driving laws vary by state, with between 3 and 12 months of seizure freedom required for a valid license.
- The minimal seizure-free time needed for safe driving is not known, although one study suggested that 3 months is no worse than 12.
- Even when allowed to drive, patients should be counseled to minimize driving when possible, as the seizure risk is never zero.
- In high-risk professions, the seizure-free time recommended must be tailored to the individual risk.

**Further Reading**


Berg AT, Vickrey BG, Sperling MR, et al. Driving in adults with refractory localization-related epilepsy. Multi-Center Study of Epilepsy Surgery. *Neurology.* 2000;54:625-630.

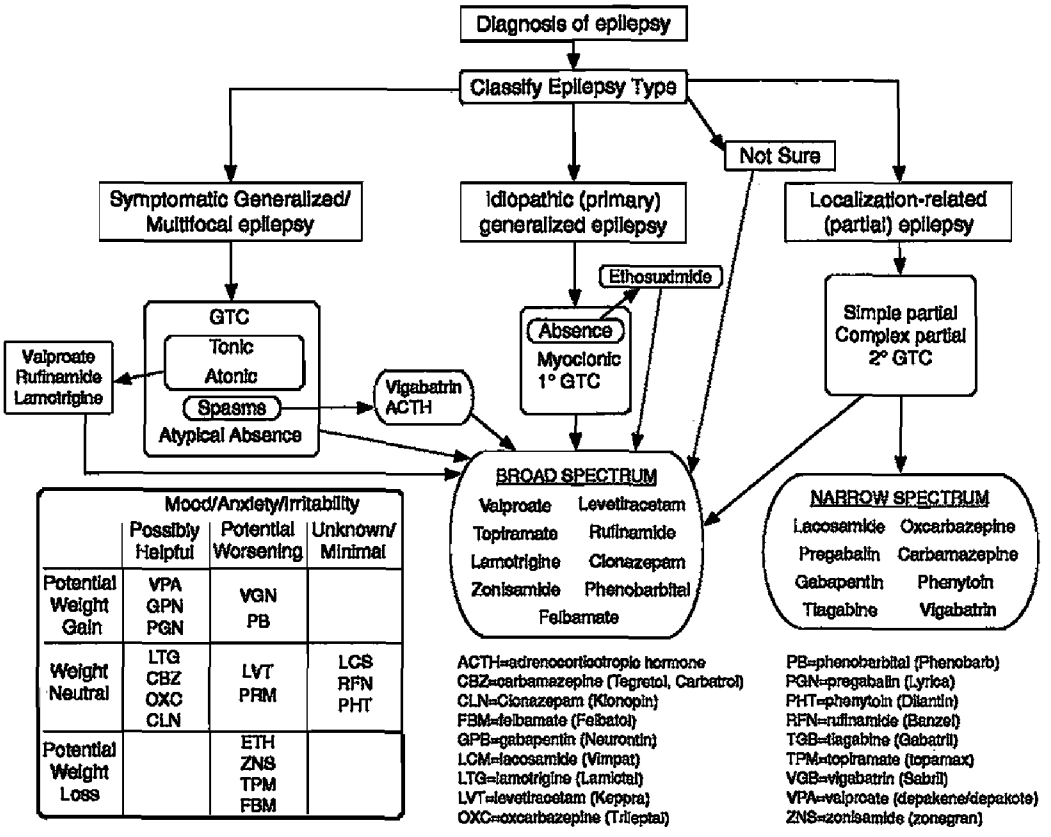
Drazkowski JF. Driving and flying with epilepsy. *Curr Neurol Neurosci Rep.* 2007;7: 329-334.

Drazkowski JF, Fisher RS, Sirven JI, et al. Seizure-related motor vehicle crashes in Arizona before and after reducing the driving restriction from 12 to 3 months. *Mayo Clin Proc.* 2003;78:819-825.

Krauss GL, Ampaw L, Krumholz A. Individual state driving restrictions for people with epilepsy in the US. *Neurology.* 2001;57:1780-1785.

# Appendix I

This flowchart shows the decision-making process in the choice of AED.




The first step is to classify the epilepsy syndrome. Partial epilepsy can be treated with both narrow-spectrum and broad-spectrum agents. For idiopathic generalized epilepsy and unclear syndromes, it is safest to restrict usage to the broad-spectrum agents. Some specific syndromes tend to respond to specific agents, as highlighted for tonic/atonic seizures and spasms. Ethosuximide has been found to be a treatment for in absence seizures although it does not reliably treat any other seizure type. Tolerability is the last step in choosing a medication, but it is extremely important for the overall success of the treatment. The inset in the bottom-left corner shows two of the most common tolerability issues: behavioral in terms of mood/anxiety/irritability, and the potential for weight changes. While each medication is not certain to help or worsen each issue, this table indicates their tendencies to occur in clinical practice which may assist with matching of medication to patient priorities.

# Appendix II: The Basics of AED Usage

| Drug | Dosage Forms | Usual adult starting dose (mg/day) | Usual adult dose (mg/day) | Dosing schedule | Minimum Titration time (days) | Usual effective plasma conc[a] (μg/mL) | Pediatric maintenance dose (mg/kg/day) | Issues to monitor[b] |
|---|---|---|---|---|---|---|---|---|
| Carbamazepine (Tegretol) | Tabs Chewtab | 200 | 800-1600 | TID | 7-14 | 8-12 | 10-30 | LFT, Na, CBC |
| Carbamazepine XR(Carbatrol, Tegretol XR) | Tabs Capsules | 200 | 800-1600 | BID | 7-14 | 8-12 | 10-30 | LFT, Na, CBC |
| Clonazepam (Klonopin) | Tabs ODT | 0.5 | 0.5-1.5 | BID-TID | 1-7 | NE | 0.1-0.2 | |
| Ethosuxamide (Zarontin) | Capsules Solution | 250 | 750-1500 | BID | 7-14 | 40-100 | 15-40 | CBC, LFT |
| Felbamate (Felbatol) | Tabs Solution | 600 | 2400-3600 | BID-TID | 14-21 | 20-140[c] | 15-60 | CBC, LFT, reticulo-cyte |
| Gabapentin (Neurontin) | Tabs Capsules | 1800 | 1800-3600 | TID-QID | 1-14 | 4-16 | 30-90 | None |
| Lacosamide (Vimpat) | Tabs IV | 100 | 400 | BID | 28 | NE | NE | None |
| Lamotrigine (Lamictal-IR) | TabsODT Chewtab | 12.5-50[d] | 100-600[d] | QD-BID | 28-42 | 2-16 | 5-15[d] | None |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lamotrigine XR (Lamictal XR) | Tabs | 12.5-50[d] | 100-600[d] | QD-BID | 28-42 | 2-16 | 5-15[d] | None |
| Levetiracetam (Keppra-IR) | Tabs<br>Solution<br>IV | 1000 | 1000-3000 | BID-TID | 1 | 5-45[c] | 60 | None |
| Levetiracetam XR (Keppra-XR) | Tabs | 1000 | 1000-3000 | QD-BID | 1 | 5-45 | 60 | None |
| Oxcarbazepine (Trileptal) | Tabs<br>Solution | 300 | 1200-2400 | BID-TID | 7-14 | 10-35[e] | 20-40 | CBC, Na |
| Phenobarbital | Tabs<br>IV | 90 | 90-180 | QD | 1 | 15-40 | 3-5 | LFT |
| Phenytoin (Dilantin, Phenytek) | Capsule<br>Suspension<br>Chewtab<br>IV | 300 | 300-400 | QD | 1 | 10-20 | 4-8 | LFT |
| Fos-phenytoin (Cerebryx) | IV, IM | 10-20 PE/kg | 4-6 PE/kg/d | QD | 1 | 10-20 | 4-8 PE | EKG |
| Pregabalin (Lyrica) | Capsules | 150 | 150-600 | BID/TID | 1 | NE | NE | None |
| Primidone (Mysoline) | Tabs | 100-125 | 750-1500 | TID | 10 | 5-12 µg | 10-25 | LFT |

| Drug | Dosage Forms | Usual adult starting dose (mg/day) | Usual adult dose (mg/day) | Dosing schedule | Minimum Titration time (days) | Usual effective plasma conc[a] (µg/mL) | Pediatric maintenance dose (mg/kg/day) | Issues to monitor[b] |
|---|---|---|---|---|---|---|---|---|
| Rufinamide (Banzel) | Tabs | 800 | 3200 | BID | | NE | 45, up to 3200mg/d | EKG |
| Tiagabine (Gabitril) | Tabs | 4 | 32-56 | BID-QID | 28-42 | NE | Up to 32mg/day | None |
| Topiramate (Topamax) | tabs | 25 | 200-600 | BID | 28-42 | 4-10 | 5-6 | None |
| Valproate (Depakene) | Capsule IV Spinkles Solution | 500 | 1000-3000 | TID | 7-14 | 50-120 | 15-60 | LFT, NH4, plt |
| DiValproate (Depakote) | Tabs | 500 | 1000-3000 | BID | 7-14 | 50-120 | 15-60 | LFT, NH4, plt |
| Divalproate ER (Depakote ER) | Tabs | 500 | 1000-3500 | QD-BID | 7-28 | 50-120 | 15-70 | LFT, NH4, plt |
| Vigabatrin (Sabril) | Tabs, solution | 1000 | 3000 | BID | 29 | NE | 150 | Opth |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Zonisamide (Zonegran) | capsules | 100 | 100-600 | QD-BID | 1 | 10-40 [c] | 4-8 | none | |

[a] In general older patients (over 65) may require lower doses of all drugs due to reduced renal clearance and/or hepatic function.

[b] Labs should be monitored, in general, at initiation of treatment, once on maintenance dose, then at most every six months or (usually) as needed to monitor adverse effects.

The exception is felbamate, where labs should be monitored every 2-4 weeks during the first year of treatment, then at least every 3 months thereafter.

[c] Not established; represents usual concentration in patients receiving therapeutic dose

[d] Varies with concomitant AED (lower with enzyme inducers; higher with enzyme inhibitors)

[e] of MHD, active metabolite

NE not established

NA not available

PE Phenytoin Equivalents (75mg fosphenytoin is equivalent to 50mg phenytoin)

Opth: mandatory quarterly ophthalmological assessments

# Appendix III: Summary of AED Advantages and Disadvantages

| Drug | Advantages | Disadvantages |
|---|---|---|
| carbamazepine | Inexpensive<br>Mood stabilizer<br>Treats some neuropathic pain<br>Known rate of teratogenesis | drug interactions (incl OC)<br>hypersensitivity<br>possible bone density loss<br>rare sedation<br>hyponatremia, leukopenia (us. asymptomatic)<br>rare aplastic anemia |
| clonazepam | Broad spectrum, appears effective for myoclonus<br>Useful for anxiety<br>Can be used as abortive/ rescue therapy | Tachyphylaxis<br>Physical addiction and dependence |
| ethosuximide | Oral solution available | Narrow spectrum, only for absence seizures<br>Potential to worsen irritability |
| felbamate | Oral solution available | Serious potential side-effects, including liver failure and aplastic anemia |
| gabapentin | no drug interactions<br>rapid titration<br>useful in neuropathic pain and spasticity | TID/QID dosing<br>dose-dependent absorption |
| lacosamide | No drug interactions | sedation |
| lamotrigine | broad spectrum<br>few drug interactions<br>QD/BID dosing<br>Useful in bipolar disease | hypersensitivity<br>slow titration<br>levels affected by OC |
| levetiracetam | no drug interactions<br>rapid titration<br>BID dosing, XR provides QD option | Possible neurobehavioral side-effects |
| oxcarbazepine | few drug interactions<br>rapid titration | interferes with OC<br>hypersensitivity<br>hyponatremia |

| Drug | Advantages | Disadvantages |
|---|---|---|
| phenobarbital | Inexpensive<br>QD dosing<br>IV available | sedation<br>withdrawal<br>drug interactions (incl. OC)<br>possible bone density loss |
| phenytoin | Inexpensive<br>QD dosing<br>IV available<br>IM available as fosphenytoin | complicated pharmacokinetics<br>drug interactions (incl. OC)<br>highly protein bound<br>hypersensitivity<br>bone density loss<br>sedation<br>cosmetic effects |
| pregabalin | No drug interactions<br>Rapid titration<br>useful in neuropathic pain and spasticity<br>some anxiolytic effects | weight gain |
| rufinamide | Specifically tested in LGS | GI side-effects |
| tiagabine | few drug interactions | highly protein bound<br>slow titration<br>cognitive, GI effects |
| topiramate | broad spectrum<br>few drug interactions<br>BID dosing<br>Useful in migraine<br>Potential for weight loss | slow titration<br>cognitive effects<br>interferes with OC<br>potential for weight loss<br>renal stones (rare) |
| vigabatrin | proven efficacy in infantile spasms | Risk for loss of visual field - mandatory in depth ophthalmological assessments<br>Potential for psychiatric side-effects<br>Weight gain |

| Drug | Advantages | Disadvantages |
|---|---|---|
| valproic acid and derivatives | broad spectrum<br>useful in migraine, bipolar disease<br>IV, sprinkles and QD forms available | drug interactions<br>high protein binding<br>dose-dependent hematological toxicity (including thrombocytopenia and acquired von Willebrand disease)<br>tremor, parkinsonism<br>weight gain<br>teratogenic and in utero neurodevelopmental risks<br>rare sedation<br>hepatic toxicity esp. in pediatrics |
| zonisamide | broad spectrum<br>few drug interactions<br>potential for weight loss<br>mildantiparkinsonian agent<br>may provide headache prophylaxis<br>QD dosing | Hypersensitivity<br>Potential for weight loss<br>Possible mood worsening<br>rare renal stones |

QD: once daily. BID: twice daily. TID: three times daily. QID: four times daily. IV: intravenous. OC: oral contraceptives.

# Index

Note: Page numbers followed by '*f*' and '*t*' denote figures and tables, respectively.

CPSIA information can be obtained at www.ICGtesting.com
Printed in the USA
BVOW02s1357171214
379775BV00005B/23/P

**What Do I Do Now?** Patients with seizures and epilepsy pose many clinical challenges. Even experienced clinicians occasionally arrive at the point where diagnostic, work-up, treatment, or prognostic thinking becomes blocked.

*Epilepsy* is the fifth volume in the "What Do I Do Now?" series and provides the clinician with the necessary tools to evaluate and treat an epilepsy patient. Applying a case-based approach of curbside consultation, the authors present 31 actual cases, providing key points to remember, recommendations for further reading at the end of each case, and EEGs and imaging where applicable. Concise and readable, *Epilepsy* is the perfect quick-reference guide for anyone working with epilepsy or seizure patients.

**Key Features**

- Provides a fresh, practical, case-based approach
- Highlights the most important points of seizure and epilepsy patient management
- Addresses clinical dilemmas in a reader-friendly manner
- Includes information on differential diagnosis, anticonvulsants and alternative therapies, and surgical evaluation
- Written by epilepsy specialists

**Praise for *Epilepsy***

"This book will be welcomed by any clinician who sees epilepsy patients in their practice. The organization by commonly presenting problems makes the book easy to access, and easy to use. Once each chapter is accessed through the initial patient's vignette, clinicians will find comprehensive and useful content, relating to the topic as indicated by the chapter titles. Also extremely useful are MRI and EEG clips that clearly illustrate each case. Diagnostic and therapeutic issues are each addressed with equal clarity. The inclusion of chapters related to epilepsy co-morbidities highlights their importance when caring for epilepsy patients. Students, house staff, general neurologists, and epilepsy specialists will all find important and useful tips in this book."

—Jacqueline A. French, MD, NYU Comprehensive Epilepsy Center, New York, NY

"Drs. Bazil, Chong, and Friedman have delivered a practical and accessible guide to the clinical care of patients with epilepsy. The book answers the most relevant questions with case histories and examples that both illustrate and educate. It has remarkably valuable information for all physicians caring for epilepsy patients. [This book is] filled with useful maxims and answers to the questions we often ask when sitting across from a patient, but are rarely addressed by standard texts."

—Orrin Devinsky, MD, Director, NYU Comprehensive Epilepsy Center and Professor of Neurology, Neurosurgery, and Psychiatry, NYU Langone School of Medicine, New York, NY

*Cover photograph* Bland Images / Alamy

*Cover design* Peter Grant

OXFORD
UNIVERSITY PRESS

www.oup.com

ISBN 978-0-19-974350-6
90000
9 780199 743506