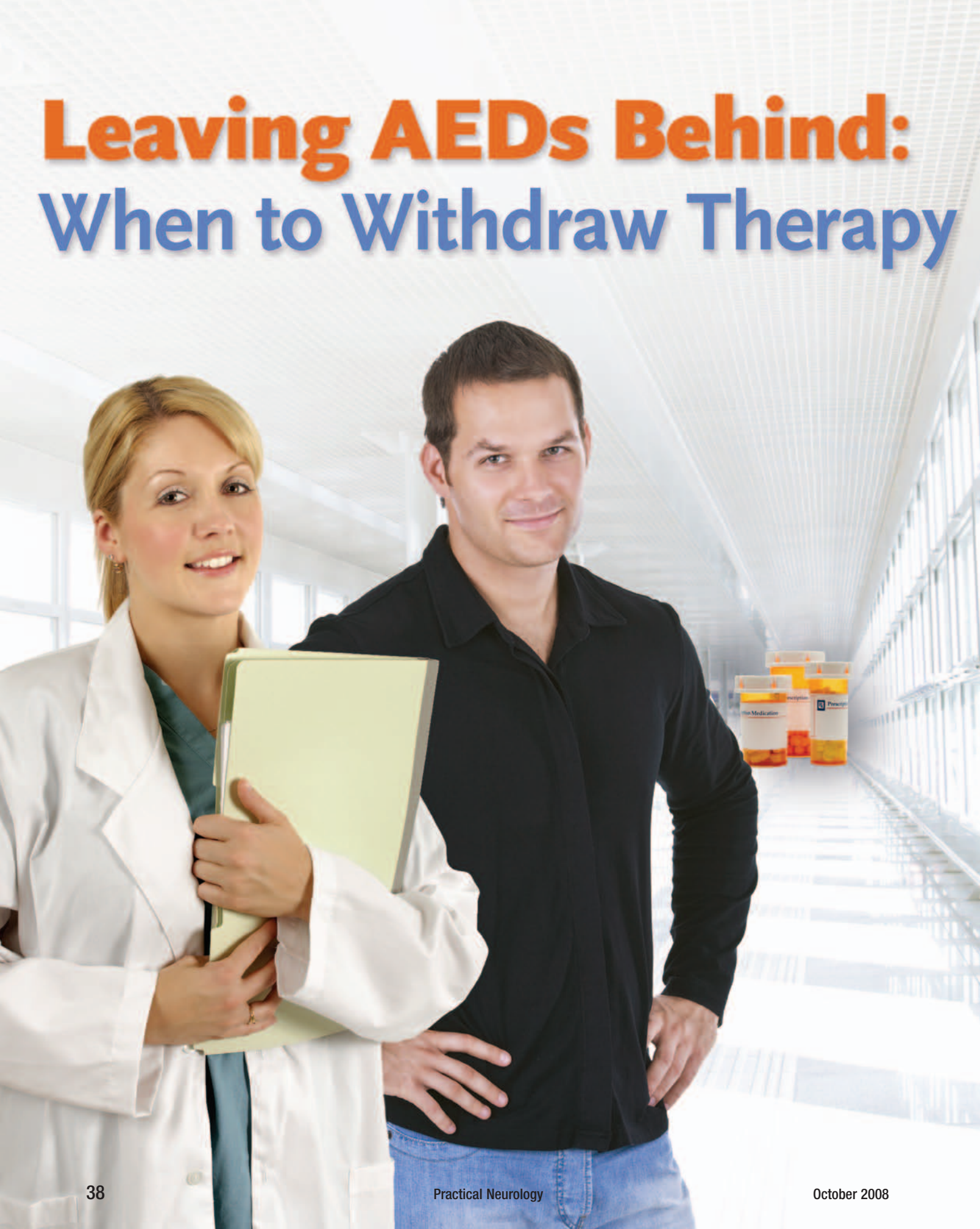
Leaving AEDs Behind: When to Withdraw Therapy



in Seizure-free Patients

A specialist answers the common question, "My patient is seizure-free—now what do I do?"

By Carl W. Bazil, MD, PhD

For patients with epilepsy and the neurologists who treat them, the primary goal usually is to attain complete control of seizures—at least of debilitating seizures. In some syndromes, primarily childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy)—assuming correct diagnosis—patients will inevitably become seizure-free and it may make sense to avoid anticonvulsant treatment even if some nonproblematic seizures occur. For those patients who start therapy, it is appropriate to withdraw AEDs once the age of high risk passes (usually before the patient begins to drive). By contrast, in some other syndromes, such as juvenile myoclonic epilepsy, seizure susceptibility is felt to be a lifelong condition, and medication withdrawal is not usually recommended.

The majority of patients, however, will require medication to achieve control of seizures but may be candidates for medication withdrawal once seizure-free. In fact, nearly two-thirds of patients with epilepsy become seizure-free with the first or second anticonvulsant (AED) administered.[1] In any medical condition, limiting the duration of drug exposure decreases the patient's risks of adverse events and long-term health problems, therefore discontinuation of AED therapy in a seizure-free patient is often desirable. Yet the desire to withdraw therapy may be tempered by reluctance to modify the AED regimen and potentially experience seizure recurrence. The following is a discussion of AED withdrawal based on available evidence. Additionally, for those cases where complete AED withdrawal does not seem to be indicated, important considerations related to treatment modification and long-term management (such as switching AEDs, monitoring AED levels, laboratory testing, and adverse effects) are addressed.

Withdrawal of AEDs

Several considerations impact the decision to withdraw AEDs in an epilepsy patient who is seizure-free. Primary among these is risk of recurrence. Most studies of AED withdrawal have involved patients who have been seizure-free for at least two years. A review of 28 studies including over 4,000 patients with all types of seizures suggested that 35-57 percent of adults continued to be seizure-free, while 61-91 percent of children were seizure-free.[2] A meta-analysis of 25 studies showed the overall risk of recurrence to be 24-34 percent at two years.[3] Patients with remote symptomatic epilepsy and patients with abnormal EEG were more likely to relapse. A

prospective study of 84 patients with partial seizures who were seizure-free for over two years showed that relapse following AED withdrawal was more common in patients with hippocampal atrophy or increased signal.[4] Most available information therefore suggests that the risk of recurrence with AED withdrawal, after two years of seizure freedom, is roughly 30 percent.

There are few randomized studies of AED withdrawal, but one study of 1,013 individuals included all patients with at least two seizures, except those with a progressive neurological disorder.[5] The average age of onset was about 13 years, and average duration of epilepsy was about five years. About half had tonic clonic seizures that were either generalized or unclassifiable; the majority of the remainder had partial seizures with or without secondary generalization. Within two years of randomization, 78 percent of patients randomized to no drug withdrawal remained seizure-free, while 59 percent randomized to drug withdrawal remained seizure-free. Nearly half of seizure recurrences in the drug withdrawal group occurred during the withdrawal period. Duration of seizure freedom prior to drug withdrawal was inversely related to risk of recurrence: the relative risk was 0.67 after three to five years and 0.27 after more than 10 years seizure-free. The study also showed higher rates of recurrence in patients with generalized tonic clonic seizures and generalized spike-wave discharges on EEG but not with focal spikes or nonspecific EEG abnormalities. A subsequent analysis of withdrawal from monotherapy showed a decrease in recurrence for patients remaining on phenytoin, valproate, or phenobarbital/primidone but puzzlingly not for carbamazepine.[6]

These numbers suggest that patients who are seizure-free for two or more years on medication have a reasonably good chance of remaining seizure-free after medication withdrawal. However, it is impossible to have zero risk of relapse. The physician and patient must base the decision to withdraw medication on the patient's individual circumstances and aversion to risk. The randomized study mentioned above provides a good perspective: after four years, there is no appreciable difference in seizure recurrence whether the patient was randomized to drug withdrawal or not.[5]

Discontinuation of AEDs always carries some risk of recurrence, particularly during the period of withdrawal. A patient may accept this risk for various reasons. Consider, for example, a woman attempting to conceive, in which case medication withdrawal should be attempted before pregnancy to minimize risk of seizures during pregnancy.

Withdrawal to monotherapy in patients seizure-free on two or more medications may be an easier decision. While no published trials assess the rate of recurrence in patients controlled on two or more drugs when an agent is withdrawn, the rates are almost certainly lower than those with complete withdrawal of anticonvulsant treatment.

Changing AED

Questions also arise when a well-controlled patient who is not a candidate for AED withdrawal requires a change in medication. For example, a coexisting condition, such as migraine, bipolar disease or neuropathic pain, may require a medication that is also an effective AED. Should the patient continue on both the original and the new AED? Other reasons to consider AED change may include difficult drug interactions, long-term adverse effects, and therapy costs.

The main concern when switching AEDs is risk of recurrent seizures. No published studies directly address this risk. However, many direct comparisons of drugs for partial[7-10] and generalized[11] seizures suggest that the overall effectiveness of drugs is not appreciably different. Experience further suggests that a patient well controlled on one drug is likely to be controlled on another (assuming an adequate dose is tolerated), however a small possibility of seizure recurrence remains.

Coexisting Conditions

Patients with epilepsy have higher rates of migraine, depression, anxiety, and sleep disorders compared to the general population. The AED chosen to manage seizures may offer efficacy for these.

Migraine prophylaxis: Valproate, topiramate are FDA approved, and other agents including zonisamide are possibly effective.[12]

Depression: No AED is widely used for the treatment of depression; several are useful in the treatment of bipolar disease (carbamazepine, lamotrigine, valproate, and possibly gabapentin and oxcarbazepine). Lamotrigine seems to be particularly useful for the treatment of bipolar depression.[13]

Anxiety: Pregabalin has been shown to be effective for the treatment of generalized anxiety disorder[14] and, while not approved by the FDA, is approved in the European Union for this indication.

Restless legs syndrome: RLS may respond to AEDs (gabapentin, and possibly pregabalin, carbamazepine, and valproate).[15,16]

Neuropathic pain: Not necessarily more common in patients with epilepsy, neuropathic pain is a common condition, and patients may coincidentally require treatment for it with gabapentin or pregabalin,[17] both FDA-approved for this indication.

Recurrence is probably more likely if control was difficult to obtain initially (if the patient had failed other drugs).

Changing AED could result in adverse effects not seen with the current AED. Differences in adverse effects are more difficult to quantify; available comparisons suggest that overall tolerability is similar for many agents. Yet there are some specific side effects more commonly associated with particular agents. These require careful consideration for each individual patient. A patient already overweight may not be a good candidate for an AED associated with weight gain, or a patient already at risk for psychiatric problems is a poor candidate for an agent that may exacerbate these.

A patient who requires an AED for one of the conditions described above may be able to maintain seizure control with the add-on AED alone and may be able to withdraw the initial agent. The decision to withdraw the first drug is always individualized and should be attempted only when it is clear the patient tolerates the second drug at a level reasonable for seizure control. It is prudent to recommend that the patient avoid driving at least during the withdrawal of the original drug.

AED causing or exacerbating conditions. By contrast, the current AED may either cause or exacerbate a comorbid condition. Examples include cognitive or psychiatric problems (topiramate, levetiracetam) or rash (which can occur with any agent, but is very uncommon with valproate, gabapentin, levetiracetam, or pregabalin).[18] Benzodiazepines and barbiturates can exacerbate obstructive sleep apnea. It may be difficult or impossible to know whether the AED plays a role in the other condition. Switching AED, however, presents a small but real risk of recurrent seizures or additional adverse effects. Therefore, a switch requires careful consideration. In some instances, change in drug may be the only way to know if the original AED played a role in the comorbid condition.

Drug-drug interactions. Many AEDs, particularly those that affect hepatic metabolism, have a high potential for drug-drug interactions. Risks increase when more than one AED is taken simultaneously. Interactions with new or existing drugs prescribed for reasons other than epilepsy also is a concern. In general, many interactions can be anticipated and managed by monitoring blood levels (see below). Some interactions, such as that between warfarin and phenytoin, may be sufficiently concerning to warrant a therapeutic switch.

To manage complicated medical conditions some patients require multiple other drugs that AEDs may affect. Complicating matters, these non-AED drugs may be changed frequently or the doses altered, increasing the risk of unrecognized interactions and requiring a high degree of vigilance. At other times, the AED may not cause enzyme induction but may be very sensitive to other agents (such as is the case with lamotrigine).[19] One concerning example is the treatment of HIV, where many of the common agents are also hepatically metabolized; concurrent administration of enzyme- inducing drugs can result in failure of antiretroviral therapy.[20] A more common consideration is for a woman who desires to use an oral contraceptive agent; AEDs that cause enzyme induction can lead to contraceptive failure. In some patients, then, it may make sense to consider transitioning to a drug that has few or no interactions so there is less concern regarding drug levels and decreased need for close monitoring.

Table 1 provides a summary of drug interaction potential.

Long-term adverse effects. While most anticonvulsants are thought to be quite safe for long-term use, a relatively recent concern is exacerbation of osteoporosis, particularly in older women. Bone effects may be more common with drugs that cause enzyme induction, particularly phenytoin.[21,22] One study showed increased bone turnover with phenytoin and lower calcium with phenytoin, carbamazepine, and valproate compared to lamotrigine.[21] In patients who require long-term AED therapy and who have been diagnosed with osteopenia or osteroporosis, it may be difficult or impossible to know whether the AED contributes to the problem. However, if a patient has been well controlled on phenytoin for a long period of time, a change to a drug thought not to contribute to osteoporosis poses little risk of worsening seizures.

A more unusual case is a patient who has developed hepatic failure. Though the incidence of hepatic failure caused by AEDs in adults is probably very low even with valproate, it may occasionally make sense to change such patients to a drug that is

Lifestyle Issues

Patients who are seizure-free must care for their general health, perhaps more than other people. Treating physicians should be vigilant for signs of coexistent conditions discussed in the sidebar on the previous page, as all can worsen quality of life even in the absence of seizures. Encourage patients to have regular checkups by a primary care physician; many believe seeing a neurologist once or twice a year is sufficient. Regular exercise is important for general health, stress reduction, good sleep hygiene, and to improve quality of life in epilepsy (shown in a randomized clinical trial).[36] Relaxation techniques, such as yoga or meditation, can help for the same reasons.

Finally, many patients have questions about diet, especially for weight loss. While no weight loss program is ideal, a modified Atkins diet has been shown to improve epilepsy,[37] and even in seizure-free patients may further protect against seizures if weight reduction is desired.

Table 1. Drug Interaction Potential

Level of AED enzyme induction	AED affected by enzyme inducers	AEDs	Potential for AED effects on other drugs	Potential for other drug effects on AEDs
High	Yes	Phenobarbital Phenytoin Carbamazepine	High	High
Medium	Yes	Oxcarbazepine Topiramate	Medium	High
Low or none	Yes	Lamotrigine Zonisamide	Minimal	High
	No	Gabapentin Levetiracetam Pregabalin	Minimal	Minimal
Enzyme inhibition	Yes	Valproate	Medium	High

thought to have no potential for such problems and perhaps one that is not metabolized in the liver, such as gabapentin or pregabalin. In a patient taking felbamate, deterioration of either hepatic function or blood counts warrants consideration for medication change if at all possible.

Cost. While it is rarely advisable from a medical standpoint to change a patient who is doing well on a particular AED to an alternative solely for reasons of cost, practically this question arises frequently. The patient may inquire because of a high copay relative to other (usually older) AEDs, or there may be pressure directly from insurers to change a patient to a lower cost AED or to a generic formulation. Of the newer agents, generic preparations are available for gabapentin, zonisamide, oxcarbazepine, and lamotrigine. Switching to a generic equivalent may have implications other than cost, particularly in epilepsy. FDA guidelines mandate generic preparations must fall between 80 and 125 percent of peak levels and area under the curve (AUC) compared to brand drugs. The epilepsy community has argued that this may not be sufficient for patients with epilepsy, as many of these agents have relatively narrow therapeutic ranges, and variability allowed by the FDA may be amplified when multiple generic preparations are available, as each is compared to the branded drug but not to each other. Some agents have over 20 generic manufacturers licensed, each potentially slightly different. The clinical impact of changing an epilepsy patient from brand to generic agents or between generic agents has not been systematically studied. However, some recent studies suggest increased switchback rates and health care utilization, suggesting complications with the change to generics.[38,39]

The American Academy of Neurology has published a position statement regarding use of generic agents in epilepsy.[23] When changing to generic preparations in a patient who has been well controlled, it may be prudent to monitor drug levels to ensure equivalent absorption. Both the patient and the prescribing physician should be aware of the change. Finally, patients and prescribing physicians should be alert to changes to generics from different manufacturers. Whenever possible, maintain therapy on the same generic preparation. Report suspected problems to the FDA's MedWatch program at http://www.fda.gov/medwatch/.

Monitoring of Anticonvulsant levels, Liver function, Electrolytes

In general, "routine" collection of serum anticonvulsant levels is not necessary or recommended.[28] In clinical practice it is generally helpful to obtain at least a baseline, steady-state level of the AED. This serves several functions. First, it documents patient compliance.

Second, it will demonstrate that the patient is in the general range thought to be useful for seizure control. Some patients may be well controlled with levels lower than the usual "therapeutic window," but a slight dose increase usually poses little risk but can provide both the patient and physician reassurance that adequate seizure control is present. By contrast, patients in the "toxic" range may be able to tolerate high levels, but the dose could probably be lowered slightly.

Once a baseline level is obtained, repeat levels prove helpful in various scenarios. If a patient develops breakthrough seizures, labs will document whether a lower level was present due to noncompliance or other reasons. If potentially toxic symptoms develop but the level is unchanged, it is less likely

that the AED produced the symptom. If other drugs with potential interactions are added or removed, another level will help to determine necessary changes in the AED dose. Older agents, including carbamazepine and phenytoin, have relatively narrow therapeutic windows and are susceptible to drug-drug interactions. Of the newer agents, lamotrigine in particular is very sensitive to changes in metabolism due to other drugs or pregnancy, and toxicity is highly correlated with serum levels, rarely occurring at less than 10mg/ml.[29]

In the absence of clinical evidence of very rare adverse effects, following liver function, electrolytes, and blood counts is not generally necessary. Obtaining these levels at baseline (when a steady state has been achieved) helps to avoid concerns at a later date. Note that frequent testing is recommended for felbamate, at least for the first year of treatment, although whether this helps avoid serious toxicity is controversial.[30]

Summary

The primary goal in treating epilepsy patients is generally elimination of seizures—at least debilitating seizures. Fortunately, this is possible in the majority of patients. Once patients are seizure-free, care does not end, but additional considerations may arise. Elimination or decrease in AED, or change to an alternative agent, may be necessary or advisable for a variety of reasons.

Treatment—or withdrawal of treatment—decisions are always individual, and require careful assessment of risks versus benefits. Monitoring of anticonvulsant levels, hepatic function, electrolytes, and blood counts may be useful in specific instances. Patients should also be counseled with regard to their general health and common coexisting conditions, particularly depression, anxiety, and sleep disorders. **PN**

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