ASSESSING AND PREVENTING THE METABOLIC SIDE EFFECTS OF ANTIEPILEPTIC DRUGS

Barry E. Gidal, PharmD, BCPS, RPh*

**ABSTRACT**

The introduction of the newer antiepileptic drugs (AEDs) has increased the number of effective treatment options for the management of seizures. Because of the similar efficacies of the older and newer AEDs, selecting an appropriate AED often involves evaluating side effects that are commonly associated with each medication and their potential impact on individual patients. Metabolic side effects, such as weight gain, weight loss, hyperlipidemia, and poor bone health, may cause life-threatening conditions in certain patients. Routine monitoring of a patient's weight, lipid parameters, and bone health increases the likelihood of early detection of any abnormalities that may be indicative of more serious health problems, such as polycystic ovaries, cardiovascular disease, and osteoporosis. Although data regarding metabolic side effects of the newer AEDs are limited, studies to date suggest that the newer AEDs may cause fewer metabolic side effects compared to older AEDs. Selection of an AED may become less complex as we learn more about the newer AEDs and their potential benefits.


DURING THE PAST DECADE, several new antiepileptic medications (AEDs) have entered clinical practice. The results of a number of clinical trials have shown that these new agents are at least as effective for the management of seizures as the older AEDs. Because of the similarities in effectiveness between the traditional and the newer AEDs, treatment decisions for individual patients are often made on the basis of the expected side effects associated with the different available medications. Selecting an appropriate therapy can be complicated because of the growing number of available AEDs and because patients differ in the types of side effects they experience and in their ability or willingness to tolerate specific side effects. For example, a medication that causes weight gain may not be the best choice for patients who are obese or adolescent patients who are concerned about their appearance. Adverse reactions of AED treatment can vary from relatively mild effects that are primarily cosmetic in nature to severe or even potentially life-threatening conditions. Cosmetic side effects, such as acne or hair loss, may resolve over time without any changes to the treatment plan. More serious metabolic side effects can lead to obesity, cardiovascular disease, and osteoporosis and may require changes to the treatment regimen or to the patient’s lifestyle. This article reviews the metabolic effects of AEDs and some strategies to help prevent these side effects or their progression to more serious life-threatening conditions.

**CHANGES IN BODY WEIGHT**

**ANTIEPILEPTIC DRUGS AND WEIGHT GAIN**

Weight gain is a side effect of several AEDs, includ-
ing valproate, gabapentin, and carbamazepine.\(^1\) In addition to causing health problems, weight gain also can affect the patient’s body image and self-esteem. A patient who takes an AED and gains weight may decide to stop taking the medication, which increases the risk of additional seizures, without consulting a healthcare provider.

The effects of valproate on body weight have been extensively studied. Results of clinical studies and experience in clinical practice commonly associate valproate with weight gain, which can be mild, moderate, or excessive.\(^1\) Women taking valproate may have a higher risk of an endocrine disorder known as polycystic ovary syndrome, which is associated with an increased likelihood of obesity and lipid abnormalities.\(^2\) Some studies show that the weight gain associated with valproate may be caused by its ability to inhibit lipid oxidation, which results in a decreased resting energy expenditure.\(^3\) Patients treated with valproate can have resting energy expenditures that are significantly lower than predicted expenditures.\(^3\)

Weight gain with valproate often occurs within the first 3 months of treatment and peaks by the sixth month.\(^1\) Studies have shown that valproate is more likely to cause weight gain and elevated insulin (and insulin resistance) and testosterone concentrations than any of the other AEDs.\(^4\) Weight gain may be reversible when valproate is replaced with another medication. A study conducted by Isojarvi et al evaluated the risks related to valproate-induced hyperinsulinemia and their reversibility after discontinuing valproate.\(^5\) Endocrine and lipid parameters were measured in 16 women with valproate-related polycystic ovaries or hyperandrogenism; these patients had centripetal obesity with associated hyperinsulinemia and unfavorable serum lipid profiles. Patients were observed for 12 months after lamotrigine was substituted for valproate. After 1 year of treatment with lamotrigine, body mass index, fasting serum insulin, and testosterone concentrations decreased.\(^1\) This study has been controversial.

Obesity may lead to the development of insulin resistance, which may give rise to hyperinsulinemia and poor lipid profiles. Elevated insulin levels may stimulate the ovaries, causing polycystic ovaries and hyperandrogenism.\(^6\) Because of the limited amount of available data, there is some controversy regarding the association between valproate and polycystic ovaries, but the available evidence cannot be entirely dismissed.\(^7\) Studies have shown that up to 60% of women with epilepsy treated with valproate have polycystic-appearing ovaries compared with 25% to 30% of women who receive treatment with other AEDs.\(^8\) The increased prevalence of polycystic ovaries in women taking valproate may be because of the higher rate of obesity among these women.\(^7\) Some studies have found that switching from valproate to another AED may reduce the number of polycystic-appearing ovaries.\(^4\)

Studies that compared carbamazepine with valproate have shown that carbamazepine is less frequently associated with weight gain in clinical practice.\(^1\) Gabapentin also has been associated with weight gain, but it has not been extensively examined in clinical trials in comparison to placebo or other AEDs.\(^1\) The newer agents levetiracetam and lamotrigine appear to be weight neutral.\(^1,10\)

**Screening for Obesity**

Measures of body weight are noninvasive and provide useful information regarding short-term and long-term changes in body fat. Regular measurement can help guide weight management goals and monitor outcomes of weight-loss therapy.\(^11\) Body mass index (BMI), the standard measurement for determining weight status, is calculated by dividing the patient’s weight in kilograms (kg) by the square of the patient’s height in meters (m\(^2\)). Weight classifications by BMI are shown in Table 1.

### Table 1. Weight Classification by Body Mass Index

<table>
<thead>
<tr>
<th>BMI (kg/m(^2))</th>
<th>Weight Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0–39.9</td>
<td>Obesity</td>
</tr>
<tr>
<td>≥40</td>
<td>Extreme obesity</td>
</tr>
</tbody>
</table>

BMI = body mass index.


**Strategies for Promoting Weight Management**

Decreasing caloric intake, increasing physical activity, and making other lifestyle changes can help to pre-
vent weight gain or to stop additional weight gain. Patients should decrease their intake of saturated fat and total fat. A dietician can assess food behavior and provide treatment recommendations, nutrition education, and guidance. Another important component of weight management is exercise, which should be approved by the patient’s physician. Physical activity should be initiated slowly in most obese patients and should increase gradually in intensity.

Patients who are trying to lose weight must understand the importance of realistic goals and expectations. Long-term goals should be emphasized, thus patients do not become discouraged if they experience minor setbacks. Behavior modification techniques may help patients adhere to their diet and exercise plan. Some of these techniques include self-monitoring of eating habits and physical activity, stress management, problem solving, and social support. Measurements of progress (eg, body weight, laboratory values, and blood pressure) should be documented and reviewed with the patient on a regular basis. These measures can be used to evaluate the effectiveness of the management program and can also encourage positive behavior change in patients. Because of the potential for adverse effects and drug interactions, patients should be advised not to self-treat with various nonprescription herbal or dietary weight-loss supplements or drugs without seeking the counsel of their healthcare provider.

**Antiepileptic Drugs and Weight Loss**

Weight loss has been associated with the use of topiramate, felbamate, and zonisamide. In some patients, weight loss induced by an AED may worsen a pre-existing nutritional deficiency. Patients with neurodevelopmental disorders who are at risk for undernutrition because of behavioral and other problems are not good candidates for treatment with these AEDs. However, weight loss may be a desirable side effect for patients who are overweight or obese.

Weight loss is one of the most common adverse effects reported in clinical trials of topiramate for the treatment of epilepsy. Studies evaluating the use of topiramate to treat headache or neuropathic pain have also reported weight loss. A prospective study published in 2003 evaluated the predictors of weight loss associated with the use of topiramate. Topiramate was added to an existing anticonvulsant therapy in 39 adults with partial seizures. Baseline weight was reduced in 82% of the patients at 3 months after treatment and in 86% of the patients after 1 year of treatment. The average weight lost was 3.0 kg (3.9% of baseline weight) at 3 months and 5.9 kg (7.3% of baseline) at 1 year. Obese patients (those patients with BMI ≥30 kg/m²) lost an average of 4.2 kg (4.3%) at 3 months and 10.9 kg (11%) at 1 year. The amount of weight lost at the end of 1 year was significantly correlated with the baseline BMI (P = .0007); patients with a higher baseline BMI lost more weight compared to patients with a lower baseline BMI. Another study that enrolled 51 patients found that treatment with topiramate for 1 year (median dose 200 mg/d) significantly reduced body weight and food intake in patients with epilepsy (P < .01). Patients who were obese (BMI >30 kg/m²) experienced the greatest weight loss, an average of 11% of their body weight. In addition, these patients’ blood glucose levels decreased by 16% and insulin levels by 24%. These parameters remained unchanged in nonobese patients who received topiramate.

Weight loss associated with felbamate ranges from mild to severe. An evaluation of 65 patients who received felbamate as adjunctive therapy in clinical trials found that 75% of the patients lost weight during the trials, with an average weight loss of 4.11% of body weight in patients older than 15 years. Approximately 33% of the patients lost more than 4 kg, and another 11% of the patients lost more than 8 kg.

In a randomized, double-blind, placebo-controlled trial of zonisamide (n = 203), weight loss was reported more often in patients who received zonisamide (400 mg/d) than in those patients who received a placebo. Weight loss of more than 2.3 kg occurred in 21.6% of the patients who received zonisamide compared to 10.4% of the patients who received a placebo (P <.05). Anorexia was also more common in patients who received zonisamide.

**Hyperlipidemia**

**Effects of Antiepileptic Drugs on Lipids**

High levels of total cholesterol and low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol have been associated with the development of coronary artery disease in men and women. The data regarding the effects of AEDs on lipid profile are limited, especially for the newer AEDs.
A study published in 1993 evaluated the effects of valproic acid, carbamazepine, and phenobarbital on serum lipids. Compared to controls, total cholesterol levels were significantly lower ($P \leq 0.001$) in patients who received valproic acid and significantly higher ($0.05 \leq P > 0.01$) in patients who received phenobarbital. Patients treated with carbamazepine had significantly higher ($P \leq 0.001$) HDL levels, and patients who were treated with valproic acid had significantly lower ($P \leq 0.001$) LDL cholesterol levels. There were no differences in triglycerides among the 3 groups and the control group.

A recently published study evaluated the effects of chronic treatment with carbamazepine, phenobarbital, or valproic acid on blood lipids. Lipid levels were measured in a total of 101 patients with epilepsy (48 were taking valproic acid, 34 carbamazepine, and 19 phenobarbital) and 75 age-matched and sex-matched control subjects. Compared to controls, the total cholesterol level was significantly higher ($P < 0.001$) in patients who were taking carbamazepine and significantly lower ($P < 0.05$) in patients taking valproate. Patients who received carbamazepine also had significantly higher HDL levels ($P < 0.001$). The carbamazepine and phenytoin groups had significantly higher LDL cholesterol levels ($P < 0.05$). Valproate lowered triglyceride levels, and carbamazepine, phenytoin, and phenobarbital increased triglyceride levels. However, these changes were not significant.

The AEDs may influence blood lipids because of their effects on the cytochrome P450 (CYP450) enzyme system, which is found mainly in the liver and is important in the metabolism of many drugs. The AEDs also influence total cholesterol, HDL, LDL, and triglyceride levels. As suggested by some studies, AEDs that induce the activity of CYP450 enzymes are most likely to affect blood lipid levels. Table 2 lists drugs that induce CYP450 enzymes and those drugs that inhibit or have no effect on CYP450. Topiramate, which is a relatively weak inducer of CYP450, was shown in one study to reduce fasting triglyceride levels significantly in obese patients but not in nonobese patients.

Serum lipid patterns may differ between men and women who receive long-term treatment with AEDs. A study that evaluated the effects of long-term anticonvulsant treatment on serum lipid patterns enrolled 97 patients undergoing long-term (more than 6 months) anticonvulsant treatment. Twenty-four patients were receiving phenytoin monotherapy, 26 were receiving carbamazepine monotherapy, 11 were receiving valproate monotherapy, 2 were receiving barbiturate monotherapy, and 34 were receiving polytherapy (13 of these patients were receiving phenytoin plus carbamazepine, which was the most common combination). All of the patients in the study had increased total cholesterol and decreased HDL levels compared with population means. These differences were significant in men, but only the differences in HDL reached the level of statistical significance in women.

**Monitoring Lipids**

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recommends obtaining a patient’s complete lipoprotein profile rather than just screening for total cholesterol and HDL levels. The complete profile includes total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels. Optimal levels of lipids and lipoproteins for women are shown in Table 3. Patients whose LDL and triglyceride levels are above the optimal level and patients whose HDL levels are below the optimal level may benefit from lifestyle modifications and pharmacotherapy.

**Strategies for Maintaining a Healthy Lipid Profile**

The NCEP recommends making therapeutic

---

### Table 2. Effects of Antiepileptic Drugs on CYP450 Liver Enzymes

<table>
<thead>
<tr>
<th>Induce/Inhibit CYP450 Enzymes</th>
<th>No Effect on CYP450 Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Oxcarbazepine*,†</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Primidone</td>
<td></td>
</tr>
<tr>
<td>Topiramate*,†</td>
<td></td>
</tr>
<tr>
<td>Valproate‡</td>
<td></td>
</tr>
</tbody>
</table>

†Selective inhibitor of CYP 2C19 enzyme.
‡Inhibitor of certain CYP and UDP-glucuronyl transferase isozymes.
Data from Pack and Morrell; Morrell.®
lifestyle changes to reduce risk for coronary heart disease. Patients should reduce their intake of saturated fats to less than 7% of their total daily calories and cholesterol to less than 200 mg a day. Patients who may benefit from medical nutrition therapy should be referred to a dietician. Patients also should be encouraged to increase physical activity.

Some patients who take AEDs may need to use cholesterol-lowering drugs in addition to making therapeutic lifestyle changes. Drug-to-drug interactions may develop when AEDs that inhibit CYP450 are used in combination with statins (Table 2).

**Adding Antiepileptic Drugs to Lipid-Lowering Drugs**

Data regarding the concomitant use of AEDs and lipid-lowering drugs are limited. Ucar et al. examined the effects of carbamazepine on the pharmacokinetics of simvastatin in a randomized 2-phase crossover trial with a 2-week washout period. The study enrolled 12 healthy volunteers who received no drug or received carbamazepine for 14 days. Volunteers who were randomly assigned to receive carbamazepine were administered 200 mg once a day for the first 2 days and 300 mg twice a day from days 3 to 14. On day 15, all subjects received 80 mg simvastatin. Serum concentrations of simvastatin and its active metabolite simvastatin acid were measured for up to 24 hours. The area under the concentration time curve of simvastatin and simvastatin acid were significantly lower (75% and 82%, respectively) in patients who received carbamazepine compared to those patients who received placebo (P < .001). In addition, carbamazepine significantly shortened the half-life of simvastatin acid (P < .01). If simvastatin is to be used in patients receiving carbamazepine, the dose of simvastatin may need to be considerably increased.

Phenytoin also may affect the cholesterol-lowering ability of some statins. A case report of a 50-year-old woman who was taking simvastatin and valproate described the effects of phenytoin on lipid management. When the patient’s AED was switched from valproate to phenytoin, her total cholesterol level increased. Her lipid-lowering therapy was then modified several times: simvastatin was replaced by fluvastatin, and eventually fluvastatin was replaced by atorvastatin. Despite these changes, the patient’s cholesterol level remained elevated. When phenytoin was discontinued, the patient’s total cholesterol level decreased. The authors concluded that phenytoin, a CYP450 inducer, may have reduced the efficacy of the statins by reducing them to their less active metabolites. Additional studies are necessary to evaluate the effects of other AEDs on lipid-lowering drugs.

**Osteoporosis**

**Which Antiepileptic Drugs Increase Risk?**

Several AEDs can affect bone health in children, adolescents, and adults. Women are especially vulnerable to these effects. The CYP450 enzyme-inducing AEDs phenytoin, phenobarbital, carbamazepine, and primidone have been associated with decreased bone density and with an increased risk for fractures. However, AED-induced bone loss appears to be driven by several different mechanisms (Table 4).

### Table 3. Optimal Levels of Lipids and Lipoproteins for Women

<table>
<thead>
<tr>
<th>Lipid/Lipoprotein</th>
<th>Optimal Levels for Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;50 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>Non-HDL-C (total cholesterol minus HDL-C)</td>
<td>&lt;130 mg/dL</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Data from Mosca et al.

### Table 4. Proposed Mechanisms of Bone Disease Associated with Antiepileptic Drugs

- Reduced levels of vitamin D caused by the induction of CYP450 enzymes
- Decreased calcium absorption
- Impaired response to parathyroid hormone
- Hyperparathyroidism
- Impaired bone formation
- Vitamin-K deficiency
- Calcitonin deficiency

Data from Pack et al.
Data regarding the effects of the newer AEDs on bone health are limited. Published studies have focused on the CYP450 enzyme-inducing AEDs that are most often associated with abnormalities in bone, presumably by induction of the metabolism of vitamin D. A study published in 2002 evaluated the effects of long-term AED therapy (≥6 months) on bone density in 71 ambulatory patients between the ages of 5 years and 64 years; 42 (22 women and 20 men) of these patients were older than 18 years. The enzyme-inducing AEDs in the study included phenytoin, phenobarbital, carbamazepine, and primidone. Agents that do not induce CYP450 enzymes included valproic acid, lamotrigine, clonazepam, gabapentin, and ethosuximide. Topiramate was included in the study and was classified as a noninducer. In adults who were using AEDs, bone mineral density (BMD) measurements at all skeletal sites were lower than BMD values in young adults and age-matched controls. Although the differences were not statistically significant, adults taking enzyme-inducing AEDs tended to have lower BMD values for the spine, total hip, femoral neck, trochanter, and total body compared to patients taking noninducing AEDs. There were no differences in BMD of the lumbar spine and total body among children who were taking enzyme-inducing AEDs and among those patients who were taking noninducing AEDs. This study also showed that patients taking a single AED tended to have higher vitamin-D levels, bone mineral content, and BMD of the lumbar spine and total body compared to patients taking multiple AEDs, although these differences were not statistically significant. Other studies have shown that AED polytherapy including an enzyme-inducing agent is associated with a higher risk of bone metabolism abnormalities than treatment with a single AED. No specific combination of AEDs has been shown to be more likely to cause bone disease. Therefore, the evidence to date would suggest that men and women receiving enzyme-inducing AEDs may be at increased risk for accelerated bone loss.

**Maintaining Bone Mass**

Patients on chronic AED therapy should undergo skeletal monitoring. Postmenopausal women and any women with prolonged AED use (>5 years) should have a BMD evaluation with dual-energy X-ray absorptiometry. Bone mass is inversely correlated with fracture risk. Decreased BMD increases the risk of fracture. A patient’s BMD is the best predictor of fracture risk. Men with epilepsy have a risk of osteoporosis and should also be monitored.

Vitamin-D supplementation is the only therapy that has been studied for the treatment of bone disease in patients taking AEDs. The recommended daily allowance of vitamin D is 400 IU to 800 IU. Some studies have shown that high-dose vitamin-D supplementation (400 IU/d–4000 IU/d) improves biochemical measures of bone mineral metabolism and BMD. Clinicians should be aware that large doses of vitamin D may be required to normalize serum concentrations of vitamin D. Other therapies that may improve bone health include calcium supplementation, hormone replacement therapy, calcitonin, and vitamin K supplementation. Although bisphosphonates, such as alendronate and risedronate, may prove to be effective treatments for patients with AED-associated bone loss, there are no placebo-controlled trials to provide evidence of efficacy or safety in this particular population. Patients may also benefit from weight-bearing exercise and should be advised to avoid risk factors, such as alcohol use and smoking, which are associated with bone disease.

**Fractures and Falls**

Patients with bone disease are at increased risk for sustaining fractures. More than 1 million fractures result from osteoporosis in the United States each year. The high prevalence of osteoporosis among older women and increased frailty associated with aging may explain why elderly women taking AEDs have an increased risk for falls and are more likely to sustain intracranial bleeding compared to younger people with seizures. Fractures can cause devastating consequences, including hospitalization, loss of independence, and even death. Ensrud et al noted that women receiving AEDs (primarily phenytoin, carbamazepine, phenobarbital, or primidone) had a 50% greater rate of bone loss per year compared to women not taking AEDs. The rate of bone loss was nearly twice as great in those women receiving phenytoin. In this study, women who were regular users of AEDs had an estimated 29% increase in hip fractures over 5 years. Therefore, it is important to identify patients with poor seizure control and patients who are at increased risk for sustaining fracture during a seizure. Not all fractures in patients with epilepsy are associated with seizures. In other words, a patient who is seizure-free may still be at increased risk for fracture.
Guidelines developed by the American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention recommend using a combination of interventions to help prevent falls. It is important to assess all of the factors that may put a patient at risk for falls. Assistive devices, such as walkers and canes, can be helpful for some patients. Modification or elimination of medications should be considered when patients are taking 4 or more medications or psychotropic medications, such as neuroleptics, benzodiazepines, and antidepressants. Participation in exercise programs with balance training also may reduce risk. Patients should be asked about their vision, which may affect the likelihood of falls and fractures.

CONCLUSIONS

Metabolic side effects are possible with any of the AEDs. Valproate is associated with greater weight gain compared to any of the other AEDs. Obesity can lead to many serious health problems, including elevated insulin levels, poor lipid profiles, and other endocrine disorders. Weight loss may occur in patients who receive topiramate, felbamate, or zonisamide. Although this may be a desirable side effect for patients who are overweight or obese, it may be problematic in patients with a pre-existing nutritional deficiency. Newer drugs, such as lamotrigine or levetiracetam, do not appear to adversely impact body weight. The use of CYP450 enzyme-inducing drugs, such as phenobarbital, phenytoin, and carbamazepine, have been associated with increased lipid levels. Data regarding the effects of newer AEDs on lipids are limited. The older CYP450 enzyme-inducing AEDs also have been associated with abnormalities in bone, which may eventually place patients at increased risk for fractures. Changes in body weight, lipid parameters, and bone health often occur over time and easily can be overlooked unless patients routinely are monitored for any changes. Early detection of any abnormalities can help to prevent more serious health problems, such as polycystic ovaries, cardiovascular disease, and osteoporosis.

REFERENCES


