

## Review of the Newer Antiepileptic Drugs

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### AUDIENCE

This activity is designed for pharmacists, pharmacy directors, managed care organization medical directors and administrators, and payers for health services.

### GOAL

To review the newer agents for treating epilepsy and their unique properties and roles in treatment.

### LEARNING OBJECTIVES

Upon successful completion of this educational program, the reader should be able to:

1. Compare the similarities and differences between each antiepileptic drug.
2. Describe the key indications for use of each medication.
3. Identify the major drug interactions of each individual agent.
4. Describe side-effect profiles and pharmacokinetics of each drug.
5. Identify how to appropriately monitor each agent, and how dosing should be initiated and maintained.

This review article discusses the newer anti-epileptic drugs gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam, oxcarbazepine, and zonisamide. Emphasis is given to FDA-approved indications and place in therapy. The mechanisms of action and pharmacokinetics of each drug is provided and the most common adverse effects are reviewed. Clinical studies leading to FDA approval are discussed. Practical points on proper dosing and monitoring are stressed, and drug interactions are also included.

*(Am J Manag Care 2003;9:253-276)*

Data from the World Health Organization suggest that as many as 1 in 20 people may have an epileptic seizure during their lives and that at least 1 in 200 people will have epilepsy.<sup>1</sup> In the past, carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid have been the usual medications for partial seizures, the most common type of seizure in adults.<sup>2</sup> Patients with primary generalized seizures usually were treated with valproic acid or phenytoin. Because phenytoin is available in intravenous formulation and is commonly given as the first-line agent for new-onset status epilepticus, it is often continued for the treatment of generalized seizures. Approximately 70% of patients achieve adequate control on the first or second standard antiepilepsy drug as monotherapy in partial epilepsy.<sup>3</sup> Within the last 10 years, however, 8 new drugs for the treatment of epilepsy have been released.

In 1993, felbamate was approved for use in the United States. Unfortunately, fatal hepatotoxicity and aplastic anemia were reported, and usage has consequently decreased drastically.<sup>4</sup> A recent review suggested the incidence of aplastic anemia in patients receiving felbamate was 27 to 209 cases per million compared with 2.0 to 2.5 cases per million persons in the general population.<sup>5</sup> Although the drug remains on the US market, guidelines for the use of felbamate stress that the agent should be used only for adults and children with severe



### CONTINUING EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-03-210-H01. This course expires on March 31, 2004.

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**Table 1.** Recommended Antiepileptic Drug Therapies Based on Seizure Type<sup>6</sup>

| Seizure Type  | Preferred Agent                             | Alternative Therapies  |
|---|---|--|
| <b>Partial seizure types</b>  |   |  |
| Simple partial, complex partial, or secondarily generalized partial seizures* | Carbamazepine<br>Phenytoin<br>Valproic acid | Gabapentin <sup>†</sup><br>Lamotrigine <sup>‡</sup><br>Topiramate <sup>†</sup><br>Tiagabine <sup>†</sup><br>Oxcarbazepine<br>Levetiracetam <sup>†</sup><br>Zonisamide <sup>†</sup><br>Phenobarbital<br>Primidone |
| <b>Generalized seizure types</b>  |   |  |
| Absence seizures  | Ethosuximide<br>Valproic Acid               | Clonazepam<br>Lamotrigine <sup>‡</sup>   |
| Myoclonic   | Valproic Acid                               | Lamotrigine<br>Clonazepam  |
| Atonic  | Valproic Acid                               | Lamotrigine  |
| Tonic, clonic, or tonic-clonic (grand mal) seizures                           | Carbamazepine<br>Phenytoin<br>Valproic Acid | Lamotrigine <sup>‡</sup><br>Oxcarbazepine<br>Phenobarbital<br>Primidone<br>Topiramate  |

\*Includes simple and complex partial seizures evolving to secondarily generalized seizures.

<sup>†</sup>FDA-approved as adjunctive therapy only.

<sup>‡</sup>Lamotrigine is approved by the FDA as add-on therapy for adults with partial seizures. It appears to be effective as add-on therapy for generalized seizures but is not approved by FDA for such use.

refractory epilepsy despite therapeutic treatment with other available antiepileptic agents.

The indications, pharmacokinetics, dosing, clinical efficacy, monitoring, and adverse effects of the other 7 new agents—gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam, oxcarbazepine, and zonisamide—are discussed below. The following tables will be referred to throughout this review summarizing indications by seizure type (Table 1), pharmacokinetics (Table 2), and drug interactions (Table 3).

### GABAPENTIN (NEURONTIN)

#### Food and Drug Administration–Approved Indication

Gabapentin (Neurontin; Parke-Davis, Morris Plains, NJ) was approved by the US Food and Drug Administration (FDA) in 1994 as adjunctive treatment in adults for partial seizures with and without secondary generalization. Gabapentin has also been approved for pediatric patients aged 3 to 12 years as adjunctive therapy for partial seizures.<sup>7</sup> Patients with primary generalized seizures receive no benefit, and studies show gabapentin may potentiate myoclonic and absence seizure types.<sup>14</sup>

**Table 2.** Pharmacokinetic Parameters of the Newer Antiepileptic Drugs

| Drug                        | Bioavailability (%) | PPB (%) | T <sub>max</sub> | Food  | Vd (L/kg)          | T <sub>1/2</sub>                                | Metabolism                 |
|-----------------------------|---------------------|---------|------------------|---|--------------------|---|----------------------------|
| Gabapentin <sup>7*</sup>    | 60*                 | 0       | 2-3 h            | No effect   | 0.8                | 5-7 h   | 0                          |
| Levetiracetam <sup>8</sup>  | 100                 | < 10    | 1 h              | ↓ C <sub>max</sub> 20%<br>Delays T <sub>max</sub> | 0.6                | 7 ± 1 h   | 24% Hepatic                |
| Lamotrigine <sup>9</sup>    | 98                  | 55      | 1.5-5 h          | No effect   | 0.9-1.3            | 33 h (monotx)<br>12-14 h (EIAEDs)<br>59 h (VPA) | Hepatic<br>glucuronidation |
| Oxcarbazepine <sup>10</sup> | 100                 | 40      | 4 h for MHD      | No effect   | 0.7-0.8<br>for MHD | 2 h OXC<br>9 h MHD                              | Hepatic                    |
| Tiagabine <sup>11</sup>     | 90                  | 96      | 0.75 h           | Delays absorption                                 |                    | 7-9 h   | Hepatic                    |
| Topiramate <sup>12</sup>    | 80                  | 13-17   | 2 h              | No effect   |                    | 21 h  | 30% Hepatic                |
| Zonisamide <sup>13</sup>    | 80                  | 40      | 2-6 h            | Delays peak<br>to 4-6 h                           | 0.8-1.6            | 50-70 h (monotx)<br>25-40 h<br>(EIAEDs)         | Minimal<br>hepatic         |

\*Bioavailability is dose dependent.

PPB indicates plasma protein binding; Vd, volume of distribution; monotx, monotherapy; EIAEDs, enzyme-inducing antiepileptic drugs; OXC, oxcarbazepine; MHD, active monohydroxy metabolite of OXC; VPA, valproic acid.

**Table 3.** Drug Interactions Among Antiepileptic Drugs<sup>6</sup>

| Antiepileptic Drug   | Effect on Plasma Level of Other Antiepileptic Drugs   |
|--|---|
| Carbamazepine  | ↓ Clonazepam<br>↓ Ethosuximide<br>↓ Felbamate<br>↓ Lamotrigine<br>↓ Oxcarbazepine (↓ MHD)<br>↑ ↓ Phenytoin<br>↓ Primidone (↑ Phenobarbital)<br>↓ Tiagabine<br>↓ Topiramate<br>↓ Valproic acid<br>↓ Zonisamide     |
| Ethosuximide   | ↑ Carbamazepine<br>↑ Phenytoin<br>↓ Valproic acid   |
| Felbamate  | ↓ Carbamazepine (↑ CBZ-E)<br>↑ Phenobarbital<br>↑ Phenytoin<br>↑ Valproic acid  |
| Gabapentin   | None  |
| Lamotrigine  | ↑ CBZ-E   |
| Levetiracetam  | None  |
| Oxcarbazepine  | None*   |
| Phenobarbital and Primidone (primidone effects stem from phenobarbital metabolite) | ↓ Carbamazepine<br>↓ Clonazepam<br>↓ Ethosuximide<br>↓ Felbamate<br>↓ Lamotrigine<br>↔ Oxcarbazepine (↓ MHD)<br>↑ ↓ Phenytoin<br>↓ Tiagabine<br>↓ Topiramate<br>↓ Valproic acid<br>↓ Zonisamide                   |
| Phenytoin  | ↓ Carbamazepine<br>↓ Clonazepam<br>↓ Ethosuximide<br>↓ Felbamate<br>↓ Lamotrigine<br>↔ Oxcarbazepine (↓ MHD)<br>↑ ↓ Primidone (↑ Phenobarbital)<br>↓ Tiagabine<br>↓ Topiramate<br>↓ Valproic acid<br>↓ Zonisamide |
| Tiagabine  | ↓ Valproic acid   |
| Topiramate   | ↑ Phenytoin<br>↓ Valproic acid  |
| Valproic acid  | ↓ Carbamazepine (↑ CBZ-E)<br>↑ Ethosuximide<br>↑ Felbamate<br>↑ Lamotrigine<br>↑ Phenobarbital<br>↑ ↓ Phenytoin (total)<br>↑ Phenytoin (free)<br>↑ Primidone (↑ Phenobarbital)<br>↓ Topiramate<br>↓ Zonisamide    |
| Zonisamide   | None  |

\*Oxcarbazepine is a weaker inducer than carbamazepine; drug levels of concomitant medications may increase when oxcarbazepine is substituted for carbamazepine.

MHD indicate active monohydroxy metabolite of oxcarbazepine; CBZ-E, carbamazepine-epoxide.

Gabapentin is now FDA approved for postherpetic neuralgia as well.

**Mechanism of Action**

The specific mechanism of action of gabapentin

is unknown. Although the drug is structurally related to gamma-aminobutyric acid (GABA), gabapentin increases the release of GABA without any direct effects on GABA or any of its binding sites.<sup>15</sup>

### Pharmacokinetics

See Table 2 for a pharmacokinetic summary and comparison with other agents. Absolute bioavailability of gabapentin is 57% for a single 300-mg dose, and 42% for a single 600-mg dose, illustrating the characteristic of dose-dependent bioavailability. Plasma concentrations are proportional to dose up to 1800 mg daily, and thereafter increase disproportionately to dose, until a plateau is reached at a 3600-mg daily dose. Upon reaching a 4800-mg daily dose, absolute bioavailability is estimated to decrease to 35%.<sup>16</sup> Volume of distribution of gabapentin is widespread at approximately 58 L, as gabapentin possesses no plasma protein binding. Concentrations in brain tissue have been quantitated to be 80% of that in the plasma, and drug concentrations in the cerebrospinal fluid are 20% of that in the plasma. Peak plasma concentrations occur 2 to 3 hours after dosing, and are not affected by food. Capsules may be broken and administered with food without bioavailability being compromised, and data suggest that high protein foods may increase  $C_{max}$  and area under the curve (AUC) favorably (32% higher, and 26% greater, respectively).<sup>17</sup> Because gabapentin is not associated with CYP

450 hepatic enzyme induction or inhibition, no interactions are expected with the metabolism of other antiepileptic drugs, and no adjustments of antiepileptic drug regimens should be necessary. The drug does not undergo metabolism; absorbed gabapentin is excreted unchanged in the urine, and unabsorbed drug is eliminated in the feces.  $T_{1/2}$  in patients with normal renal function is 5 to 9 hours, and steady state can be achieved in 1 to 2 days after titration to therapeutic dose is achieved. Elimination is directly affected by decreases in renal function; guidelines have been established for dosing adjustments (Table 4).<sup>7</sup> No published information is available regarding drug elimination in patients undergoing continuous ambulatory peritoneal dialysis.

### Clinical Trials

Three large, randomized, parallel-group, multicenter, double-blinded, placebo-controlled clinical trials were completed and data analyzed in a similar fashion to evaluate the dose-response relationship in patients with refractory partial seizures with secondary generalization (Table 4).<sup>18-20</sup> Patients randomized to the 1800 mg/day treatment arm of the US

**Table 4.** Efficacy of Gabapentin<sup>18-20</sup>

| Study  | Design (Patients Treated With 1 or More AEDs: CBZ, Pb, PHT, or VPA)   | Patient Population (Adults) | Results   |
|--|---|-----------------------------|---|
| UK Gabapentin Study Group <sup>18</sup>            | GBP 1200 mg/day vs placebo. Randomized, double-blind, placebo-controlled, add-on therapy, parallel group.               | 127                         | Median reduction in partial seizure frequency during 12 weeks of therapy was 29.2% for active drug, vs 12.5% for the placebo group. 25% of patients taking GBP had the number of seizures halved vs 9.8% of placebo patients.                           |
| US Gabapentin Study Group Number 5 <sup>19</sup>   | GBP 600, 1200, or 1800 mg/day vs placebo. Randomized, double-blind, placebo-controlled, add-on therapy, parallel group. | 306                         | Partial seizures (simple, complex, not secondarily generalized).<br>Placebo (n = 95) 8.4% RR<br>GBP 600 mg/day (n = 49) 18.0% RR ( $P = .007$ )<br>GBP 1200 mg/day (n = 91) 17.6% RR ( $P < .023$ )<br>GBP 1800 mg/day (n = 53) 26.4% RR ( $P = .001$ ) |
| International Gabapentin Study Group <sup>20</sup> | GBP 900 or 1200 mg/day vs placebo. Randomized, double-blind, placebo-controlled, add-on therapy, parallel group.        | 272                         | GBP 900 mg/day (n = 111) 22.9% RR<br>GBP 1200 mg/day (n = 52) 28.0% RR<br>Placebo (n = 109) 10.1% RR  |

These 3 pivotal studies assessed the efficacy of gabapentin in add-on clinical trials.

AEDs indicates antiepileptic drugs; CBZ, carbamazepine; Pb, phenobarbital; PHT, phenytoin, VPA, valproic acid; GBP, gabapentin; RR, responder rates (the percentage of patients with  $\geq 50\%$  reduction in seizure frequency) from baseline to therapeutic dose.

Gabapentin Study showed the highest response in reduction of seizures. Mean decrease in frequency with 1800 mg/day was 31.9% decrease in seizure frequency, with 26.4% of patients in the treatment arm having at least a 50% decrease in seizure frequency from baseline.<sup>21</sup>

**Adverse Reactions**

In controlled add-on trials, reported adverse effects of gabapentin occurring in more than 5% of patients included somnolence (19.3%), dizziness (17.1%), ataxia (12.5%), fatigue (11%), nystagmus (8.3%), tremor (6.8%), and diplopia (5.9%).<sup>22</sup> Since approval of this drug, some evidence suggests that weight gain can be a problem.<sup>22</sup>

**Drug Interactions**

See Table 3 for a summary of drug interactions. Essentially none are clinically significant with gabapentin.

**Dosing**

See Table 5 for gabapentin dosing. Dosing recommendations involve a simple titration schedule to a goal maintenance dose of at least 900 to 1800 mg/day, beginning with 300 mg TID, then increase to target maintenance dose appropriately. The drug has recently been approved for pediatric patients aged 3 to 12 years. Dosing should start at 10 to 15 mg/kg per day in 3 divided doses. Children aged 3 and 4 years should be titrated up to a maximum of 40 mg/kg per day, divided TID. Children aged 5 to 12 years should be titrated up to a maximum of 25 to 35 mg/kg per day, divided TID.<sup>7</sup>

**Use in Pregnancy**

Gabapentin is classified as pregnancy category C.<sup>7</sup>

**Clinical Monitoring**

Monitoring of plasma concentration is not necessary, as gabapentin dosing is sufficient to predict therapeutic efficacy.

**Table 5.** Dosing Guidelines for Gabapentin Administration Based on Renal Function in Adults and Children 12 Years or Older<sup>7</sup>

| CrCl (mL/min)             | Total Daily Dose Range (mg/d) | Regimen (mg)                             |         |         |        |         |
|---------------------------|-------------------------------|--|---------|---------|--------|---------|
|                           |                               | 300 QD                                   | 300 BID | 300 TID | 500 QD | 500 BID |
| ≥ 60                      | 900-3600                      | 100 QD                                   | 200 QD  | 300 QD  | 400 QD | 500 QD  |
| > 30-59                   | 400-1400                      | 100 QD                                   | 200 QD  | 300 QD  | 400 QD | 500 QD  |
| > 15-29                   | 200-700                       | 100 QD                                   | 200 QD  | 300 QD  | 400 QD | 500 QD  |
| < 15*                     | 100-300                       | 100 QD                                   | 125 QD  | 150 QD  | 200 QD | 300 QD  |
|                           |                               | Post-Hemodialysis Supplemental Dose (mg) |         |         |        |         |
| Hemodialysis <sup>†</sup> |                               | 125                                      | 150     | 200     | 250    | 350     |

TID, three times a day; BID, twice a day; QD, every day.

\*For patients with creatinine clearance < 15 ml/min, reduce daily dose in proportion to creatinine clearance.

†Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated above and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis.

**Place in Therapy**

Gabapentin is not presently approved as monotherapy for seizures; however, there are several studies evaluating the efficacy of gabapentin as monotherapy for partial seizure types.<sup>23-25</sup> Due to gabapentin's favorable safety profile and lack of drug interactions, studies are currently under way to evaluate the efficacy of gabapentin for further use in pain and psychiatry.<sup>26</sup> Gabapentin is heavily used for neuropathic pain syndromes, with several studies documenting efficacy in diabetic neuropathy and postherpetic neuralgia.<sup>27-30</sup> Because gabapentin possesses a benign safety profile, few drug interactions, and is eliminated renally, it may be particularly useful for patients taking multiple medications or patients with hepatic dysfunction. Disadvantages of gabapentin include multiple daily doses, and lack of efficacy in generalized seizures.<sup>7</sup> The patent for Neurontin ran out in December 2000; however, a generic formulation is not available at the time of this publication.

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**LAMOTRIGINE (LAMICTAL)**

**FDA-Approved Indication**

Lamotrigine (Lamictal; Glaxo Wellcome, Research Triangle Park, NC) received FDA approval in 1995 as adjunctive treatment of partial seizures in adults and as adjunctive therapy for the generalized

seizures of Lennox-Gastaut syndrome in pediatric and adult patient populations.<sup>9</sup> Lamotrigine has been recently approved for conversion to monotherapy in patients being treated with a single enzyme-inducing antiepileptic drug.<sup>31</sup>

### Mechanism of Action

The precise mechanism of action of lamotrigine is unknown; however, one proposed mechanism is through direct inhibition of voltage-sensitive sodium channels, leading to stabilization of neuronal membranes and modulation of presynaptic transmitter release of the excitatory amino acids glutamate and aspartate.<sup>15</sup>

### Pharmacokinetics

See Table 2 for a pharmacokinetic summary and comparison with other agents. Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. Absolute bioavailability is 98%, and is not affected by food. Peak plasma concentrations of the drug occur approximately 1.4 to 4.8 hours after administration. The chewable dispersible tablet formulations are found to be equivalent to standard tablets. The mean apparent volume of distribution after oral administration ranges from 0.9 to 1.3 L/kg. The volume of distribution is independent of dose and is similar after single and multiple doses in both patients with epilepsy and healthy volunteers. Data from *in vitro* studies of lamotrigine indicate that the drug is bound approximately 55% to human plasma proteins at concentrations from 1 to 10  $\mu\text{g/mL}$  (10  $\mu\text{g/mL}$  is 4-6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant drug-drug interactions through competition for protein binding are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproic acid. Lamotrigine did not displace other antiepileptic drugs from protein binding sites.<sup>9</sup>

Lamotrigine is metabolized predominantly by glucuronic acid conjugation into 2-N-glucuronide conjugate. After oral administration of 240 mg of lamotrigine in 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. In the urine, recovered drug consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).<sup>32</sup> After multiple doses of 150 mg BID in healthy vol-

unteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in  $t_{1/2}$  and a 37% increase in clearance at steady state compared with values obtained in the same volunteers after a single dose. Plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg.<sup>9</sup>

The pharmacokinetic parameters of lamotrigine in patients with impaired hepatic function have not been studied. Twelve volunteers with chronic renal failure (mean CrCl = 13 mL/min, range 6-23 mL/min) and another 6 undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The mean plasma  $t_{1/2}$ s determined in the study were 42.9 hours in patients with chronic renal failure and 13.0 hours during hemodialysis, compared with 26.2 hours in healthy volunteers without renal impairment. Approximately 20% of the amount of lamotrigine present in the body was eliminated during a 4-hour hemodialysis session.<sup>33</sup>

### Clinical Trials

The effectiveness of lamotrigine in adults as adjunctive therapy was established in 3 multicenter placebo-controlled, double-blind clinical trials in 355 patients with refractory partial seizures (Table 6). The patients had a history of at least 4 partial seizures per month despite receiving 1 or more antiepileptic drugs at therapeutic concentrations; in 2 of the studies, patients were observed on their established antiepileptic drug regimen during baselines of 8 to 12 weeks. In the third study, patients were not monitored in a prospective baseline study phase. Patients were then randomized to lamotrigine or placebo in addition to existing anticonvulsant therapy. The primary measure of effectiveness was change from baseline in seizure frequency.<sup>34-36</sup>

The more recent lamotrigine monotherapy trial was a double-blind, double-dummy, active-control study designed to evaluate the efficacy and safety of lamotrigine administered as monotherapy to adult outpatients with partial seizures.<sup>31</sup> After an 8-week baseline, during which patients continued their baseline antiepileptic drug (carbamazepine or phenytoin monotherapy), 156 patients were randomly assigned to receive increasing doses of lamotrigine at a target dose of 250 mg BID, or valproic acid at a target low dose of 500 mg BID during the first 4 weeks of an 8-week transition period. Carbamazepine or phenytoin was withdrawn over weeks 5 through 8, after which patients entered a

**Table 6.** Clinical Study Results for Lamotrigine<sup>34-36</sup>

| Study Characteristics*   | Participants (n) | Dose   | Reduction in Seizure Frequency  |
|--|------------------|--|---|
| <b>Matsuo et al</b> <sup>34</sup><br>Parallel trial<br>24 week treatment period<br>≤ 2 other AEDs (no VPA)   | 216              | 300 mg/day or 500 mg/day   | Placebo = 8%;<br>300 mg/day = 20%;<br>500 mg/day = 36%  |
| <b>Messenheimer et al</b> <sup>35</sup><br>Crossover trial<br>Two 14-week treatment periods<br>(the last 2 weeks were dose tapered)<br>4-week washout period<br>≤ 2 other AEDs (no VPA)                | 98               | 400 mg/day   | Median change in seizure frequency when the first 12 weeks of the treatment period were analyzed was a 25% reduction compared with placebo. |
| <b>Schapel et al</b> <sup>36</sup><br>Crossover trial<br>Two 12-week treatment periods<br>(the last 2 weeks were dose tapered)<br>4-week washout period<br>≤ 2 other AEDs<br>(13 patients were on VPA) | 41               | 300 mg/day for patients not on VPA<br><br>150 mg/day for patients on VPA | The median change in seizure frequency was a 25% reduction in patients randomized to lamotrigine compared with placebo.                     |

\*All 3 studies were multicenter, double-blind, randomized, placebo-controlled trials. AEDs indicates antiepileptic drugs; VPA, valproic acid.

12-week monotherapy period. Study therapy was discontinued in patients who met predetermined criteria for seizure worsening; 56% of patients receiving lamotrigine compared with 20% of patients receiving valproic acid were successfully maintained on monotherapy during the study protocol, and patients remained enrolled in the lamotrigine arm significantly longer than valproic acid (168 days versus 57 days). The incidence of adverse events during the monotherapy period was lower than during the transition period. Four lamotrigine patients and 5 valproate patients reported serious adverse events. Two of the 4 lamotrigine patients experienced a rash resulting in therapeutic withdrawal soon after the addition of lamotrigine to carbamazepine, leading to withdrawal of lamotrigine.<sup>31</sup>

### Adverse Reactions

Lamotrigine now carries a black box warning. Serious rashes requiring hospitalization and discontinuation of therapy have been reported in patients taking lamotrigine. The incidence of these rashes, including Stevens-Johnson syndrome, is approximately 1% in pediatric patients (younger than 16 years) and 0.3% in adults. International postmarketing experience reports rare cases of toxic epidermal necrolysis and/or rash related death; however, numbers are too few to permit a precise estimate of the rate. Because the rate of serious rash is higher among

pediatric populations, lamotrigine is approved only for use in pediatric patients younger than 16 years who have seizures associated with Lennox-Gastaut syndrome. Other than age, no known or identified factors predict the risk of occurrence or severity of rash associated with lamotrigine. It is thought that the risk of rash may be increased by the coadministration of lamotrigine with valproic acid; exceeding the recommended initial dose of lamotrigine; or exceeding the recommended dose escalation for lamotrigine.<sup>31,37</sup> However, cases have been reported in the absence of these factors. Nearly all cases of life-threatening rashes with lamotrigine have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have been reported after prolonged treatment (eg, 6 months). Therefore, duration of therapy cannot be a reliable predictor of potential risk associated with rash. Although benign rashes also occur with lamotrigine, predicting which rashes will prove to be serious or life threatening is not possible. Accordingly, lamotrigine should be discontinued at the first sign of rash, unless the rash is obviously not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening, or prevent permanent disability or disfigurement.<sup>9</sup>

Case reports of lamotrigine-associated anticonvulsant hypersensitivity syndrome comparable to that induced by older aromatic anticonvulsants have been reported; however, the significance is not

**Table 7.** Summary of Antiepileptic Drug Interactions with Lamotrigine<sup>9</sup>

| Antiepileptic Drug       | AED Concentration* | Lamotrigine Concentration <sup>†</sup> |
|--------------------------|--------------------|--|
| Phenytoin                | ↔                  | ↓                                      |
| Carbamazepine            | ↔                  | ↓                                      |
| CBZ epoxide <sup>‡</sup> | Conflicting data   | Conflicting data                       |
| VPA                      | ↓                  | ↑                                      |
| VPA plus DPH and/or CBZ  | Not evaluated      | ↔                                      |

↔ No significant effect.

\*From add-on clinical trials and volunteer studies.

<sup>†</sup>Net effects were estimated by comparing the mean clearance values obtained in add-on clinical trials and volunteer studies.

<sup>‡</sup>Active CBZ metabolite.

AED indicates antiepileptic drug; CBZ, carbamazepine; VPA, valproic acid; DPH, diphenylhydantoin or phenytoin.

known.<sup>37</sup> Evaluation of antiepileptic drug therapy is recommended when seizure control changes or with an appearance or worsening of adverse effects. If a decision is made to discontinue lamotrigine, a stepwise reduction of dose over at least 2 weeks (approximately 50% decrease each week) is recommended unless safety concerns warrant a more rapid withdrawal. In general, discontinuing an enzyme-inducing antiepileptic drug should prolong the  $t_{1/2}$  of lamotrigine, and discontinuing valproic acid should shorten the  $t_{1/2}$  of lamotrigine.

In clinical trials, other adverse events reported more often than placebo and occurring in at least

5% of patients treated with lamotrigine include the following: dizziness (38%), headache (29%), diplopia (28%), ataxia (22%), nausea (19%), blurred vision (16%), somnolence (14%), rhinitis (14%), rash (10%), pharyngitis (10%), vomiting (9%), increased cough (8%), flu syndrome (7%), dysmenorrhea in women (7%), incoordination (6%), insomnia (6%), fever (6%), diarrhea (6%), and dyspepsia (5%).<sup>9</sup>

### Drug Interactions

See Table 3 and Table 7 for a summary of drug interactions.

Lamotrigine has little effect on

other drugs as it is not an inducer or inhibitor of hepatic enzymes and is metabolized primarily by glucuronidation. The  $t_{1/2}$  of lamotrigine is 25.4 to 32.8 hours as monotherapy. When lamotrigine is taken in combination with enzyme-inducing antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin, or primidone, the  $t_{1/2}$  of lamotrigine is 12.6 to 14 hours. When taken in combination with the enzyme inhibiting antiepileptic drug valproate, the  $t_{1/2}$  of lamotrigine becomes 58.8 hours. Thus care must be taken in dosing and monitoring lamotrigine, depending on what other antiepileptic drugs the patient is taking.<sup>9</sup>

### Dosing

Table 8 outlines the manufacturer's recommended dosing titration schedule for patients beginning lamotrigine therapy. Slow titration is highly recommended as rash is associated with rapid titration schedules.

Children aged 2 to 12 years may receive lamotrigine. If the pediatric patient is taking an enzyme-inducing antiepileptic drug, therapy for weeks 1 and 2 should begin at 0.6 mg/kg per day, divided BID, and rounded down to the nearest whole tablet. Weeks 3 and 4 should be 1.2 mg/kg per day, divided BID, and rounded down to the nearest whole tablet. The usual

**Table 8.** Dosing Guidelines for Lamotrigine in Adults (>16 Years)<sup>9</sup>

| Patient Population        | Weeks 1 and 2 | Weeks 3 and 4 | Usual Maintenance Dose   |
|---------------------------|---------------|---------------|--|
| With EIAEDs, no VPA       | 50 mg QD      | 50 mg BID     | 300-500 mg/day, divided BID<br>Escalate dose 100 mg/day every week   |
| With EIAEDs, VPA included | 25 mg QOD     | 25 mg QD      | 100-400 mg/day,* divided BID.<br>Escalate 25-50 mg/day every 1-2 weeks. The usual dose with VPA alone ranges from 100 to 200 mg/day. |

\*The clearance of lamotrigine is decreased approximately 50% in the presence of VPA. Due to the increased incidence of rash in patients receiving VPA, the initial dose of lamotrigine should not exceed 25 mg QOD. EIAEDs include carbamazepine, phenobarbital, diphenylhydantoin, and primidone.

EIAEDs indicates enzyme-inducing antiepileptic drugs; VPA, valproic acid or phenytoin; QD, every day; QOD, every other day; BID, twice a day.



maintenance dose is 5 to 15 mg/kg per day (titrated up every 1 to 2 weeks by increments of 1.2 mg/kg per day added to the previous week's dose). For pediatric patients taking valproic acid, start at 0.15 mg/kg per day, divided BID, rounding down to the nearest whole tablet. Weeks 3 and 4 increase to 0.3 mg/kg per day, divided BID, rounding down to the nearest whole tablet. The usual maintenance dose is 1 to 5 mg/kg per day titrated up every 1 to 2 weeks by increments of 0.3 mg/kg per day added to the previous dose. In each case, the calculated dose should be rounded down to the nearest whole tablet.<sup>9</sup>

#### Use in Pregnancy

Lamotrigine is classified as pregnancy category C. Lamotrigine was not found to be teratogenic in animal studies; however, it is an inhibitor of dihydrofolate reductase, which leads to decreased fetal folate concentrations known to be associated with teratogenesis in humans.<sup>9</sup>

#### Clinical Monitoring

Due to potential pharmacokinetic interactions between lamotrigine and other antiepileptic drugs, monitoring may be indicated during dosage adjustments. No guidelines have been established for plasma concentration monitoring of lamotrigine, therefore dosing of lamotrigine should be based on clinical therapeutic response, and not serum drug concentration monitoring.<sup>9</sup>

#### Place in Therapy

Lamotrigine is indicated as adjunctive therapy and conversion to monotherapy for partial seizures in adults. It is also indicated as add-on therapy for Lennox-Gastaut syndrome in adult and pediatric patients. Lamotrigine has also been shown to be effective as add-on treatment of several types of generalized seizures, including tonic-clonic, typical and atypical absence, myoclonic, and atonic seizure types.<sup>9</sup> A primary advantage of lamotrigine is its wide applicability for treatment of multiple seizure types; however, lamotrigine has a large disadvantage of potentially serious rash, which causes practitioners to be hesitant in initiating therapy with lamotrigine.

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### TIAGABINE (GABITRIL)

#### FDA-Approved Indication

Tiagabine (Gabitril; Cephalon, Inc., West Chester, Penn) was approved in October 1997 for

the use as an adjunctive treatment of partial seizures in adults and children over 12.<sup>11</sup>

#### Mechanism of Action

The precise mechanism of action of tiagabine is unknown, but is believed to be related to the ability to enhance the activity of GABA through binding to recognition sites associated with the GABA uptake carrier. Therefore, tiagabine is theorized to block GABA uptake into presynaptic neurons, and to allow more GABA to be available for postsynaptic receptor binding. Tiagabine increases the amount of GABA available in the extracellular space of the globus pallidus, ventral pallidum, and the substantia nigra in rat models, suggesting that tiagabine prevents the propagation of neural impulses, which precipitate seizure activity through GABA-ergic action.<sup>15</sup>

#### Pharmacokinetics

See Table 2 for a pharmacokinetic summary and comparison with other agents. Tiagabine is 95% absorbed, and possesses 90% bioavailability. Following absorption, tiagabine concentration peaks in 45 minutes in fasting subjects. High-fat meals decrease the  $C_{max}$  by 40% and prolong the  $T_{max}$  to 2.5 hours. Although the absorption rate of tiagabine is decreased after a high-fat meal, the extent of absorption is not altered. Plasma protein binding is 96%, binding mainly to albumin and  $\alpha$  1-acid glycoprotein. Pharmacokinetics are linear over single-dose ranges of 2 to 24 mg. Steady-state levels are reached after 2 days of multiple dosing. The  $t_{1/2}$  of tiagabine in normal volunteers was 7 to 9 hours, but in patients on concomitant therapy with hepatic-inducing drugs, the  $t_{1/2}$  of tiagabine was decreased to 4 to 7 hours.

Tiagabine is metabolized primarily by oxidation to an inactive metabolite and glucuronidation. The drug likely undergoes hepatic metabolism through the CYP 3A subfamily; however, contributions to tiagabine metabolism by other substrates have not been ruled out. Elimination is 25% urinary, and 63% eliminated as inactive metabolites in the feces. The pharmacokinetics of tiagabine are relatively unchanged in patients with impaired renal function, and unaffected by hemodialysis. In moderate hepatic impairment (Child-Pugh class B), clearance of unbound tiagabine was decreased approximately 60% in comparison to patients with normal hepatic function, and, therefore, may require lower dosage initiation and titration of tiagabine. Valproic acid decreases the plasma protein binding of tiagabine from 96.3% to 94.8%, which results in a 40% increase

**Table 9.** Median Percent Reduction in Seizure Frequency from Baseline in 4-Week Seizure Rates in 3 Studies of Tiagabine<sup>38-40</sup>

| Study                                | n   | Median % Reduction* |             |
|--------------------------------------|-----|---------------------|-------------|
|                                      |     | Complex Partial     | All Partial |
| <b>Uthman et al<sup>38</sup></b>     |     |                     |             |
| Placebo                              | 91  | 9                   | 3           |
| Tiagabine 16 mg/day                  | 61  | 13                  | 12          |
| Tiagabine 32 mg/day                  | 87  | 25                  | 24          |
| Tiagabine 56 mg/day                  | 56  | 32                  | 36          |
| Combined 32 and 56 mg/day            | 143 | 29                  | 27          |
| <b>Sachdeo et al<sup>39</sup></b>    |     |                     |             |
| Placebo                              | 107 | 4                   | 5           |
| Tiagabine 16 mg BID                  | 106 | 22                  | 19          |
| Tiagabine 8 mg QID                   | 104 | 15                  | 13          |
| <b>Kalviainen et al<sup>40</sup></b> |     |                     |             |
| Placebo                              | 77  | -1                  | -7          |
| Tiagabine 30 mg/day                  | 77  | 14                  | 11          |

\*Statistical significance for median percentage reduction was not assessed. BID indicates twice a day; QID, four times a day.

in free tiagabine concentration (clinical results are unknown). The enzyme-inducing antiepileptic drugs carbamazepine, phenytoin, and phenobarbital increase the clearance of tiagabine by 60%. Tiagabine is classified as a noninducing antiepileptic drug, along with valproic acid and gabapentin.<sup>11</sup>

### Clinical Trials

The effectiveness of tiagabine as adjunctive therapy was in the treatment of partial seizures examined in 3 multicenter, double-blind, placebo-controlled, parallel-group clinical trials in patients with refractory partial seizures who were taking at least 1 hepatic enzyme-inducing antiepileptic drug, and 2 placebo-controlled crossover studies in 90 patients (Table 9). Patients in the parallel studies had a history of at least 6 complex partial seizures (study 1 and study 2), or 6 partial seizures of any type (study 3), occurring alone or with any other seizure type within the 8-week period preceding the first study visit and independent of receiving 1 or more antiepileptic drugs at therapeutic concentrations.<sup>38-40</sup>

Uthman and colleagues (study 1)<sup>38</sup> compared tiagabine at 16, 32, and 56 mg/day, divided QID with placebo (Table 9). After the prospective 12-week baseline period, patients were randomized to a treatment group. The 16-week treatment phase consisted

of a 4-week titration period and a 12-week fixed-dose regimen. Primary outcome measures were assessed for the combined 32 and 56 mg/day groups compared with placebo.<sup>38</sup>

Sachdeo and coworkers (study 2)<sup>39</sup> compared tiagabine at 16 mg BID and 8 mg QID with placebo (Table 9). After the 8-week baseline phase of the trial, the drug was titrated over 4 weeks, and patients randomly assigned to a fixed-dose regimen for 8 weeks. The primary outcome measure was assessed separately for each group treated.<sup>39</sup>

In the last study for FDA approval, Kalviainen and colleagues (study 3)<sup>40</sup> compared tiagabine 10 mg TID with placebo (Table 9). Patients were followed prospectively during a 12-week baseline phase before

randomization to active drug or placebo. Tiagabine was titrated over 6 weeks to 30 mg/day, and maintained for 12 weeks. The primary outcome measure was achievement of at least 50% reduction from baseline in partial seizure rate, which did not reach statistical significance.<sup>40</sup>

### Adverse Reactions

In clinical trials, adverse events reported more often than placebo and occurring in at least 5% of patients treated with tiagabine include the following: dizziness (27%), asthenia (20%), somnolence (18%), nausea (11%), nervousness (10%), tremor (9%), abdominal pain (7%), vomiting (7%), diarrhea (7%), pharyngitis (7%), rash (5%), difficulty with concentration (6%), insomnia (6%), ataxia (5%), confusion (5%), and unspecified pain (5%).<sup>11</sup>

### Drug Interactions

See Table 3 for a summary of drug interactions. Tiagabine does not induce or inhibit hepatic enzymes.

### Dosing

Dosing guidelines for adolescents aged 12 to 18 years vary from those of adult dosing. Initial therapy in adolescents is 4 mg daily. If necessary, dosing may be increased at week 2 by 4 mg, divided BID.

The dose may be increased by 4 to 8 mg at week 4, and increased by 4 to 8 mg/day every week until clinical response is achieved, or the maximum dose of 32 mg/day is reached (Table 1). Daily doses of tiagabine of more than 32 mg/day were tolerated in small numbers of adolescents for a short duration; however, results of long-term therapy have not been published. Concomitant antiepileptic drug dosages do not need to be adjusted when initiating tiagabine, unless otherwise clinically indicated. For patients older than 18 years, initiate tiagabine therapy at 4 mg/day, and increase the dose by 4 to 8 mg/day on a weekly basis until a clinical response is achieved, or a maximum dose of 56 mg/day (Table 10). A dose-frequency study showed that at 32 mg/day, patients given the drug every 12 hours did as well as those given the drug every 6 hours.<sup>39</sup>

**Use in Pregnancy**

Tiagabine is classified as pregnancy category C.<sup>11</sup>

**Clinical Monitoring**

Modification of other concurrent antiepileptic drugs appears unnecessary as tiagabine does not induce or inhibit hepatic enzymes. Routine laboratory monitoring is not recommended.<sup>39</sup>

**Place in Therapy**

Tiagabine is indicated as adjunctive therapy in adults and children 12 years and older for partial seizures. Its use as monotherapy and in pediatrics has not yet been established. One disadvantage of tiagabine may include its propensity to exacerbate some generalized seizure types, specifically absence seizures.<sup>41</sup> Long-term safety studies thus far indicate that no persistent cognitive problems or laboratory interactions or alterations normally occur.<sup>42</sup> Clinicians should be aware of the possible occurrence of confusion during titration that can be confused with absence status.<sup>43</sup>

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**TOPIRAMATE (TOPAMAX)**

**FDA-Approved Indication**

Topiramate (Topamax; Ortho-McNeil, Raritan, NJ) was approved in 1997 and is used in children

**Table 10.** Typical Dosing Titration for Tiagabine in Patients Taking Enzyme-Inducing Antiepileptic Drugs<sup>11\*</sup>

| Time (Week) | Initiation and Titration | Total Daily Dose               |
|-------------|--------------------------|--------------------------------|
| 1           | 4 mg QD                  | 4 mg/day                       |
| 2           | ↑ by 4 mg/day            | 8 mg/day (divided BID)         |
| 3           | ↑ by 4 mg/day            | 12 mg/day (divided TID)        |
| 4           | ↑ by 4 mg/day            | 16 mg/day (divided BID-QID)    |
| 5           | ↑ by 4-8 mg/day          | 20-24 mg/day (divided BID-QID) |
| 6           | ↑ by 4-8 mg/day          | 24-32 mg/day (divided BID-QID) |

\*The usual adult maintenance dose is 32–56 mg/day in 2 to 4 divided doses. QD indicates every day; BID, twice a day; TID, three times a day; QID, four times a day.

and adults as adjunctive treatment of partial seizures as well as add-on therapy for primary generalized tonic-clonic seizures. It has recently been approved for treatment of Lennox-Gastaut syndrome in patients older than 2 years.<sup>12</sup>

**Mechanism of Action**

Topamax has 3 possible mechanisms of action: blockade of state-dependent sodium channels, potentiation of GABA-mediated neuroinhibition, and blockade of glutamate-mediated neuroexcitation through the kainate/ $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors, and no apparent effects on *N*-methyl-D-aspartate activity. Topiramate also inhibits some isoenzymes of carbonic anhydrase; however, the pharmacologic effect is weaker than that of acetazolamide and is not thought to be a contributing factor to antiepileptic activity.<sup>15</sup>

**Pharmacokinetics**

See Table 2 for a pharmacokinetic summary and comparison with other agents. Absorption of topiramate is rapid, with the peak occurring approximately 2 hours after dosing. The sprinkle formulation is bioequivalent to the immediate-release formulation and therefore may be substituted. Bioavailability, unaffected by food, is approximately 80%. Pharmacokinetics are linear at doses ranging from 200 to 800 mg/day. The  $t_{1/2}$  after single and multiple dosing is 21 hours. Steady-state levels are reached in approximately 4 days for patients with normal renal function. Plasma protein binding is 13% to 17%, 70% of the administered dose is eliminated unchanged in the urine, and the remaining portion undergoes metabolism by hydrol-

ysis, hydroxylation, or glucuronidation. Plasma clearance<sup>12</sup> is approximately 20 to 30 mL/min.

### Clinical Trials

The efficacy of topiramate as adjunctive treatment of partial onset seizures was established in 5 multicenter, randomized, double-blind, placebo-controlled trials (Table 11). Two trials compared multiple differing doses versus placebo, and 3 trials compared single doses versus placebo in patients with a history of partial onset seizures with or without secondary generalization. Enrolled patients were allowed 2 concomitant antiepileptic drugs and were stabilized on optimum dosages of concomitant drugs during an 8-week to 12-week baseline phase. Patients experiencing 8 partial onset seizures during the 8-week baseline or 12 partial seizures during the 12-week baseline were enrolled and randomized to topiramate or placebo. Patients on active drug were initiated at 100 mg/day, and increased by 100 to 200 mg/day every 1 to 2 weeks, until assigned doses were achieved or intolerance occurred. After titration, patients went through an 8-week to 12-week stabilization period. The reduction in seizure frequency and the responder rate (percentage of patients with

at least a 50% reduction in seizures) were the clinical end points.<sup>12,44,45</sup>

Regarding precautions of topiramate therapy, 32 of 2086 (1.5%) patients reported kidney stones, which is an incidence 2 to 4 times greater than the standard population. A plausible explanation for the increased incidence of nephrolithiasis is that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors promote stone formation by reducing urinary citrate excretion and through increasing urinary pH. Patients given carbonic anhydrase inhibitors or on a ketogenic diet may be at increased risk of developing renal calculi, and should avoid topiramate use. Hydration to increase urine output is recommended to reduce stone formation.<sup>12</sup>

### Adverse Reactions

In clinical trials, other adverse events reported more often than placebo and occurring in at least 5% of patients given topiramate 200 to 400 mg/day include the following: somnolence (29%), dizziness (25%), ataxia (16%), nervousness (16%), fatigue (15%), speech disorders (13%), psychomotor slowing (13%), abnormal vision (13%), memory difficulty

**Table 11.** Key Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Trials of Topiramate for Partial Onset Seizures<sup>12,44,45</sup>

| Protocol   | Measure             | Placebo | Target Topiramate Dose (mg/day) |      |      |      |      |
|--|---------------------|---------|---------------------------------|------|------|------|------|
|  |                     |         | 200                             | 400  | 600  | 800  | 1000 |
| Topiramate Study YD <sup>44</sup><br>(Faught et al)    | Number of patients  | 45      | 45                              | 45   | 46   | —    | —    |
|  | Median % reduction* | 11.6    | 27.2                            | 47.5 | 44.7 | —    | —    |
|  | % Responders        | 18      | 24                              | 44   | 46   | —    | —    |
| Topiramate Study YE <sup>45</sup><br>(Privitera et al) | Number of patients  | 47      | —                               | —    | 48   | 48   | 47   |
|  | Median % reduction  | 1.7     | —                               | —    | 40.8 | 41.0 | 36.0 |
|  | % Responders        | 9       | —                               | —    | 40   | 41   | 36   |
| Topiramate Study Y1 <sup>12</sup>                      | Number of patients  | 24      | —                               | 23   | —    | —    | —    |
|  | Median % reduction  | 1.1     | —                               | 40.7 | —    | —    | —    |
|  | % Responders        | 8       | —                               | 35   | —    | —    | —    |
| Topiramate Study Y2 <sup>12</sup>                      | Number of patients  | 30      | —                               | —    | 30   | —    | —    |
|  | Median % reduction  | -12.2   | —                               | —    | 46.4 | —    | —    |
|  | % Responders        | 10      | —                               | —    | 47   | —    | —    |
| Topiramate Study Y3 <sup>12</sup>                      | Number of patients  | 28      | —                               | —    | —    | 28   | —    |
|  | Median % reduction  | -20.6   | —                               | —    | —    | 24.3 | —    |
|  | % Responders        | 0       | —                               | —    | —    | 43   | —    |

\*Median percent reduction and percent responders are reported for primary generalized tonic-clonic seizures.

(12%), paresthesia (11%), confusion (11%), anorexia (10%), nystagmus (10%), diplopia (10%), nausea (10%), tremor (9%), weight loss (9%), dyspepsia (7%), rhinitis (7%), language problems (6%), asthenia (6%), back pain (5%), abdominal pain (6%), difficulty concentrating (6%), pharyngitis (6%), and sinusitis (5%). A newly reported ocular syndrome consisting of acute myopia and secondary angle closure glaucoma has now been reported to the FDA, with 23 cases thus far in approximately 825 000 patients exposed to the drug.<sup>12</sup>

**Drug Interactions**

See Table 3 for a summary of drug interactions. Topiramate can potentially compromise the efficacy of oral contraceptive therapy by increasing the clearance of the estrogen component, although the mechanism is unknown.<sup>12</sup>

**Dosing**

Recently the FDA altered the recommended rate of topiramate titration, because of fewer adverse effects and decreased discontinuation of drug with slower titration. A common dosing strategy is to begin at 25 to 50 mg daily, and titrate by 25 to 50 mg per week until an effective target dose is reached. This slow titration regimen does delay the onset of efficacy, but minimizes side effects. The target dose of topiramate is 400 mg/day, divided BID. In studies of adults with partial onset seizures, a daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. Daily doses above 1600 mg/day have not been studied. In children 2 to 16 years, the dose is 5 to 9 mg/kg/day, divided BID. Titration should begin at 25 mg or less nightly for the first week and then should be increased at 1-week to 2-week intervals by increments of 1 to 3 mg/kg per day.<sup>12</sup>

**Use in Pregnancy**

Topiramate is classified as pregnancy category C.<sup>12</sup>

**Clinical Monitoring**

The levels of concomitant antiepileptic drugs may need to be monitored, although the degree of the interaction is thought to be mild.<sup>12</sup>

**Place in Therapy**

Topiramate is indicated as adjunctive therapy for adults and children with partial onset seizures, primarily generalized tonic-clonic seizures, and in Lennox-Gastaut syndrome. Some evidence suggests that topiramate may be beneficial in the manage-

ment of absence seizures. Advantages include potential for treatment of multiple seizure types, and a trend toward better efficacy. Disadvantages of topiramate include an increased incidence of renal calculi. A recent postmarketing review indicated that cognitive effects often described as psychomotor slowing were the most common reason to discontinue topiramate.<sup>46</sup> The manufacturer recently announced that although preliminary results from 1 study showed promise in the use of topiramate for neuropathic pain, 3 subsequent phase III trials have failed to show a statistically significant efficacy advantage over placebo.<sup>47</sup>

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**LEVETIRACETAM (KEPPRA)**

**FDA-Approved Indication**

Levetiracetam (Keppra; UCB Pharma, Smyrna, Ga) was approved in November 1999 for adjunctive therapy in the treatment of partial onset seizures in patients 16 years and older.<sup>8</sup>

**Mechanism of Action**

Levetiracetam expresses an antiepileptic effect by a mechanism that has not been fully elucidated. It has not been shown to have any interaction with known mechanisms involved with excitatory or inhibitory neurotransmission. Second messenger systems, ion-channel proteins, glutamate receptor-mediated neurotransmission, and GABA-transaminase and glutamate decarboxylase activities were not affected by levetiracetam. Epileptiform activity recordings from the hippocampus have shown that levetiracetam inhibits burst firing without altering normal neuronal excitability. This finding suggests levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. Levetiracetam also demonstrates stereoselective binding to synaptic plasma membranes in the central nervous system, but not in the periphery.<sup>8</sup>

**Pharmacokinetics**

See Table 2 for a pharmacokinetic summary and comparison with other agents. Levetiracetam has 100% bioavailability and is rapidly and completely absorbed, with peak plasma concentrations occurring at 1 hour in fasting subjects. Food delays T<sub>max</sub> by 1.5 hours and decreases C<sub>max</sub> by 20%, but does not decrease bioavailability. Pharmacokinetics are linear with doses ranging from 500 to 1500 mg. T<sub>1/2</sub> is 6 to 8 hours in healthy subjects, and increases

**Table 12.** Levetiracetam Clinical Trials for FDA Approval<sup>48-50</sup>

| Study                                       | n   | Response  |   |
|---|-----|---|---|
|   |     | Percent Reduction in Weekly Frequency of Partial Onset Seizures | Percent Responder Rate (≥50% Reduction in Weekly Seizure Rates From Baseline) |
| <b>Cereghino et al<sup>48</sup></b>         |     |   |   |
| Keppra 1000 mg/day                          | 97  | 26.1 ( $P < .001$ )   | 37.1  |
| Keppra 3000 mg/day                          | 101 | 30.1 ( $P < .001$ )   | 39.6  |
| Placebo                                     | 95  | —   | 7.4   |
| <b>Shorvon et al<sup>49</sup></b>           |     |   |   |
| Keppra 1000 mg/day                          | 106 | 17.1 ( $P \leq .001$ )  | 20.8  |
| Keppra 2000 mg/day                          | 105 | 21.4 ( $P \leq .001$ )  | 35.2  |
| Placebo                                     | 111 | —   | 6.3   |
| <b>Ben-Menachem and Falter<sup>50</sup></b> |     |   |   |
| Keppra 3000 mg/day                          | 180 | 23.0 ( $P < .001$ )   | 39.4  |
| Placebo                                     | 104 | —   | 14.4  |

with decreasing renal function. Levetiracetam and its metabolites are eliminated renally through glomerular filtration; therefore, dosing adjustments should be made in patients with decreased renal function. Steady-state levels are reached after 2 days of therapy. Levetiracetam and its carboxylic acid metabolites are less than 10% plasma protein bound, and 24% of levetiracetam is metabolized by enzymatic hydrolysis to a compound identified as "ucb L057." Levetiracetam and its metabolites are neither inhibitors nor substrates for the CYP 450 pathways, and the "ucb L057" compound is inactive in animal seizure models. Approximately 66% of the administered dose of levetiracetam is eliminated via renal glomerular filtration as unchanged drug. No dose adjustment is needed for patients with hepatic impairment.<sup>8</sup>

### Clinical Trials

Efficacy of levetiracetam has been estimated in 3 multicenter, randomized, double-blind, placebo-controlled clinical studies in patients with refractory partial onset seizures with or without secondary generalization (Table 12).<sup>48-50</sup> A total of 904 patients were randomized to placebo, or 1000, 2000, or 3000 mg/day. Patients enrolled in the study by Cereghino and colleagues<sup>48</sup> (study 1) or the study by Shorvon and coworkers<sup>49</sup> (study 2) had refractory partial onset seizures for at least 2 years and had taken 2 or more classical antiepileptic drugs. Patients remained on a stable dosing regimen of at least 1 antiepilep-

tic drug during the study and had to have at least 4 partial onset seizures during each 4-week period.<sup>48,49</sup> The study by Ben-Menachem and Falter<sup>50</sup> (study 3) included patients with refractory partial onset seizures, with or without secondary generalization, and receiving only 1 concomitant antiepileptic drug.

Study 1 was conducted at 41 sites in the United States, comparing 1000 mg/day ( $n = 97$ ), 3000 mg/day ( $n = 101$ ), and placebo ( $n = 95$ ) given in equally divided doses twice daily.<sup>48</sup> After completion of a 12-week baseline period, patients were randomized and treated for 18 weeks (6-week titration period, followed by a 12-week fixed-dose interval). Patients receiving 1000 mg/day experienced a 26.1% reduction in weekly partial seizure frequency compared with placebo, and patients receiving 3000 mg/day experienced a 30.1% reduction compared with placebo ( $P < .001$ ). Of patients taking 1000 mg/day and 3000 mg/day, 37.1% and 39.6%, respectively, achieved at least a 50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire treatment period (titration and evaluation phases), compared with 7.4% of patients in the placebo group ( $P < .001$ ).<sup>48</sup>

Study 2 was a double-blind, placebo-controlled crossover study conducted at 62 centers in Europe comparing levetiracetam 1000 mg/day ( $n = 106$ ), 2000 mg/day ( $n = 105$ ), and placebo ( $n = 111$ ) given in equally divided doses twice daily.<sup>49</sup> After a 12-week prospective baseline phase, patients were

randomized to 1 of the 3 treatment groups and treated for 16 weeks (4-week titration period, followed by a 12-week fixed-dose evaluation period). The doses of concomitant antiepileptic drugs were held constant during the study. Patients receiving 1000 mg/day experienced a 17.1% reduction in weekly partial seizure frequency compared with placebo, and patients receiving 2000 mg/day experienced a 21.4% reduction compared with placebo. A total of 20.8% of patients taking 1000 mg/day and 35.2% of patients taking 2000 mg/day achieved at least a 50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire treatment period (titration and evaluation phases), compared with only 6.3% of patients taking placebo.<sup>49</sup>

Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing levetiracetam 3000 mg/day (n = 180) and placebo (n = 104) in patients with refractory partial onset seizures with or without secondary generalization, receiving only 1 concomitant antiepileptic drug.<sup>50</sup> Study drug was given in equally divided doses twice daily. After a 12-week prospective baseline phase, patients were randomized to 1 of the 3 treatment groups and treated for 16 weeks (4-week titration period, followed by a 12-week fixed-dose evaluation period). The doses of concomitant antiepileptic drugs were held constant during the study. Patients receiving active drug experienced a 23.0% reduction in weekly partial seizure frequency over the entire treatment period (titration and evaluation phases), compared with placebo. A total of 39.4% of patients taking levetiracetam achieved at least a 50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire treatment period (titration and evaluation phases), compared with 14.4% of patients taking placebo.<sup>50</sup>

### Adverse Reactions

The most frequently reported adverse events occurred during the first 4 weeks of treatment. In clinical trials, adverse events reported more often than placebo and occurring in at least 5% of patients given levetiracetam include the following: asthenia (15%), somnolence (15%), headache (14%), infection (13%), dizziness (9%), pain (7%), and pharyngitis (6%). In controlled trials of epilepsy, a total of 13.3% of patients receiving levetiracetam experienced behavioral symptoms compared with 6.2% of placebo patients (reported as agitation, hostility, anxiety, apathy, emotional lability, depersonalization, depression, etc). Only 1.7% of patients discon-

tinued therapy due to these effects. However, 4 patients attempted suicide during the study. Minor decreases in total red blood cells (RBC), mean hemoglobin, and hematocrit were seen in controlled trials. A total of 3.2% of patients receiving active drug compared with 1.8% of placebo patients had one possibly significant decrease in white blood cells ( $2.8 \times 10^9/L$  or less), and 2.4% of treated patients compared with 1.4% of placebo patients had at least one possibly significant decrease in neutrophil count ( $1.0 \times 10^9/L$  or less). No patients discontinued therapy due to decreases in white blood cell or absolute neutrophil count; these laboratory values increased toward baseline on continued therapy, with the exception of 1 patient.<sup>8</sup>

### Drug Interactions

See Table 3 for a summary of drug interactions. Levetiracetam is thought to have no effect on hepatic enzymes. Oral contraceptives are unaffected by coadministration of levetiracetam. Digoxin and warfarin have no clinical interactions with levetiracetam, and INR was unaffected in patients undergoing anticoagulation.<sup>47</sup>

### Dosing

Treatment should be initiated at 1000 mg/day, divided BID. Dose may be increased by 1000 mg/day every 2 weeks, to the maximum recommended daily dose of 3000 mg/day. The highest administered dose in clinical trials was 6000 mg/day, with no known adverse drug effects, other than drowsiness.<sup>8</sup> Renal dosing-adjustment guidelines<sup>8</sup> for levetiracetam are outlined in Table 13.

### Use in Pregnancy

Levetiracetam is classified as pregnancy category C.<sup>8</sup>

### Clinical Monitoring

Monitoring of drug levels of other antiepileptic drugs and levetiracetam are not needed. Clinical monitoring should guide treatment. As noted previously, minor drops in erythrocyte count, hemoglobin level, and leukocyte counts may occur and may need to be monitored.<sup>8</sup>

### Place in Therapy

Advantages to levetiracetam for treatment of partial onset seizures include the lack of any known drug interactions, low plasma protein binding, renal elimination, and the fact that dose titration is unnecessary. Behavioral and psychiatric symptoms includ-

**Table 13.** Renal Dose Adjustment for Levetiracetam<sup>8</sup>

| Group                     | CrCl (mL/min) | % Decrease in Renal Clearance | Dose (mg) | Frequency (hours) |
|---------------------------|---------------|-------------------------------|-----------|-------------------|
| Normal renal function     | > 80          | —                             | 500-1500  | Q12               |
| Mild renal impairment     | 50-80         | 40%                           | 500-1000  | Q12               |
| Moderate renal impairment | 30-50         | 50%                           | 250-750   | Q12               |
| Severe renal impairment   | < 30          | 60%                           | 250-500   | Q12               |
| ESRD w/ HD                | —             | 70%                           | 500-1000  | Q24*              |

\*250-500 postdialysis supplement recommended. A standard 4-hour hemodialysis session removes 50% of the levetiracetam drug pool.

ESRD indicates end-stage renal disease; HD, hemodialysis; Q = every.

ing psychosis may be of concern, especially early in treatment. Some evidence suggests that the drug is better tolerated and possesses a lower incidence of cognitive dysfunction in comparison with other antiepileptic drugs.<sup>51</sup>

## OXCARBAZEPINE (TRILEPTAL)

### FDA-Approved Indication

Oxcarbazepine (Trileptal; Novartis, East Hanover, NJ) was approved in January 2000 for treatment as monotherapy or adjunctive therapy for partial seizures with or without secondary generalization in adults and children aged 4 to 16 years.<sup>10</sup>

### Mechanism of Action

Oxcarbazepine is a keto-homologue of carbamazepine, which retains the therapeutic benefits of carbamazepine, but possesses an improved tolerability profile. Oxcarbazepine is a prodrug that undergoes conversion to a monohydroxy derivative (MHD), which leads to stabilization of hyperexcited neural membranes, and repetitive firing inhibition as well as diminution of impulse propagation in the synapse. Although the mechanism of action is not completely understood, electrophysiologic studies indicate blockage of voltage-sensitive sodium channels in the presence of the active MHD metabolite, and possibly through the modulation of high-voltage calcium channels in the neuronal pathways. The ability of oxcarbazepine and MHD to limit repetitive high-frequency firing of sodium-dependent action potentials on neurons can contribute to inhibition of the spread of seizure activity from a focal point.<sup>10</sup> Increased potassium

conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects of oxcarbazepine.<sup>15</sup>

### Pharmacokinetics

See Table 2 for a pharmacokinetic summary and comparison with other agents. The pharmacokinetic activity of oxcarbazepine is primarily exerted through MHD.<sup>15</sup> Oxcarbazepine is

metabolized by reduction reactions and is not dependent on the cytochrome P450 metabolic pathway, whereas carbamazepine is converted to an epoxide metabolite by epoxidase enzymes known to be responsible for the adverse effects and drug–drug interactions of carbamazepine therapy.<sup>10,52</sup> Unlike carbamazepine, oxcarbazepine does not undergo autoinduction. Absorption is nearly complete (96%–100%), and unaffected by food. The drug is then rapidly converted to the MHD metabolite. Plasma protein binding of oxcarbazepine is 60%, whereas 40% of the MHD is plasma protein bound. Serum levels of oxcarbazepine peak approximately 1 hour after dosing, and MHD has a delayed peak up to 4 hours after administration. The  $t_{1/2}$  of oxcarbazepine is 2.5 to 5 hours and MHD is 8 to 10 hours. BID dosing was found to be as efficacious as TID.<sup>53</sup> Because of its neutral and lipophilic nature, the drug readily penetrates the blood–brain barrier; and has a large volume of distribution of 0.6 to 0.7 L/kg. MHD undergoes approximately 50% glucuronidation, and the remainder is excreted unchanged in the urine.<sup>10</sup>

### Clinical Trials

Oxcarbazepine is used for the treatment of partial seizures as monotherapy or adjunctive therapy in adults, and adjuvant therapy in children aged 4 to 16 years. Efficacy has been established in several trials and the drug has been available outside the United States for several years (Table 14).

### Adverse Reactions

The safety profile for oxcarbazepine is similar to carbamazepine; however, hyponatremia is more pronounced with oxcarbazepine because of the release of



**Table 14.** Efficacy Trials of Oxcarbazepine\*<sup>53</sup>

| Trial                                  | Design   | Patient Population   | Results   |
|--|--|--|---|
| <b>Monotherapy trials</b>              |  |  |   |
| Bill et al <sup>54</sup> (1997)        | OXC 450–2400 mg/day vs PHT 150–800 mg/day. Randomized, double-blind, parallel-group.   | 287 adults with previously untreated partial or generalized tonic-clonic seizures  | <ul style="list-style-type: none"> <li>No significant differences in efficacy</li> <li>Fewer dropouts due to adverse effects in OXC arm.</li> <li>OXC rated preferable in tolerability by patients and physicians.</li> <li>Gum hyperplasia, diplopia, nervousness significantly more common with PHT.</li> </ul>                             |
| Guerreiro et al <sup>55</sup> (1997)   | OXC 450–2400 mg/day vs PHT 150–800 mg/day. Randomized, double-blind, parallel-group.   | 193 adolescents/children with newly diagnosed partial or generalized tonic-clonic seizures   | <ul style="list-style-type: none"> <li>No significant differences in efficacy.</li> <li>Significantly lower dropout rate due to side effects with OXC.</li> <li>Gum hyperplasia, diplopia, nervousness significantly more common with PHT.</li> </ul>   |
| Christie et al <sup>56</sup> (1997)    | OXC 900–2400 mg/day vs VPA 900–2400 mg/day. Randomized, double-blind, parallel-group.  | 249 adults with newly diagnosed partial or generalized tonic-clonic seizures   | <ul style="list-style-type: none"> <li>No significant differences in efficacy.</li> <li>No significant differences in rates of premature discontinuation or in overall assessment of effectiveness or tolerability.</li> </ul>  |
| Schachter et al <sup>57</sup> (1999)   | OXC (1500 mg/day on day one, 2400 mg/day on days 2–10) vs placebo. Randomized, double-blind, placebo-controlled, 2-arm parallel-group; monotherapy design. | 102 hospitalized patients with refractory partial seizures with or without secondarily generalized seizures (surgical) candidates                          | <ul style="list-style-type: none"> <li>OXC significantly better than placebo in time to exit criteria.</li> <li>Rate of partial seizures and secondarily generalized seizures significantly lower with OXC.</li> </ul>  |
| Reinikainen et al <sup>58</sup> (1987) | OXC 600-900 mg/day vs CBZ 400-800 mg/day as replacement for PHT. Randomized, double-blind, parallel-group.   | 40 adults with chronic epilepsy who had uncontrolled seizures or unwanted side effects on PHT monotherapy  | <ul style="list-style-type: none"> <li>Seizure control apparently improved with either CBZ or OXC; no significant difference in efficacy.</li> <li>Number of reported side effects significantly lower with OXC.</li> </ul>   |
| Dam et al <sup>59</sup> (1989)         | OXC 300–1800 mg/day vs CBZ 300–1400 mg/day. Randomized, double-blind, parallel-group.  | 235 adult patients with newly diagnosed untreated primary generalized tonic-clonic seizures; or partial seizures with or without secondary generalization. | <ul style="list-style-type: none"> <li>No significant differences in efficacy.</li> <li>Overall incidence of side effects not significantly different, but OXC apparently caused significantly fewer “severe” side effects.</li> <li>No difference in global tolerability assessment.</li> </ul>  |
| <b>Combination therapy trial</b>       |  |  |   |
| Houtkooper et al <sup>60</sup> (1987)  | OXC 900–3600 mg/day as replacement for CBZ 500–2000 mg/day in patients on combination therapy. Double-blind, crossover.                                    | 48 adult inpatients with incompletely controlled partial, generalized, or mixed seizures   | <ul style="list-style-type: none"> <li>Significant reduction in frequency of tonic-clonic and tonic seizures with OXC.</li> <li>No significant change in other seizure types.</li> <li>Apparent decrease in seizure severity with OXC.</li> <li>Approximately equal preference for OXC and CBZ by nursing staff and investigators.</li> </ul> |

\*Adapted from Lott RS, Helmboldt K. Oxcarbazepine: a carbamazepine analogue for partial seizures in adults and children with epilepsy. *Formulary*. 2000;35:219–233.

OXC indicates oxcarbazepine; PHT, phenytoin; VPA, valproic acid; CBZ, carbamazepine.

antidiuretic hormone, but is uncommon and does not normally require dosage adjustments. Allergic skin reactions occur in fewer than 10% of patients; however, caution should be exercised in patients with sensitivity

to carbamazepine because of a 30% cross-sensitivity reported between the 2 agents.

In clinical trials, adverse events reported more often than placebo and occurring in at least 5% of

**Table 15.** Potential Drug Interactions of Oxcarbazepine<sup>10</sup>

| Potentially Interacting With OXC                       | Potential Effects on OXC  |
|--|---|
| <b>Enzyme Inhibitors</b>                               |   |
| Cimetidine   | No effect on clearance of OXC or MHD.   |
| Dextropropoxyphene                                     |   |
| Erythromycin   |   |
| Valproic acid  | Decrease of MHD by 18%.   |
| <b>Enzyme Inducers</b>                                 |   |
| Phenytoin  | Possible increased conversion of MHD to inactive trans-hydroxy carbamazepine metabolite; decreased MHD concentration; clinical significance is unknown. |
| Phenobarbital  |   |
| Carbamazepine  |   |
| <b>Other Drugs</b>                                     |   |
| Verapamil  | Potential to decrease concentration of MHD, and decrease antiepileptic effects of OXC; clinical significance not yet known.                             |
| <b>OXC Potentially Interacting With Other Drugs</b>    |   |
| Warfarin   | Warfarin not altered by OXC.  |
| Oral contraceptives (ethinyl estradiol/levonorgestrel) | 40%–50% increase in clearance of contraceptives with 1200 mg/day dose. Loss of efficacy may occur, and breakthrough bleeding has been reported.         |
| Felodipine   | 28% decrease in felodipine serum concentration.   |
| Antipyrine   | Marker for hepatic metabolism. High OXC doses (2400 mg/day) reported to increase antipyrine clearance.  |
| Lamotrigine  | Lamotrigine clearance may increase. Reduced plasma concentrations and clinical effect may occur. Dosage increase may be required.                       |

OXC indicates oxcarbazepine; MHD, active monohydroxy metabolite of oxcarbazepine.

patients given oxcarbazepine alone at 2400 mg daily include the following: headache (31%), dizziness (28%), nausea (22%), fatigue (21%), somnolence (19%), vomiting (15%), abnormal vision (14%), diplopia (12%), upper respiratory tract infection (10%), diarrhea (7%), viral illness (7%), anxiety (7%), ataxia (7%), confusion (7%), nervousness (7%), insomnia (6%), tremor (6%), dyspepsia (6%), amnesia (5%), aggravated convulsions (5%), anorexia (5%), abdominal pain (5%), hyponatremia (5%), coughing (5%) taste perversion (5%), and urinary tract infection (5%).<sup>10</sup>

### Drug Interactions

Oxcarbazepine has a lower likelihood of causing drug interactions than carbamazepine because

oxcarbazepine is not extensively metabolized by the cytochrome P450 system, and therefore its metabolism is not likely to be influenced by inducers or inhibitors. Potential interactions are listed in Table 3 and Table 15. Both oxcarbazepine and MHD have mild inhibitory effects on CYP 2C19 and a modest inducing effect on CYP 3A4 and CYP 3A5.<sup>10</sup>

### Dosing

See Table 16 for dosing guidelines for oxcarbazepine.<sup>10</sup> For adjunctive therapy in adults, begin dosing at 600 mg, divided BID; then increase dosing by 600 mg daily at weekly intervals. The recommended dose for adjunctive therapy is 1200 mg/day, because of side effects at higher doses. For initiation of monotherapy in patients not previously given antiepileptic drugs, begin with 600 mg/day, divided BID; increase the drug by 300 mg every 3 days to a maximum of 2400 mg/day. In patients being converted to oxcarbazepine monotherapy from other antiepileptic drugs, the starting dose is 600 mg/day, divided BID, with a simultaneous dose reduction of concomitant

antiepileptic drugs and complete withdrawal achieved in 3 to 6 weeks. Oxcarbazepine dosing may be increased by 600 mg/day each week until the recommended maintenance dose of 2400 mg/day is achieved in patients on monotherapy.

Pediatric dosing in patients aged 4 to 16 years is 8 to 10 mg/kg per day, divided BID, with a maximum of 600 mg/day upon initiation. Achievement of the recommended maintenance dose is accomplished over a 2-week period through a titration based on patient weight (20–29 kg = 900 mg/day; 29–39 kg = 1200 mg/day; >39 kg = 1800 mg/day). In patients with renal impairment (CrCl ≤ 30 mL/min), initiate dose at 50% of recommended guidelines, and titrate slowly.<sup>10</sup>

**Table 16.** Dosing Schedule for Oxcarbazepine<sup>10</sup>

|  | Starting Dose  | Maximum Dose   |
|--|--|--|
| Adult adjunctive therapy                   | 600 mg, divided BID.<br>Increase by 600 mg/day every week  | 1200 mg/day. Doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients cannot tolerate 2400 mg/day due to CNS side-effects with adjunctive therapy |
| Adult monotherapy                          | 600 mg, divided BID.<br>Increase by 300 mg/day every 3 days  | 1200 mg/day in patients not currently being treated with AEDs; 2400 mg/day in patients converted from other AEDs.  |
| Change from other AED to adult monotherapy | 600 mg, divided BID<br>Achieve withdrawal of concomitant AED in 3-6 weeks, while achieving maximum dose of oxcarbazepine in 2-4 weeks. | 2400 mg/day  |
| Pediatric dosing for ages 4-16 years       | 8-10 mg/kg per day, divided BID.<br>Maximum starting dose is 600 mg/day.<br>Increase to recommended maintenance dose over 2 weeks.     | Approximately 30 mg/kg per day   |
|  | 20-29 kg   | 900 mg/day   |
|  | 29-39 kg   | 1200 mg/day  |
|  | >39 kg   | 1800 mg/day  |
| Renal impairment (CrCl > 30 mL/min)        | Decrease by 50%  | Decrease by 50%  |

BID indicates twice a day; CNS, central nervous system; AEDs, antiepileptic drugs.

**Use in Pregnancy**

Oxcarbazepine is classified as pregnancy category C.<sup>10</sup>

**Clinical Monitoring**

Due to a potential for less drug interactions, oxcarbazepine patients switching from carbamazepine should have levels of concomitant antiepileptic drugs monitored. Therapeutic levels for oxcarbazepine itself have not been established. Although the manufacturer has no formal guidelines for laboratory monitoring, checking chemistries including sodium, liver function tests, thyroid tests, and CBC at baseline and periodically would be prudent.

**Place in Therapy**

Oxcarbazepine is approved for use as adjunctive and as monotherapy for partial seizures in adults, and as adjunctive therapy for partial seizures in children at least 4 years of age. Studies have demonstrated its efficacy in the management of generalized tonic-clinic seizures as well. Oxcarbazepine appears to be comparable in efficacy to carbamazepine, but is better tolerated. Therefore, although oxcarbazepine is more expensive than carbamazepine, it

may be particularly useful for patients intolerant to carbamazepine or patients receiving concomitant medications with a high potential for interaction with carbamazepine.<sup>10</sup>

.....  
**ZONISAMIDE (ZONEGRAN)**

**FDA-Approved Indication**

Zonisamide (Zonegran; Elan Pharmaceuticals, San Francisco, Calif) was approved in March 2000 for the add-on treatment of partial seizures in patients 16 years and older.<sup>13</sup>

**Mechanism of Action**

The mechanism of action elucidated from in vitro studies suggests zonisamide blocks the sustained repetitive firing of voltage-sensitive sodium channels and reduces voltage-dependent inward T-type Ca<sup>2+</sup> currents to stabilize neuronal membranes and suppress hypersynchronization. In vitro binding studies revealed that zonisamide binds to the GABA-benzodiazepine receptor complex; however, binding does not induce any changes in chloride flux, or potentiate the synaptic activity of GABA. Zonisamide is also a weak inhibitor of carbonic anhydrase; however,

this effect is not thought to be a contributing factor to the antiseizure activity of zonisamide.<sup>15</sup>

### Pharmacokinetics

See Table 2 for a pharmacokinetic summary and comparison with other agents. Following a 200-mg to 400-mg oral dose, peak plasma concentrations of 2 to 5 µg/mL in normal volunteers occur within 2 to 6 hours. Food delays time to  $C_{max}$ , occurring at 4 to 6 hours, but food does not alter bioavailability. Zonisamide binds extensively to erythrocytes, with concentrations in RBCs 8-fold higher than in the plasma. The pharmacokinetic of zonisamide are dose proportional in the 200-mg to 400-mg range, but the  $C_{max}$  and AUC increase disproportionately at 800 mg, perhaps because of saturable binding of zonisamide to RBCs. Steady state concentrations are achieved within 14 days of dose initiation or dose change. The elimination  $t_{1/2}$  in plasma is 63 hours, and 105 hours in RBCs. The volume of distribution is 1.45 L/kg after a 400-mg oral dose. At concentrations of 1 to 7 µg/mL, zonisamide is approximately 40% bound to plasma proteins. Protein binding of zonisamide is unaffected by therapeutic concentrations of phenytoin, phenobarbital, or carbamazepine.<sup>13</sup>

Zonisamide is eliminated chiefly in the urine as the parent drug and the glucuronide metabolite, and is reduced by the CYP 3A4 isoenzyme to the 2-sulfamoylacetophenol, which accounts for 50% of the excreted dose. Zonisamide does not induce its own metabolism. Plasma clearance is 0.3 to 0.35 mL/min per kilogram for patients not taking enzyme-inducing antiepileptic drugs and increased to 0.5 mL/min per kilogram for patients currently taking enzyme-inducing antiepileptic drugs. Renal plasma clearance is 3.5 mL/min, whereas clearance from RBCs is 2 mL/min.<sup>13</sup>

### Clinical Trials

Zonisamide has been administered to 1598 individuals thus far during all clinical trials, only some of which were placebo-controlled. The effectiveness of zonisamide as adjunctive therapy has been established in 3 multicenter, double-blind, placebo-controlled, 3-month clinical trials (2 domestic, 1 European) in 499 patients with refractory partial onset seizures with or without secondary generalization. Each patient had a history of 4 or more partial onset seizures per month despite receiving 1 or 2 antiepilepsy drugs at therapeutic concentrations. The primary measure of effectiveness was median percent reduction from baseline in partial seizure

frequency. The secondary measure was proportion of patients achieving at least a 50% reduction in seizures from baseline responders. The results described are for all partial seizures in the intent-to-treat populations<sup>13,61,62</sup> (Table 17).

In the first study (n = 203), all patients had a 1-month baseline observation period, then received placebo or zonisamide on 1 of 2 dose escalation regimens: 100 mg/day for 5 weeks, 200 mg/day for 1 week, 300 mg/day for 1 week, and then 400 mg/day for 5 weeks; or 100 mg/day for 1 week, followed by 200 mg/day for 5 weeks, then 300 mg/day for 1 week, then 400 mg/day for 5 weeks. This design allowed a comparison of 100 mg with placebo over weeks 1 through 5 and a 200 mg with placebo over weeks 2 through 6; the primary comparison was 400 mg (both escalation groups combined) with placebo over weeks 8 through 12. The total daily dose was given divided BID. Statistically significant treatment differences favoring zonisamide were seen for doses of 100, 200, and 400 mg/day.<sup>13,61,62</sup> Only patients who reached week 8 for study 1 are included in the Table 17.

In the second (n = 152) and third (n = 138) studies, patients had a 2-month to 3-month baseline, and then were randomly assigned to placebo or zonisamide for 3 months. Zonisamide was initiated at 100 mg/day for the first week, 200 mg/day for the second week, then 400 mg/day for 2 weeks, after which the dose could be adjusted as necessary to a maximum dose of 20 mg/kg daily or a maximum plasma level of 40 µg/mL. In the second study, the total daily dose was given as BID dosing; in the third study, it was given as a single daily dose. The average final maintenance doses received in the studies were 530 mg/day in the second study and 430 mg/day in the third study. Both studies demonstrated statistically significant differences favoring zonisamide for doses of 400 to 600 mg/day, and no apparent difference was noted between once-daily and twice-daily dosing. Analysis of the data during the first 4 weeks of titration demonstrated statistically significant differences favoring zonisamide at doses between 100 and 400 mg/day. The second study has not been published at the time this article was written.<sup>13</sup> Patients in the third study had to receive at least 7 days of treatment to be included in the statistical analysis.<sup>62</sup>

### Adverse Reactions

*Cautions With Zonisamide.* Of 991 patients with epilepsy treated during the development of zonisamide, clinically possible or confirmed kidney

**Table 17.** Median % Reduction in All Partial Seizures and % Responders in Primary Efficacy Analyses with Zonisamide: Intent-To-Treat Analysis<sup>13,61,62</sup>

| Study  | Median % Reduction in Partial Seizures |         | % Responders |         |
|--|--|---------|--------------|---------|
|  | Zonegran                               | Placebo | Zonegran     | Placebo |
| Faught et al (study 1) <sup>61</sup>                       | n = 98                                 | n = 72  | n = 98       | n = 72  |
| Weeks 8-12   | 40.5*                                  | 9.0     | 41.8*        | 22.2    |
| Zonisamide prescribing information (study 2) <sup>13</sup> | n = 69                                 | n = 72  | n = 69       | n = 72  |
| Weeks 5-12   | 29.6*                                  | -3.2    | 29.0         | 15.0    |
| Schmidt et al (study 3) <sup>62</sup>                      | n = 67                                 | n = 66  | n = 67       | n = 66  |
| Weeks 5-12   | 27.2*                                  | -1.1    | 28.0*        | 12.0    |

\* $P < .05$  compared to placebo.

stones (by clinical symptomatology or sonography) developed in 40 (4.0%). Analyzed stones were composed of calcium or urate salts. Therefore, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors for renal calculi. Zonisamide should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in blood urea nitrogen or serum creatinine concentrations. A statistically significant 8% mean increase in baseline serum creatinine and blood urea nitrogen concentration has also been reported in clinical studies. Zonisamide should not be used in patients with an estimated glomerular filtration rate of less than 50 mL/min, as there has been insufficient experience concerning drug dosing and toxicity.<sup>13</sup>

**Contraindications.** Because zonisamide is a sulfonamide, it is contraindicated in patients with a history of hypersensitivity to other sulfonamide agents. Potentially fatal reactions to sulfonamides have occurred as a result of severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necroses, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately.<sup>13</sup>

**Warnings.** Seven deaths from severe rash (ie, Stevens-Johnson syndrome and toxic epidermal necrolysis) were reported in the first 11 years of marketing in Japan. All of the patients were receiving

other drugs in addition to zonisamide. In postmarketing experience from Japan, 49 cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported (reporting rate of 46/1 000 000 patient-years of exposure). The incidence of reported incidences of rash is most likely an underestimate of true incidences because of the low frequency of adverse drug reporting. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been confirmed in the United States, European, or Japanese development programs. In the US and European randomized, controlled trials, 6 of 269 (2.2%) zonisamide patients discontinued treatment because of rash compared with none in placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12.0 events per 1000 patient-years of exposure). Rash normally had an early onset during treatment course, with 85% reported within 16 weeks in the US and European studies and 90% reported within 2 weeks in Japanese studies. There was no apparent relationship of dose to rash occurrence.<sup>13</sup>

Two confirmed cases of aplastic anemia and 1 confirmed case of agranulocytosis were reported during the first 11 years of marketing in Japan. No cases of aplastic anemia and 2 confirmed cases of agranulocytosis were reported during the US, European, or Japanese development programs. The information is inadequate to determine if a relationship exists between dose and duration of treatment with any of these hematologic effects.<sup>13</sup>

In clinical trials, other adverse events reported more often than placebo and occurring in at least 5%

of patients given zonisamide include the following: somnolence (17%), anorexia (13%), dizziness (13%), headache (10%), agitation (9%), nausea (9%), fatigue (8%), depression (6%), insomnia (6%), ataxia (6%), confusion (6%), difficulty concentrating (6%), difficulty with memory (6%), abdominal pain (6%), diplopia (6%), diarrhea (5%), dyspepsia (5%), and speech abnormalities (5%).<sup>13</sup>

### Drug Interactions

See Table 3 for a summary of drug interactions. Zonisamide had no appreciable effect on steady-state plasma concentrations of phenytoin, carbamazepine, or valproic acid during clinical trials. Zonisamide did not inhibit cytochrome P450 enzymes and, therefore, is not expected to interact with drugs metabolized by cytochrome pathways. The  $t_{1/2}$  of zonisamide after a 400-mg dose in patients concurrently taking phenytoin carbamazepine or phenobarbital ranged from 27 to 38 hours; the  $t_{1/2}$  of zonisamide in patients on valproate was 46 hours. Concurrent medication with drugs that either induce or inhibit CYP 3A4 would be expected to alter serum concentrations of zonisamide.<sup>13</sup>

### Dosing

Initial doses are 100 mg daily. The dose may be increased 100 mg at 2-week intervals, up to a maximum of 400 mg/day. Controlled trials suggest zonisamide doses of 100 to 600 mg/day are effective. However, there is no suggestion of increasing response above 400 mg/day, and there is little experience with doses of more than 600 mg/day.<sup>13</sup>

### Use in Pregnancy

Zonisamide is classified as pregnancy category C.<sup>13</sup>

### Clinical Monitoring

Currently, laboratory-monitoring parameters have not been established for zonisamide. Zonisamide is indicated as add-on therapy for partial seizures in adults, and may have a place in therapy for the treatment of generalized seizures.<sup>13</sup>

### Place in Therapy

Zonisamide, although approved only for the adjunctive treatment of partial seizures in the United States, has been used elsewhere for generalized tonic-clonic seizures, myoclonic epilepsy, refractory absence seizures, Lennox-Gastaut syndrome, and infantile spasms. It is a sulfonamide with

a potential for serious dermatologic and hematologic adverse reactions, however. Additionally, zonisamide is associated with cognitive side effects such as psychomotor slowing, difficulty with concentration, word finding problems, and psychiatric side effects such as psychosis, mania, and depression.<sup>51</sup>

### CONCLUSION

No single antiepileptic drug is appropriate in all clinical situations. Epileptologists agree that proper seizure diagnosis and classification is important in individualizing pharmacotherapy. The seriousness of the acute seizure situation will dictate whether intravenous loading of the traditional status epilepticus protocol drugs (phenytoin, fosphenytoin, etc) is necessary or not. Subsequent therapy decisions should be made on a variety of specific factors such as seizure type(s), onset of drug effect, the presence of renal or hepatic disease, the possibility of drug or disease state interactions, the possibility of pregnancy, the age of the patient, compliance issues, substance abuse history, and prior history of antiepileptic drug use. Many of the new drugs are approved only for adjunctive use; thus, polypharmacy issues become a factor as well.

A recent review on the safety and efficacy of antiepileptic drugs found little difference between the drugs studied.<sup>63</sup> Researchers have analyzed these parameters by meta-analysis studies.<sup>64,65</sup> In 1 study,<sup>64</sup> efficacy was defined as at least a 50% reduction in seizure frequency and adverse events as a withdrawal from the study for any reason. They identified 20 studies and 3883 patients who were evaluated with one of the following: gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide. All medications were superior to placebo for controlling seizures. Only gabapentin and lamotrigine showed withdrawal rates similar to placebo. The other drugs had withdrawal rates greater than placebo. Thus, no statistically significant differences were found in the effectiveness or toxicity of these agents.<sup>64</sup>

The other meta-analysis was a review of studies with gabapentin, tiagabine, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and vigabatrin, and defined success rate as at least 50% fewer complex partial seizures on newer antiepileptic drugs or placebo.<sup>65</sup> Overall improvement was the success on antiepileptic drug minus the success on placebo to control for the variable response to placebo. Success rates are quoted as 11% for gabapentin, 15% for

tiagabine, 16% for lamotrigine, 27% for levetiracetam, 28% for oxcarbazepine, 28% for topiramate, and 30% for vigabatrin.<sup>65</sup> Calculated adverse effect rates using a cumulative toxicity scale similar to the one used in the VA Collaborative Studies on epilepsy (antiepileptic drug minus placebo) were 17 for levetiracetam, 45 for gabapentin, 52 for tiagabine, 89 for vigabatrin, 107 for oxcarbazepine, 122 for lamotrigine, and 180 for topiramate. Cumulative adverse drug effect profiles do not provide direct comparisons between drugs, but a pattern of difference in the overall impact can be seen.<sup>65</sup> All of these issues must be considered and the most appropriate choice made to optimize therapy.

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## CPE QUIZ

### CONTINUING PHARMACY EDUCATION



This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-03-210-H01. This course expires March 31, 2004.

#### Instructions

After reading the article "Review of the Newer Antiepileptic Drugs," select the best answer to each of the following questions.

#### 1) Oxcarbazepine does not undergo autoinduction because

- a) It is metabolized by different cytochrome P450 enzymes than it induces.
- b) It is not dependent on the P450 pathway.
- c) It is primarily eliminated by the kidneys without undergoing metabolism.
- d) It is highly protein bound.

#### 2) Which one of the following antiepileptic drugs is not affected by food?

- a) oxcarbazepine
- b) levetiracetam
- c) tiagabine
- d) zonisamide

#### 3) The side-effect profile of oxcarbazepine is similar to that of carbamazepine. One side effect that is more pronounced with oxcarbazepine as compared to carbamazepine is:

- a) fatigue
- b) somnolence
- c) nystagmus
- d) hyponatremia

#### 4) Studies show that oxcarbazepine is effective as adjunctive therapy in seizure control for patients as young as:

- a) 6 months
- b) 4 years
- c) 12 years
- d) 18 years

#### 5) Which of the following is true of zonisamide?

- a) Binding to red blood cells may affect the kinetics of the drug.
- b) Food will increase the  $C_{max}$  by decreasing bioavailability.
- c) The kinetics of zonisamide are dose proportional throughout the dosing range.
- d) Zonisamide is eliminated entirely unchanged in the urine.

#### 6) It is important to assess and monitor renal function in patients treated with zonisamide because:

- a) 4% of patients in trials developed kidney stones
- b) statistically significant increases in serum creatinine and blood urea nitrogen have been seen in clinical studies
- c) decreased renal function could place the patient at greater risk for side effects and toxicities
- d) all of the above

(CPE questions continued on following page)

### Review of the Newer Antiepileptic Drugs

ACPE Program Number: 064-999-03-210-H01

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Please circle your answers:

- |            |             |             |             |
|------------|-------------|-------------|-------------|
| 1. a b c d | 6. a b c d  | 11. a b c d | 16. a b c d |
| 2. a b c d | 7. a b c d  | 12. a b c d | 17. a b c d |
| 3. a b c d | 8. a b c d  | 13. a b c d | 18. a b c d |
| 4. a b c d | 9. a b c d  | 14. a b c d | 19. a b c d |
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## CPE QUIZ

7) Because zonisamide is a sulfonamide, potentially fatal reactions to the drug can occur, including all of the possibilities listed below **except**:

- a) fulminant hepatic necrosis
- b) agranulocytosis
- c) pulmonary toxicity
- e) Stevens-Johnson syndrome / toxic epidermal necrolysis

8) A meta-analysis by Marson et al has shown that:

- a) gabapentin is more effective than the other agents.
- b) vigabatrin is more effective than the other agents.
- c) gabapentin is more toxic than the other agents.
- d) No statistically significant differences were found in the effectiveness or toxicity of the agents discussed in this article.

9) A meta-analysis by Cramer et al indicated that:

- a) vigabatrin seems to be more effective than the other agents.
- b) tiagabine seems to be more effective than the other agents.
- c) oxcarbazepine has the greatest adverse effect rates.
- d) all of these agents were equally effective

10) Which of the following would most likely result in a significant drug interaction?

- a) carbamazepine plus lamotrigine
- b) carbamazepine plus gabapentin
- c) levetiracetam plus lamotrigine
- d) oxcarbazepine plus gabapentin

11) The consumption of a high-fat meal can prolong the half-life and concentration maximum in which of the following antiepileptic drugs?

- a) gabapentin
- b) topiramate
- c) lamotrigine
- d) tiagabine

12) Which of the following side effects of lamotrigine can be life threatening?

- a) insomnia
- b) rash
- c) dyspepsia
- d) nausea

13) What is the recommended starting dose of gabapentin in adults who experience partial seizures?

- a) 100 mg BID
- b) 100 mg TID
- c) 300 mg BID
- d) 300 mg TID

14) Which of the following antiepileptic drugs inhibits carbonic anhydrase and therefore increases the likelihood of kidney stones?

- a) oxcarbazepine
- b) levetiracetam
- c) lamotrigine
- d) topiramate

*(CPE questions continued on following page)*

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### CPE PROGRAM EVALUATION (064-999-03-210-H01)

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

*Please circle your answers:*

|  |                |              |                 |                   |
|--|----------------|--------------|-----------------|-------------------|
| My pharmacy practice setting is:                               | Independent    | Chain        | Hospital        | Consultant        |
| The objectives of the lesson were achieved:                    | Yes            | No           |                 |                   |
| The quality of presentation of the material was:               | Excellent      | Good         | Fair            | Poor              |
| The information presented will be useful to me in my practice. | Strongly agree | Mildly agree | Mildly disagree | Strongly disagree |

How long did it take you to read the material and respond to the Continuing Education questions: (Please specify the number of hours.)

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## CPE QUIZ

15) Which of the following antiepileptic drugs has not yet proven useful as a treatment of generalized (or secondarily generalized) seizures?

- a) oxcarbazepine
- b) topiramate
- c) lamotrigine
- d) gabapentin

16) Which of the following antiepileptic drugs is not removed by hemodialysis and is not primarily renally eliminated?

- a) lamotrigine
- b) topiramate
- c) levetiracetam
- d) tiagabine

17) Which of the following is the total targeted daily dose for topiramate?

- a) 100 mg
- b) 200 mg
- c) 400 mg
- d) 800 mg

18) Which of the following antiepileptic drugs is not metabolized and therefore does not undergo enzyme induction or inhibition by CYP 450?

- a) tiagabine
- b) topiramate
- c) zonisamide
- d) gabapentin

19) In a well-controlled patient, what is the correct method of discontinuing lamotrigine?

- a) Stop the dose without tapering.
- b) Stepwise reduction over seven days.
- c) Stepwise reduction over two weeks.
- d) Stepwise reduction over one month.

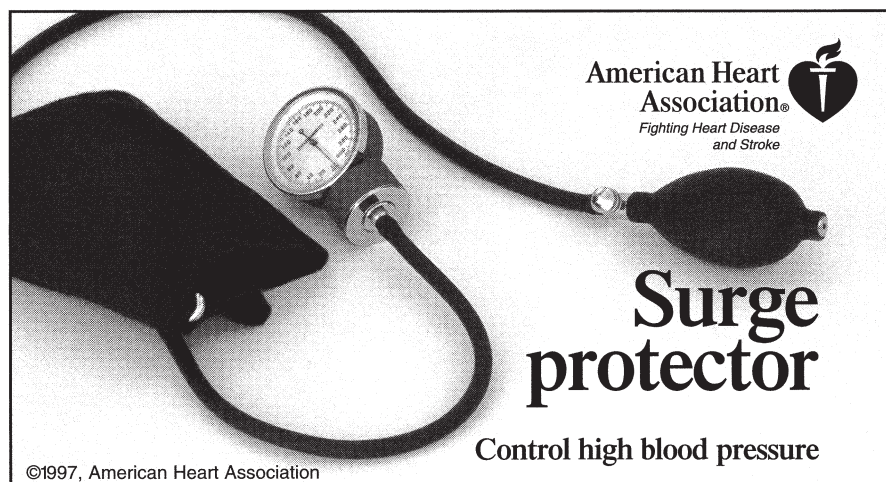
20) Gabapentin has been found to be useful in the treatment of other disease states, including:

- a) hypertension
- b) hyperlipidemia
- c) osteoporosis
- d) neuropathic pain syndromes

Please fill out the University of Tennessee College of Pharmacy program evaluation that accompanies this quiz (page 278).

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