

# Toxicology News

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## New Anti-Epileptic Drugs Feature Fewer Side Effects

*By Ginger Baker*

**S**everal new anti-epileptic drugs are now widely prescribed throughout the United States. These agents can replace older anti-seizure medications, including barbiturates, phenytoin, valproic acid, and carbamazepine. In addition, some of these new medications have found widespread use as adjunctive agents and serendipitous use as novel therapeutics.

### Gabapentin (Neurontin)

Gabapentin is an analog of the major inhibitory neurotransmitter gamma aminobutyric acid (GABA). However, the drug does not interact with the GABA receptor, is not metabolized in vivo to GABA, and does not affect GABA uptake or breakdown. Gabapentin is a synthetic derivative of cyclohexane acetic acid. The Food and Drug Administration (FDA) approved it in December 1993. Although the exact mechanism of action is unclear, it has been hypothesized that gabapentin increases GABA synthesis.

Gabapentin is currently used as an adjunctive anticonvulsant in the treatment of partial seizures in adults with epilepsy, in patients 12 years and older without secondary generalized seizures, and in children 3–12 with partial seizures. It is currently prescribed for postherpetic neuralgia in adults, and it is presently being evaluated for relief of neuropathic pain including peripheral neuropathy caused by diabetes mellitus and pain caused by dysethesias and spasticity in multiple sclerosis. Studies are in progress to determine its efficacy in treating tremors and bipolar disorder and in preventing migraines. Recently, recreational drug users have shown an interest in it and there are anecdotal reports of it being used for the treatment of gamma-hydroxybutyrate (GHB) withdrawal ([www.erowid.org](http://www.erowid.org)).

Gabapentin is administered in oral doses of 100–400 mg of free acid. Daily doses are typically in the 900–1800 mg range. Blood concentrations following a 400-mg dose average 3.4 µg/mL. Gabapentin is not metabolized, does not bind to plasma proteins, and is eliminated entirely by renal excretion. The half-life is five to seven hours. Pharmacological activity is due to the parent drug.

Gabapentin does not induce microsomal liver enzymes; however, pharmacokinetic interactions with felbamate were documented in a retrospective examination. This study found a 37% decrease in felbamate clearance. In addition, a possible delayed drug interaction resulted in a significant increase in phenytoin serum concentration in one patient.

Plasma concentrations of approximately 40 µg/mL have been associated with clinical efficacy. Documented adverse reactions include somnolence, dizziness, ataxia, fatigue, and nystagmus. Symptoms of acute overdose include slurred speech, lethargy, diarrhea, ptosis, and double vision. Patients should be advised of the potential effects of the drug on mental and psychomotor performance. Analgesic mechanisms have not yet been elucidated; however, studies show a reduction of allodynia and hyperalgesia in these patients.

Laboratory analysis has been reported using high performance liquid chromatography (HPLC) and gas chromatography with flame ionization detection (GC-FID) with detection limits of 0.02 µg/mL and 0.2 µg/mL, respectively.

### Lamotrigine (Lamictal)

Lamotrigine is a dichlorophenyltriazine derivative that is structurally unrelated to existing anti-

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## Online Data Sources Provide Information on Drug Trends

By Glynnis Ingall

A number of information sources provide timely statistical data on the prevalence of drug abuse, the populations affected, and the substances most frequently abused. These sources provide current drug abuse statistics along with data from previous years, allowing for monitoring of trends.

This article reviews three drug abuse data sources: the Drug Abuse Warning Network (DAWN), the National Household Survey on Drug Abuse (NHSDA), and the Drug Testing Index of Quest Diagnostics. These data sources differ in the types of information they present.

The DAWN data is derived from reports of drug-abuse-related cases from emergency departments and medical examiner offices. Therefore, DAWN provides an early indicator of the types of drug abuse that result in serious health consequences, either an emergency department (ED) visit or death.

The NHSDA is an interview-based survey of a large representative sampling of the U.S. population. The results are extrapolated to determine incidence and prevalence of drug, alcohol, and tobacco use, and are further correlated with the extensive demographic and health and lifestyle questions included in the survey. The NHSDA has been collecting data since 1971, so the information can be used to track long-term substance abuse trends. The prevalence information is important for planning the resource allocation for substance abuse prevention and treatment services.

The Quest Drug Testing Index is confined to workplace drug testing and is of greatest interest to employers, medical review officers, and laboratories performing workplace drug testing.

Substance abuse and mental health research data from DAWN, NHSDA, and other government sources can be obtained directly from the Substance Abuse and Mental Health Data Archive, a database formatted to allow for online analysis. The archive provides timely release of this information so individuals can perform their own analyses, statistical evaluation, and interpretation (1).

### Drug Abuse Warning Network (DAWN)

The Office of Applied Studies of the Substance Abuse and Mental Health Services Administration (SAMHSA) manages the DAWN program. DAWN obtains data from emergency departments and medi-

cal examiner/coroner offices. Reporters from the participating facilities review patient files and identify cases in which drug use was a factor. The ED data includes only cases associated with intentional drug use. It excludes adverse effects related to appropriate use of medications or accidental overdoses. Alcohol is reported only when it is used together with another reportable drug.

Patient demographic information, drugs involved, and routes of administration are reported for each drug-related case. The database also includes the reason for the visit and the discharge status for the ED patients and the cause and manner of death for the medical examiner cases. Recently, DAWN improved its data collection and analysis methods in order to publish its findings in a more timely manner. A new coding system tracks more drugs, including those recently approved by the FDA. DAWN does not provide an estimate of the prevalence of drug abuse in the population. The information from this survey is best used to ascertain which abused drugs may cause significant health risks as reflected by ED visits or deaths.

The latest statistical analysis and interpretative summaries of the DAWN data are available at the DAWN website: [www.DAWNinfo.net](http://www.DAWNinfo.net). A good summary of drug abuse trends from DAWN is in the recently released publication, *Emergency Department Trends from the Drug Abuse Warning Network, Final Estimates 1994–2001* (2). A few of the major trends noted in this publication are listed below:

- There was a significant increase (30%) in drug mentions from 1994–2001.
- Seven drug categories account for 82% of mentions: alcohol-in-combination, cocaine, heroin, marijuana, benzodiazepines, antidepressants, and analgesics. Alcohol-in-combination is the most frequent category reported.
- Significant increases in ED mentions occurred for marijuana (176%), cocaine (35%), heroin (47%), and alcohol-in-combination (36%), although the use of heroin and alcohol-in-combination appear to have plateaued in recent years.
- ED mentions of the “club” drugs, that is, methylenedioxymetamphetamine (MDMA), gamma-hydroxybutyrate (GHB), and ketamine, increased dramatically from 1994 to 2001, but the total number of reports of these drugs is still relatively small compared with the major drugs of abuse.
- The total number of benzodiazepine reports increased significantly from 1994–2001. In recent years, dramatic increases were seen in the use of the narcotics/analgesics oxycodone (325%),

methadone (230%), and hydrocodone (130%). However, mentions of codeine-containing products declined significantly.

- Monitoring of ED mentions of drugs recently approved by the FDA revealed the following agents that were not reported in 1994, but grew to over 1000 mentions by 2001: citalopram, mirtazapine, nefazodone, olanzapine, quetiapine, and tramadol.

Death information from DAWN is presented in the publication, *Mortality Data from the Drug Abuse Warning Network, 2001* (3). In 2001, DAWN received drug data from death investigation reports from 128 jurisdictions in 42 metropolitan areas. These statistics include deaths that were reported to be drug-related. A few trends in mortality data from this report follow:

- Heroin/morphine, cocaine, and alcohol-in-combination with other drugs were the agents most commonly reported in drug-related deaths.

- Most deaths involved more than one drug. Alcohol in combination with cocaine, heroin/morphine, or other narcotic analgesics; cocaine and heroin/morphine; and other narcotic analgesics together with heroin/morphine were the most frequent drug combinations reported to DAWN.

- Most drug-associated deaths occurred in individuals older than 25 years. Males accounted for the majority of these deaths.

- Overall, 48% of drug deaths were reported as accidental, 17% due to suicide, and 35% due to undetermined or other causes.

- Deaths due to methamphetamine were concentrated in the West and Midwest. The club drugs accounted for very few deaths.

- The most frequently reported prescription and over-the-counter drugs associated with deaths include diazepam, methadone, codeine, hydrocodone, oxycodone, and diphenhydramine.

### National Household Survey on Drug Abuse

The NHSDA is a project of SAMHSA. In this survey, about 70,000 people, 12 years or older, are interviewed about their use of alcohol, illicit drugs, and tobacco. The survey is restricted to civilian, non-institutionalized individuals. Residents from all 50 states are included. The large size of the survey allows for relatively accurate prevalence and incidence projections. The 2001 survey included new questions related to mental health status and treatment. The data is extensively analyzed and correlated with age, gender, ethnicity, and geographic region, among others. The latest information from this survey is available electronically at the SAMHSA website. The preliminary report of the 2001 NHSDA was released in

September 2002 as *The Office of Applied Studies, 2001 National Household Survey on Drug Abuse (NHSDA) Highlights* (4). A summary of the findings from the 2001 survey related to nonmedical use of prescription drugs is also available (5). A few of the notable findings from these reports are summarized below:

- In 2001, an estimated 15.9 million U.S. residents (7.1% of the population) 12 years or older used illicit drugs, compared with 6.3% of the population in 2000.

- Of the major drugs of abuse, marijuana, cocaine, and non-medical use of analgesics and tranquilizers showed statistically significant increases from 2000 to 2001.

- There is increasing abuse of drugs by youths aged 12–17 years. About 10.8% of youths used illicit drugs in 2001, compared with 9.7% in 2000. Illicit drug use by adults aged 26 and over showed no change.

- There were significant increases in those reporting that they had ever used MDMA, 8.1 million in 2001 compared with 6.4 million in 2000.

- Those reporting that they had ever used oxycotin for non-medical purposes increased more than fourfold from 1999–2001 (221,000 in 1999 compared with 957,000 in 2001).

- About 10% of the population reported driving under the influence of alcohol during 2001. There were 10.1 million underage drinkers (ages 12–20), which represents 28.5% of this age group.

- About 30% of the population used tobacco products in 2001. Tobacco use among youths continued to show a downward trend. The current tobacco use rate is 13% among 12–17-year-olds.

- About 16.6 million people (7.3% of the population) were classified with dependence on or abuse of alcohol and/or drugs in 2001, a significant increase from the 2000 estimate of 14.5 million (6.5% of the population).

- Individuals classified as having serious mental illness represent 7.3% of the population, and these individuals were more than three times more likely to have drug abuse problems than adults without mental illness.

- Overall, 16% of the U.S. population reported non-medical use of prescription drugs at least once in their lifetime.

- First time non-medical use of prescription drugs is reported primarily by the younger population (ages 12–25). The number of new users in this age group has increased significantly in recent years.

- Prescription pain relief medications were the most common drugs reported to be used non-

medically by youths and young adults.

In 2003, the survey name will be changed to the National Survey on Drug Use and Health (NSDUH).

### Quest Drug Testing Index

Trends in positivity rates among U.S. workers can be assessed from the review of data collected by laboratories performing workplace drug tests. Quest Diagnostics publishes its Drug Testing Index on a regular basis online (6). Another source of data about substance abuse among U.S. workers is the NHSDA survey. The summary of the year 2000 NHSDA work force findings can be accessed at [www.DrugAbuseStatistics.samhsa.gov](http://www.DrugAbuseStatistics.samhsa.gov) under the title *Substance Use, Dependence or Abuse among Full Time Workers* (7).

The Quest workplace testing database is large. In 2002, the company performed more than 7 million workplace drug tests. In addition to combined work force reports, the data is also presented separately for the federally mandated, safety-sensitive work force and for the general work force. Annual positivity rates are reported along with data from prior years in order to monitor trends.

It should be noted that most of the workplace testing was performed as pre-employment screening and that this testing covers relatively few drugs or drug classes. Federally mandated programs generally test for amphetamines, marijuana, cocaine, opiates, and PCP. In general work force testing, these additional drug classes are often included in the test panels: benzodiazepines, barbiturates, methadone, and propoxyphene.

The overall drug positivity rates, as well as rates for individual drugs, are also displayed graphically on U.S. maps according to three-digit zip codes. These maps provide a quick visual guide to regional differences in drug test positivity rates. A few highlights from the Quest Drug Testing Index and the NHSDA work force report are reported below:

- The Quest report shows that the annual combined work force positivity rates have declined from 13.6% in 1988 to 4.4% in 2002, the lowest positive rate since Quest first began reporting its statistics 15 years ago. However, some of the decline in positivity rates may reflect the use, in recent years, of higher immunoassay cutoff concentrations for some drug classes. Generally, the rate of drug test positivity seems to have plateaued at a steady 4.6–4.8% over the past five years.

- The rate of drug use reported by U.S. workers in 2000 to NHSDA was considerably higher than the 4.7% positivity rate reported by Quest. In the 2000 NHSDA survey, 7.8% of full-time workers reported illicit drug use and 8.1% reported heavy

alcohol use in the past month. About 1.9% indicated that they were dependent upon or had abused illicit drugs and 7.4% were dependent on or had abused alcohol during the past year. The differences in the positivity rates may be due to a number of factors: The Quest data comes primarily from pre-employment drug tests, while the NHSDA data is self-reported, covers a longer time period, and includes more drug categories. The NHSDA data suggests that substance abuse is still a significant problem in the U.S. work force.

- The Quest data shows that the federally mandated work force has a lower positivity rate (2.5% in 2002) than the general work force (4.8%).

- The 2002 Quest combined U.S. work force data reveals that marijuana is by far the most common drug detected (57.6% of all drug positives). Cocaine represents 14.6%, amphetamines 7.1%, opiates 5.5%, benzodiazepines 4.5%, propoxyphene 3.5%, barbiturates 2.9%, methadone 0.9%, and PCP 0.6% of the total drug positives.

- The Quest data from the five-year period 1997–2002 showed slight upward trends in positive rates (as a percentage of all drug tests) for amphetamines (0.20%–0.73%) and for propoxyphene (0.29%–0.73%). During this five-year period, the positive rate for amphetamines (which includes both amphetamine and methamphetamine) increased 70% and the positive rate for propoxyphene more than doubled. The upward trend in the amphetamine class positives is most likely due to the growth in the illegal manufacture of this drug in the United States. Workplace drug-testing for opiates is generally targeted to detect codeine, morphine, and heroin use. Therefore, the workplace drug test data would not be expected to identify trends toward abuse of other types of narcotic analgesics. However, the increase in the positive rate for the narcotic analgesic propoxyphene in workplace programs may be part of the same trend toward increasing non-medical use of oxycodone and other prescription pain relief medications as reported by the NHSDA.

### Summary

The NHSDA and DAWN reports indicate that drug abuse is increasing in the U.S. population. These reports also show growing trends towards non-medical use of narcotic analgesics, oxycodone, and hydrocodone and increasing use of benzodiazepines and the club drugs, MDMA, GHB, and ketamine. Based on the Quest data, workplace drug-test positivity rates have declined steadily over the past decade, but the rate of decline has slowed in recent years. In contrast to this general trend is the sig-

nificant rise in positive rates for amphetamine/methamphetamine in the workplace. Because of the trends toward non-medical use of oxycodone and hydrocodone, employers may be requesting more tests for these opiates in addition to the routine codeine/morphine testing.

The trend toward increasing abuse of alcohol and drugs, especially among younger people, points to a growing need for effective treatment and prevention programs. It is disturbing to find that 10% of adults reported driving under the influence of alcohol during the previous year. This suggests that stronger legal, law enforcement, or other societal measures may be needed to eradicate this problem.

A discussion of the regional differences in drug use is beyond the scope of this review. However, it should be noted that all three of the drug abuse data sources mentioned in this review have sorted results by region. This information can be used by local authorities to target their efforts toward resolving drug abuse issues specific to their region.

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## New Anti-Epileptic Drugs

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epileptic drugs. The FDA approved it in December 1994 as an adjunctive agent for clinical treatment of partial seizures in adults and partial seizures of Lennox-Gastaut syndrome in both adults and children. Recent studies have also focused on its use to treat migraines. Although lamotrigine has not been shown to be effective in migraine prevention, it may inhibit migraine aura. The therapeutic dose ranges from 25–200 mg twice daily. Peak plasma levels range from 1–4 µg/mL with a half-life of 22 hours.

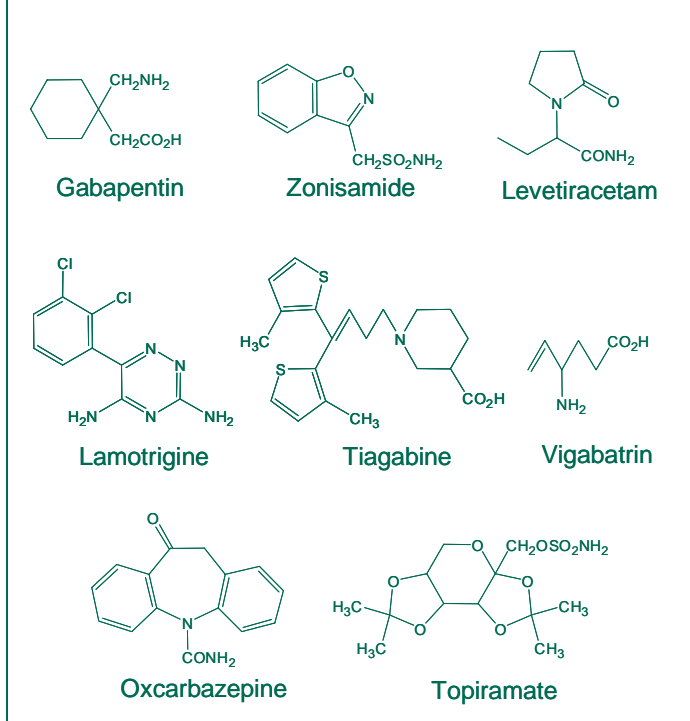
The exact mechanism of action is unclear; however, it has been suggested that the drug stabilizes neuronal membranes by blocking sodium channels that inhibit the release of the excitatory amino acid neurotransmitters glutamate and aspartate.

The drug is absorbed rapidly with little first-pass metabolism. Lamotrigine is extensively metabolized by conjugation with glucuronic acid, and its major metabolite is inactive. Competitive binding with valproic acid for the hepatic glucuronidation pathway results in a significant increase in lamotrigine's elimination half-life and a decrease in serum valproic acid concentrations. This interaction can be significant in terms of drug toxicity; fatalities have been reported in two patients who received both valproic acid and lamotrigine. It is recommended that lamotrigine be given at one-half the regular dose in patients who are treated with valproate.

In addition, serum lamotrigine concentrations can be reduced when patients are co-administered hepatic enzyme-inducing epileptic agents such as carbamazepine, phenytoin, and barbiturates. A similar potential drug interaction has been documented with chronic administration of acetaminophen, which can result in a decrease in the therapeutic effects of lamotrigine.

Adverse reactions include skin rash, dizziness, diplopia, blurred vision, headache, somnolence, ataxia, nausea, and vomiting. Hepatic hematologic disorders have also been reported. Rapid titration of lamotrigine can result in a risk of serious dermatological and nervous system effects, hepatic changes, and intravascular coagulation. Some patients developed a serious skin rash that resulted in hospitalization and cessation of drug use. Moreover, there is evidence of an increase in the risk of serious detrimental rash with concurrent administration of valproic acid and lamotrigine. Central nervous system depression has the potential to affect mental or psychomotor performance; patients should be ad-

Figure 1. Structures of new anti-epileptic drugs



vised that the drug might impair their ability to perform tasks requiring mental alertness and physical coordination.

Lamotrigine has been analyzed by reverse phase HPLC, liquid chromatography/mass spectrometry (LC/MS), and gas chromatography/mass spectrometry (GC/MS) with derivatization (silylation).

### Topiramate (Topamax)

Topiramate is a sulfamate-substituted monosaccharide, with broad-spectrum anti-epileptic activity. The FDA approved it in December 1996, and the normal dose is in the range of 400 mg/day in two divided doses. It is prescribed for the treatment of partial onset seizures and generalized tonic-clonic seizures in adults and children. Most recently the drug has been approved as adjunctive therapy for the treatment of Lennox-Gastaut syndrome. In addition, topiramate has been shown to be effective in reduction the severity and frequency of migraines.

Topiramate is rapidly absorbed and not extensively metabolized. About 70% of parent drug is found unchanged in urine after 21 hours. Peak plasma levels are achieved after two hours and steady-state plasma levels are achieved in four days.

Topiramate's mechanism of action has not been elucidated, although three possible pathways have been suggested. First, the drug may act as a sodium channel blocker to inhibit action potentials in depolarizing neurons. Second, topiramate may potentiate the inhibitory neurotransmitter GABA, thus increas-

ing the concentration of chloride ions in neurons. Finally, topiramate may act as an antagonist of kainite, which normally activates the excitatory amino acid glutamate receptor.

Adverse central nervous system effects include psychomotor deficits as well as cognitive side effects including memory, speech, and language difficulties. In addition, somnolence, dizziness, confusion, and mood disturbances have been noted. Recently, there have been reports of eye disorders including angle closure glaucoma and acute myopia.

Possible drug interactions with carbamazepine, hydantoins, and valproic acid have been documented. Carbamazepine, phenytoin, and valproic acid have all been shown to increase topiramate metabolism. Moreover, topiramate may decrease the breakdown of phenytoin and increase metabolism of valproate. Topiramate has been analyzed in biological specimens by GC with flame ionization and nitrogen phosphorus detection.

### Oxcarbazepine (Trileptal)

Oxcarbazepine is a 10-keto derivative of carbamazepine that is used in monotherapy or adjunctive therapy in adults and children with partial seizures. The FDA approved it in January 2000. Studies suggest oxcarbazepine is a useful alternative to carbamazepine because of fewer adverse reactions. Oxcarbazepine is available in tablets of 150 mg, 300 mg, and 600 mg and is given twice daily for a total dosage of 1200–2400 mg. It is also available as a 300 mg/5 mL oral suspension.

Its potency is due to oxidative transformation to its active metabolite, 10-hydroxy oxcarbazepine. The half-life is one to three hours for the parent drug and 11 to 15 hours for the active metabolite. Steady-state plasma concentrations of the active metabolite are achieved in two to three days in patients given the drug twice daily.

Oxcarbazepine's mechanism of action has not been elucidated; however, *in vitro* studies suggest that the drug and its metabolite inhibit sodium channels, which results in the stabilization of hyperexcited neural membranes, and thus, promotes a reduction of neuronal firing and a decrease of propagation of synaptic impulses. These actions are believed to be critical in the prevention of seizure dissemination in the brain. Moreover, high potassium conduction and high-voltage activated calcium channels may support the anticonvulsant activity of the drug.

Oxcarbazepine is rapidly reduced by cytosolic liver enzymes to its active metabolite, and this 10-monohydroxy metabolite is further metabolized with glucuronic acid to inactive metabolites. The drug

and its metabolites are cleared from the body primarily by renal excretion.

Adverse reactions include psychomotor effects, difficulty in concentration, fatigue, nausea, weakness, headache, dizziness, somnolence, ataxia, nystagmus, diplopia, hyponatraemia, and speech and language problems.

The parent and active metabolite have been analyzed using HPLC, GC/MS, and GC-FID.

### **Levetiracetam (Keppra)**

Levetiracetam is a pyrrolidone derivative that is chemically unrelated to other anti-convulsants. It was approved for use in the United States in November 1999. Levetiracetam is indicated for the adjunctive treatment of partial seizures and generalized seizures in adults. The initial treatment is a twice-daily administration of 500 mg for a total dosing of 1000 mg/day. Peak plasma levels are achieved after one hour, and the plasma half-life is approximately seven hours.

Levetiracetam does not appear to interact with known mechanisms involved in excitatory and inhibitory neurotransmission, and the anti-epileptic mode of action is unknown. However, studies indicate that it may act on synaptic plasma membranes of the central nervous system to inhibit burst firing without affecting normal neuronal action. Thus, the drug may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam is rapidly absorbed and not extensively metabolized. The major metabolite is inactive. Evaluation of interactions with other anti-epileptic drugs indicates a lack of major contraindications. Central nervous system effects include somnolence, weakness, nausea, and coordination difficulties. Other adverse reactions include infection, headache, and dizziness. In addition, patients should be advised of the effects of this drug on activities requiring alertness and coordination. Few overdose cases have been reported; the highest dose administered in clinical trials was 600 mg/day, and the only reported adverse effect was drowsiness.

### **Zonisamide (Zonegran)**

Zonisamide is a substituted 1,2-benzisoxazole-3-methanesulfonamide adjunctive anti-epileptic drug for the treatment of partial seizures in adults. The drug is unrelated to other anti-seizure medications.

The recommended dose is 400–600 mg per day. Steady-state plasma levels are achieved after two weeks of chronic use. The chronic therapeutic range is 10–40 µg/mL. The elimination half-life of unchanged parent drug has been reported to be 63

hours. Therapeutic monitoring is advised due to the drug's high binding affinity to erythrocytes.

The precise mechanism of action is unknown. However, the drug may exert influence by blocking sodium and calcium channels; therefore, the drug may decrease voltage-dependent transient inward currents. This activity may produce stabilization of neuronal membranes, which would result in the suppression of hypersynchronization. This cascade may occur as a result of zonisamide's affinity for the GABA/benzodiazepine ionophore complex.

Increased carbamazepine and phenytoin concentrations were noted in some patients concurrently prescribed zonisamide. Adverse reactions include somnolence, anorexia, dizziness, headache, nausea, agitation, weakness, and irritability. In addition, psychiatric symptoms including depression and psychosis have been noted. Rare hematological effects including aplastic anemia and agranulocytosis have been reported. Patients should be advised of effects on motor performance and cognitive abilities.

Laboratory analysis of parent drug has been performed using HPLC.

### **Tiagabine (Gabitril)**

Tiagabine is an adjunctive anti-seizure medication approved in the United States in September 1997. The drug is used for the treatment of partial seizures and secondary generalized seizures. The precise mechanism of action is unclear. Tiagabine is believed to enhance the activity of GABA by binding to receptor sites and inhibiting GABA uptake into presynaptic neurons, resulting in an increase in the neurotransmitter on postsynaptic cells. This action would inhibit neural impulses associated with seizures by GABAergic action.

The elimination half-life of tiagabine in patients receiving enzymatic anti-epileptic drugs is four to seven hours, and the majority of the dose is eliminated in urine as two inactive metabolites. Adverse reactions include impaired concentration, somnolence, generalized weakness, dizziness, nausea, and rash. Overdose symptoms include agitation, confusion, depression, and myoclonus. Patients should be cautioned against performing complex tasks due to the motor and cognitive effects.

### **Vigabatrin (Sabril)**

Vigabatrin is a structural analogue of GABA that indirectly increases GABA concentrations by irreversibly blocking the GABA-transaminase enzyme. The FDA approved the drug in November 1997. The drug is indicated for adjunctive treatment of partial seizures, treatment of secondarily generalized tonic-clonic seizures not satisfactorily controlled by other

anti-epileptic medicines, and the management of infantile spasms (West syndrome).

It is available in doses of 250–500 mg, and the oral daily dosing range in adults is 1–4 grams. In children, doses are initiated at 40 mg/kg per day. For the treatment of infantile spasms, the usual dose is 50–100 mg/kg per day. With chronic daily oral administration of 4 g, peak and trough plasma levels average 75 mg/L and 9 mg/L, respectively. The normal half-life is six to eight hours. Blood/plasma drug concentration ratios range from 0.6 to 0.9, and approximately 80% of parent drug is eliminated in the urine.

Vigabatrin treatment has been associated with irreversible retinal injury due to an increase in GABA brain levels. This increase in GABA can produce retinal electrophysiological changes in most patients, which results in visual field constriction and visual peripheral field defects. Additional side effects include dizziness, drowsiness, nervousness, memory disturbances, irritability, and ataxia. Caution should be advised when patients are involved in activities requiring mental alertness or physical coordination. Vigabatrin analysis has been conducted using HPLC.

The development and design of new anti-epileptic drugs has been driven by the ability of many of these agents to alter inhibitory and excitatory amino acid neurotransmitters. However, the exact mechanisms of actions of these novel agents are incompletely understood. These emerging drugs may

replace older agents or improve control of epileptic episodes as adjunctive agents, while reducing some of the toxic adverse effects of the first generation of anti-epileptic drugs.

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