North Dakota Medicaid

Drug Utilization Review Board

Drug Classification Reviews

Anticonvulsants

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Introduction

Epilepsy is a chronic neurological disorder that affects approximately 2.7 million Americans. Each year, it costs the United States about $15.5 billion in direct healthcare costs and lost or reduced work productivity. Treating patients with seizure disorder is a highly individualized endeavor and the goal of therapy is for a patient to be seizure-free, without significant side effects.

Seizures are defined as episodes of sudden and excessive neuronal discharges, and can be divided into two groups based on electroencephalogram (EEG) activity and clinical symptomatology. They are categorized as partial or generalized seizures. Partial seizures begin in one hemisphere of the brain and may spread to the other hemisphere. Partial seizures may be either simple (which occur without loss of consciousness) or complex (in which the patient loses consciousness and may experience amnesia). Generalized seizures begin in both hemispheres of the brain and may be tonic-clonic, absence, atonic, or myoclonic seizures.

This review will address agents that are primarily indicated for the treatment of seizures. Other agents, such as benzodiazepines and barbiturates, are also indicated in the treatment of seizures, but are not included in this review.

Table 1 lists the agents included in the review.

Table 1. Anticonvulsant Agents Included in this Review.

Generic Name	Brand Name	Dosage Form	Generic Availability	Manufacturer
Carbamazepine	Carbatrol®	Capsule	No	Shire
	Equetro®	Capsule	No	Shire
	Tegretol® Tegretol XR®	Tablet, chewable tablet, oral suspension	Yes (except XR formulation)	Novartis
Divalproex sodium	Depakote® Depakote ER®	Delayed-release tablet, sprinkle capsule, sustained release tablet	No	Abbott
Ethosuximide	Zarontin®	Capsule, oral syrup	Yes	Pfizer
Ethotoin	Peganone®	Tablet	No	Ovation
Felbamate	Felbatol®	Tablet, oral suspension	No	Medpointe
Gabapentin	Neurontin®	Tablet, capsule, oral solution	Yes (except liquid formulation)	Pfizer
Lamotrigine	Lamictal®	Tablet, chewable tablet	Yes (chewable tablet only)	GlaxoSmithKline
Levetiracetam	Keppra®	Tablet, oral solution	No	UCB Pharmaceuticals

Generic Name	Brand Name	Dosage Form	Generic Availability	Manufacturer
Methsuximide	Celontin®	Capsule	No	Pfizer
Oxcarbazepine	Trileptal®	Tablet, oral suspension	No	Novartis
Phenytoin sodium	Dilantin®	Capsule, chewable tablet, oral suspension	Yes (except chewable tablet formulation)	Pfizer
Pregabalin	Lyrica®	Capsule	No	Pfizer
Primidone	Mysoline®	Tablet	Yes	Valeant
Tiagabine	Gabitril®	Tablet	No	Cephalon
Topiramate	Topamax®	Tablet, sprinkle capsule	No	McNeil
Valproic acid	Depakene®	Capsule, oral syrup	Yes	Abbott
Zonisamide	Zonegran®	Capsule	Yes	Eisai

Indications

Antiepileptic drugs (AED) are commonly used for indications other than epilepsy and seizure control. Many of these agents have other FDA-approved indications as well as common off-label uses. Table 2 details the indications for each of the medications included in this review.

Table 2. Indications for the Antiepileptic Medications Included in this Review

Drug	Labeled Epilepsy Indications	Other Labeled Indications
Carbamazepine	• Partial/complex • Tonic-clonic • Mixed	• Bipolar disorder (Equetro® only) • Trigeminal neuralgia
Divalproex	• Absence • Partial/complex	• Migraine prophylaxis • Mania
Ethosuximide	• Absence	
Ethotoin	• Tonic-clonic • Partial/complex	
Felbamate	• Partial (adults) • Partial/generalized associated with Lennox-Gastaut syndrome (children)	
Gabapentin	• Partial	• Postherpetic neuralgia •
Lamotrigine	• *Monotherapy* – Partial (adults) • *Adjunctive therapy* – Partial, generalized seizures associated with	• Bipolar disorder

Drug	Labeled Epilepsy Indications	Other Labeled Indications
	Lennox-Gastaut syndrome, and tonic-clonic	
Levetiracetam	• Myoclonic/juvenile myoclonic • Partial • Tonic-clonic	
Methsuximide	• Absence	
Oxcarbazepine	• Partial	
Phenytoin	• Tonic-clonic • Partial/complex • Prevention and treatment of seizures occurring during or after neurosurgery	
Pregabalin	• Partial	• Diabetic peripheral neuropathy • Postherpetic neuralgia • Fibromyalgia
Primidone	• Tonic-clonic • Psychomotor • Focal	
Tiagabine	• Partial	
Topiramate	• *Monotherapy* – Partial, tonic-clonic • *Adjunctive therapy* – Partial, tonic-clonic seizures associated with Lennox-Gastaut syndrome	• Migraine prophylaxis
Valproic Acid	• Absence • Partial/complex	
Zonisamide	• Partial	

Pharmacology

1. Carbamazepine

The mechanism of action of carbamazepine in the treatment of bipolar disorder is not understood. Although numerous pharmacological effects of carbamazepine have been described in the published literature (e.g., modulation of ion channels [sodium and calcium], receptor-mediated neurotransmission [GABAergic, glutamatergic, and monoaminergic], and intracellular signaling pathways in experimental preparations), the contribution of these effects to the efficacy of carbamazepine in bipolar disorder is unknown.

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the posttetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic

reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia.

2. **Felbamate**
   The mechanism by which felbamate exerts its anticonvulsant activity is unknown, but in animal tests, felbamate has properties in common with other marketed anticonvulsants. Protection against maximal electroshock-induced seizures suggests that felbamate may reduce seizure spread, an effect possibly predictive of efficacy in generalized tonic-clonic or partial seizures. Protection against pentylenetetrazol-induced seizures suggests that felbamate may increase seizure threshold, an effect considered to be predictive of potential efficacy in absence seizures. Receptor-binding studies in vitro indicate that felbamate has weak inhibitory effects on GABA-receptor binding and benzodiazepine receptor binding, and is devoid of activity at the MK-801 receptor binding site of the N-methyl-D-aspartate (NMDA) receptor-ionophore complex. Felbamate does, however, interact as an antagonist at the strychnine-insensitive glycine recognition site of the NMDA receptor-ionophore complex.

3. **Gabapentin**
   The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). While the relevance to human pain is not known, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice, but does not alter immediate pain-related behaviors. Gabapentin also decreases pain-related responses after peripheral inflammation.

   As with its analgesic action, the mechanism by which gabapentin exerts its anticonvulsant action is unknown. While gabapentin is structurally related to the neurotransmitter GABA, it does not interact with GABA receptors, is not converted metabolically into GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation. Gabapentin does not exhibit affinity for a number of other common receptor sites or at voltage-sensitive sodium channel sites. Furthermore, gabapentin does not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

4. **Hydantoins**
   Ethotoin, fosphenytoin, and phenytoin are classified as hydantoins. The primary site of action of these agents appears to be the motor cortex, where the spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, hydantoins tend to stabilize the threshold against hyperexcitability, which may be caused by excessive stimulation or environmental changes capable of reducing the membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation prevents cortical seizure

foci from detonating adjacent cortical areas. Hydantoins reduce the maximal activity of brain stem centers responsible for the tonic phase of grand mal seizures.

5. Lamotrigine

The precise mechanism by which lamotrigine exerts its anticonvulsant action is unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread and prevented seizures in the visually evoked and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating pre-synaptic transmitter release of excitatory amino acids (e.g., glutamate, aspartate).

The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

6. Levetiracetam

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. In a number of animal models, protection was observed against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. In vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. Levetiracetam does not appear to directly facilitate GABAergic neurotransmission, but has been shown to oppose the activity of negative modulators of GABA- and glycine-gated currents in neuronal cell culture. A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. The identification and function of this binding site, however, is currently unknown.

7. Oxcarbazepine

The pharmacological activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine. The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce a blockade of voltage-sensitive sodium channels, resulting in stabilization of hyper-excited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in

the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

8. Pregabalin

Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the $alpha_2$-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. In vitro, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter GABA, it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration, or have acute effects on GABA uptake or degradation. In cultured neurons, however, prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

9. Primidone

Primidone raises electroshock or chemoshock seizure thresholds or alters seizure patterns in experimental animals. The mechanism of primidone's antiepileptic action is not known. Primidone itself has anticonvulsant activity, as do its two metabolites, phenobarbital (PB) and phenylethylmalonamide (PEMA). In addition to its anticonvulsant activity, PEMA potentiates the anticonvulsant activity of phenobarbital in experimental animals.

10. Succinimides

Ethosuximide and methsuximide, referred to as succinimides, suppress the paroxysmal spike and wave activity (three cycles per second) associated with lapses of consciousness common in absence (petit mal) seizures. The frequency of epileptiform attacks is reduced, apparently by motor cortex depression and elevation of the threshold of the CNS to convulsive stimuli.

11. Tiagabine

The precise mechanism by which tiagabine exerts its antiseizure effect is unknown, although it is believed to be related to its ability to enhance the activity of GABA. It is thought that tiagabine blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding on the surfaces of postsynaptic cells.

12. Topiramate

The precise mechanism by which topiramate exerts its anticonvulsant and migraine prophylaxis effects is unknown. Preclinical studies, however, have revealed four properties that may contribute to topiramate's efficacy in epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the L-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

13. Valproic Acid and Derivatives

The mechanism by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of GABA. Valproic acid and divalproex sodium dissociate to the valproate ion in the GI tract.

14. Zonisamide

Although the precise mechanism by which zonisamide exerts its antiseizure effect is unknown, this agent has demonstrated anticonvulsant activity in several experimental models. This agent may produce these effects through action at sodium and calcium channels. In vitro pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent transient inward currents (T-type Ca^{2+} currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. In vitro binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other in vitro studies have demonstrated that zonisamide (10 to 30mcg/mL) suppresses synaptically driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [3H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. In vivo microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide.

Pharmacokinetics

Table 3. Pharmacokinetic Parameters of the AEDs Included in this Review

Agent	Protein Binding (%)	Metabolism	T 1/2(hours)	Therapeutic Serum Levels (mcg/mL)
Carbamazepine	76	Liver (CP450-3A4) converts to active 10, 11–epoxide; 72% excreted in urine, 28% in feces	25 – 65 (initial) 12 – 17 (repeat dosing)	4-12
Divalproex	Concentration dependent	Hepatic	9-16	Epilepsy: 50-100 Mania: 50-125

Agent	Protein Binding (%)	Metabolism	T 1/2(hours)	Therapeutic Serum Levels (mcg/mL)
Ethotoin	nd	Liver; renal excretion of metabolites	3-9	15-50
Ethosuximide	0	Liver; 25% excreted unchanged in urine	30 (children 7-9 yrs) 40-60 (adults)	40-100
Felbamate	22-25	40% to 50% unchanged in urine, 40% as unidentified metabolites and conjugates	20-23	nd
Gabapentin	<3	Not appreciably metabolized; excreted in urine unchanged	5-7	nd
Lamotrigine	~55	Glucuronic acid conjugation to inactive metabolites; 94% excreted in urine, 2% in feces	25-33	nd
Levetiracetam	<10	Not appreciably metabolized; excreted in urine unchanged	6-8	nd
Methsuximide	nd	Liver; < 1% excreted unchanged in urine	< 2 (40, active metabolite)	nd
Oxcarbazepine	40 (MHD)	Liver to active metabolite MHD, MHD metabolized further by conjugation with glucuronic acid; 95% excreted in urine	2 (9, active metabolite)	nd
Phenytoin	≈90	Liver, renal excretion; <5% excreted unchanged	7-42; average 22	10-20
Pregabalin	0	Not appreciably metabolized; approximately 90% excreted in urine unchanged	6	nd
Primidone	20-25	Metabolized to PB and PEMA, both active	5-15 (primidone), 10-18 (PEMA), 53-140 (PB)	5-12 (primidone), 15-40 (PB)
Tiagabine	96	Thiophene ring oxidation leading to the formation of 5-oxo-tiagabine and glucuronidation; 25% excreted in urine, 63% in feces	7-9	nd
Topiramate	15-41	Not appreciably metabolized; approximately 70% excreted in urine unchanged	21	nd
Valproic acid	80-94	Liver; excreted in urine	9-16	50-150
Zonisamide	40	Liver; excreted in urine	63 (plasma)	nd

nd = not determined

Drug Interactions

1. Carbamazepine

Precipitant Drug	Object Drug	Description
Acetazolamide	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine dosage should be adjusted as needed.
Antimalarials (e.g., chloroquine,	Carbamazepine	Chloroquine and mefloquine may antagonize the activity of carbamazepine. Dosage of carbamazepine should be

Precipitant Drug	Object Drug	Description
mefloquine)		adjusted as needed.
Azole antifungals (e.g., itraconazole, ketoconazole)	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine levels should be closely monitored when an azole antifungal is started or stopped. Serum itraconazole levels may be decreased in the presence of carbamazepine.
Cimetidine	Carbamazepine	Carbamazepine plasma levels may be increased; toxicity may result. Interaction appears to be of greater clinical importance when cimetidine is added to carbamazepine during the first four weeks of therapy.
Cisplatin	Carbamazepine	Carbamazepine plasma levels may be decreased. Carbamazepine levels should be monitored closely.
Dalfopristin	Carbamazepine	Carbamazepine plasma levels may be increased, resulting in possible toxicity.
Danazol	Carbamazepine	Carbamazepine plasma levels may be increased, resulting in an increase in pharmacologic and toxic effects. Co-administration should be avoided if possible.
Delavirdine	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine levels should be monitored closely. Co-administration may lead to loss of virologic response and possible resistance to delavirdine or the class of non-nucleoside reverse transcriptase inhibitors.
Diltiazem	Carbamazepine	Carbamazepine plasma levels may be increased; toxicity may result. Serum carbamazepine levels should be monitored and the patient observed.
Doxorubicin	Carbamazepine	Carbamazepine plasma levels may be decreased. Carbamazepine levels should be monitored.
Felbamate	Carbamazepine	Carbamazepine plasma levels may be decreased. An average decrease of 25 percent in carbamazepine levels has been reported. Felbamate levels may be decreased, possibly resulting in loss of effectiveness.
Haloperidol	Carbamazepine	The therapeutic effects of carbamazepine may be increased. Consideration should be given to adjusting the dose of carbamazepine as indicated. Haloperidol serum levels and efficacy may be decreased by carbamazepine. A 60 percent decrease in levels has been reported.
Isoniazid	Carbamazepine	Isoniazid is suspected to inhibit carbamazepine metabolism. Carbamazepine toxicity may result. Carbamazepine may increase isoniazid degradation to hepatic metabolites. Isoniazid toxicity may result.
Loratadine	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine levels should be closely monitored.
Macrolides (e.g., clarithromycin, erythromycin, troleandomycin)	Carbamazepine	Carbamazepine plasma levels may be increased. This combination should be avoided if possible.
MAO inhibitors (e.g., isocarboxazid, phenelzine)	Carbamazepine	Co- administration is contraindicated. MAO inhibitor should be discontinued at least 14 days prior to administration of carbamazepine.
Nefazodone	Carbamazepine	Carbamazepine plasma levels may be increased. Lower nefazodone levels may result. Co-administration is contraindicated.
Niacin (e.g., niacinamide, nicotinamide)	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine levels should be monitored and dose adjusted accordingly.

Precipitant Drug	Object Drug	Description
Phenobarbital	Carbamazepine	Carbamazepine plasma levels may be decreased. Serum concentrations of both drugs should be monitored.
Phenytoin	Carbamazepine	Carbamazepine plasma levels may be decreased. Serum concentrations of both drugs should be monitored regularly, and their dosages adjusted appropriately. Phenytoin plasma levels may increase or decrease in the presence of carbamazepine.
Primidone	Carbamazepine	Carbamazepine plasma levels may be decreased. Primidone plasma levels may be increased or decreased. Serum concentrations of both drugs should be monitored regularly, and their doses adjusted appropriately.
Protease inhibitors (e.g., amprenavir, indinavir)	Carbamazepine	Carbamazepine plasma levels may be increased, increasing the risk of toxicity. Serum carbamazepine levels should be monitored. Antiretroviral treatment failure may occur.
Propoxyphene	Carbamazepine	Increases in carbamazepine levels between 45 percent and 77 percent have been reported. Co-administration should be avoided if possible.
Quinine	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine levels should be monitored and dosage adjusted as needed.
Quinupristin	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine levels should be monitored closely.
Rifampin	Carbamazepine	Carbamazepine plasma levels may be decreased. Serum carbamazepine levels should be monitored and patient observed.
Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine)	Carbamazepine	Carbamazepine plasma levels may be increased, producing possible toxicity. Carbamazepine serum concentrations should be monitored closely. Plasma levels of SSRIs may be decreased. Patient response should be closely monitored and SSRI dosage adjusted if needed.
Succinimides (e.g., methsuximide)	Carbamazepine	Carbamazepine plasma level may be decreased. Succinimide levels may be decreased.
Theophylline	Carbamazepine	Carbamazepine plasma levels may be decreased. Theophylline levels may be decreased or increased. Carbamazepine and theophylline levels should be monitored and dosages adjusted accordingly.
Tricyclic antidepressants (e.g., amitriptyline, desipramine, nortriptyline)	Carbamazepine	Carbamazepine toxicity was reported in one patient on concomitant desipramine. Carbamazepine may induce hepatic metabolism of tricyclic antidepressants.
Valproate	Carbamazepine	Carbamazepine plasma levels may be increased. Valproate levels may be decreased with possible loss of seizure control. Patient should be observed for seizure activity and toxicity for at least one month after starting or stopping either drug.
Verapamil	Carbamazepine	Carbamazepine plasma levels may be increased. Carbamazepine dose may need to be decreased 40 to 50 percent with co-administration.
Zileuton	Carbamazepine	Carbamazepine plasma levels may be increased.
Carbamazepine	Acetaminophen	Carbamazepine may increase the metabolism of acetaminophen, increasing the risk of acetaminophen-induced hepatotoxicity and/ or decreasing its effectiveness.
Carbamazepine	Anticoagulants (e.g., dicumarol, warfarin)	The anticoagulant effect may be reduced during co-administration. Prothrombin times should be monitored when starting or stopping carbamazepine therapy.

Precipitant Drug	Object Drug	Description
Carbamazepine	Antipsychotics (e.g., aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone)	Co-administration may reduce the plasma levels of these antipsychotics. A single case of neuroleptic malignant syndrome has been reported with clozapine.
Carbamazepine	Benzodiazepines	The pharmacological effects of benzodiazepines may be reduced. Patient response should be monitored.
Carbamazepine	Bupropion	Carbamazepine increased the hepatic P-450 metabolism of bupropion and has been reported to decrease bupropion peaks 87 percent and AUC 90 percent.
Carbamazepine	Buspirone	Plasma levels of buspirone may be decreased. Patient response should be monitored.
Carbamazepine	Clomipramine	Carbamazepine increases the plasma levels of clomipramine.
Carbamazepine	Cyclosporine	Plasma level of cyclosporine may be decreased, resulting in a reduction of pharmacologic effects. Cyclosporine levels should be monitored and patient observed for signs of rejection or toxicity.
Carbamazepine	Doxycycline	Carbamazepine may decrease the half-life and serum levels of doxycycline, possibly reducing its therapeutic efficacy.
Carbamazepine	Felodipine	Pharmacologic effects of felodipine may be decreased.
Carbamazepine	Glucocorticoids (e.g., hydrocortisone)	Plasma levels of glucocorticoids may be reduced.
Carbamazepine	HMG-CoA reductase inhibitors (e.g., atorvastatin, simvastatin)	Plasma concentration of certain HMG-CoA reductase inhibitors may be reduced, decreasing the therapeutic effect (resulting in hypercholesterolemia). The clinical response of the patient should be closely monitored.
Carbamazepine	Lamotrigine	Serum lamotrigine levels may be decreased 40 percent.
Carbamazepine	Levothyroxine	Plasma levels of levothyroxine may be decreased. Thyroid-stimulating hormone should be monitored.
Carbamazepine	Lithium	Increased CNS toxicity may occur during concomitant therapy. Serum lithium levels should be monitored and dosage adjusted accordingly.
Carbamazepine	Methadone	Pharmacologic effects of methadone may be decreased. A higher dose of methadone may be required.
Carbamazepine	Mirtazapine	Plasma levels of mirtazapine may be decreased. Patient response should be monitored.
Carbamazepine	Nondepolarizing muscle relaxants (e.g., atracurium, tubocurarine)	Nondepolarizing muscle relaxants may have shorter than expected duration or be less effective. Patient should be monitored for reduced muscle relaxant effectiveness and the dose of the nondepolarizing muscle relaxant adjusted accordingly.
Carbamazepine	Oral contraceptives (e.g., Ortho-Novum)	Breakthrough bleeding has been reported with co-administration, and the reliability of the oral contraceptive may be adversely affected.
Carbamazepine	Oxcarbazepine	Plasma levels of oxcarbazepine may be decreased.
Carbamazepine	Praziquantel	Serum praziquantel may be decreased, possibly leading to treatment failures. It may be necessary to increase the dose of praziquantel during co-administration.
Carbamazepine	Tiagabine	Plasma levels of tiagabine may be decreased.
Carbamazepine	Topiramate	Carbamazepine may decrease the pharmacologic effects of topiramate.
Carbamazepine	Tramadol	Plasma levels of tramadol may be decreased.

Precipitant Drug	Object Drug	Description
Carbamazepine	Voriconazole	Voriconazole plasma levels may be reduced. Co-administration is contraindicated.
Carbamazepine	Zonisamide	Plasma levels of zonisamide may be reduced.

2. **Felbamate**

Precipitant drug	Object drug	Description
Felbamate	Phenytoin	Felbamate causes an increase in steady-state phenytoin plasma concentrations.
Felbamate	Valproate	Felbamate causes an increase in steady-state valproate concentrations.
Phenobarbital	Felbamate	Co-administration of felbamate with phenobarbital causes an increase in phenobarbital plasma concentrations.
Carbamazepine	Felbamate	Co-administration of felbamate with carbamazepine causes a decrease in steady-state carbamazepine concentrations, but increases the carbamazepine epoxide concentrations.

3. **Gabapentin**

Precipitant Drug	Object Drug	Description
Gabapentin	Hydrocodone	Co-administration of gabapentin (125 to 500mg; n = 48) decreases hydrocodone (10mg; n = 50) Cmax and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; Cmax and AUC values are three and four percent lower, respectively, after administration of 125mg gabapentin and 21 and 22 percent lower, respectively, after administration of 500mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14 percent. The magnitude of interaction at other doses is not known.
Gabapentin	Morphine	A literature article reported that when a 60mg controlled-release morphine capsule was administered two hours prior to a 600mg gabapentin capsule (n = 12), mean gabapentin AUC increased by 44 percent compared to gabapentin administered without morphine. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin two hours after morphine. The magnitude of interaction at other doses is not known.
Cimetidine	Gabapentin	In the presence of cimetidine at 300mg four times daily (n = 12) the mean apparent oral clearance of gabapentin fell by 14 percent and creatine clearance fell by 10 percent. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.
Al- and Mg- containing antacids	Gabapentin	Maalox reduced the bioavailability of gabapentin (n = 16) by about 20 percent. This decrease in bioavailability was about five percent when gabapentin was administered two hours after Maalox. It is recommended that gabapentin be taken at least two hours following Maalox administration.
Naproxen	Gabapentin	At low doses, co-administration of gabapentin with naproxen increased gabapentin absorbed by 12 to 15%. The magnitude of this interaction at normal doses is not known.

4. Hydantoins

Precipitant drug	Object drug	Description
Clonazepam	Phenytoin	Plasma levels of clonazepam or phenytoin may be decreased with concomitant use; phenytoin toxicity may occur.
Corticosteroid	Phenytoin	Corticosteroid use may mask systemic manifestations of phenytoin hypersensitivity reactions.
Phenytoin	Dopamine	Five critically ill patients requiring dopamine to maintain blood pressure developed severe hypotension when IV phenytoin was administered.
Phenytoin	Lithium	Lithium toxicity may be increased by co-administration of phenytoin. Marked neurologic symptoms were reported despite normal serum levels of lithium.
Phenytoin	Meperidine	Meperidine's analgesic effectiveness may be decreased, while the toxic effects could be increased by phenytoin. The hepatic metabolism of meperidine is increased, but the formation of normeperidine, a potentially toxic metabolite, is also increased.
Phenytoin	Primidone	Primidone's pharmacologic effects may be increased by phenytoin administration. Toxicity has occurred. The metabolic conversion of primidone to PB and PEMA may also be increased. Serum concentrations of primidone and primidone metabolites should be monitored following alterations in hydantoin therapy.
Phenytoin	Warfarin	Warfarin may be displaced by Phenytoin. In one report, a patient died of bleeding complications.
Phenytoin Carbamazepine	Cisatracurium Besylate	Resistance to the neuromuscular blocking action of non-depolarizing agents has been demonstrated in patients who are chronically administered phenytoin or carbamazepine. Slightly shorter durations of neuromuscular block may be anticipated, and infusion rate requirements may be higher.
Hydantoins	Allopurinol Amiodarone Benzodiazepines Chloramphenicol Chlorpheniramine Cimetidine Disulfiram Ethanol (acute ingestion) Fluconazole Ibuprofen Isoniazid Metronidazole Miconazole Omeprazole Phenothiazines Phenacemide Phenylbutazone Salicylates Succinimides Sulfonamides Tricyclic antidepressants Trimethoprim Valproic acid	Increased pharmacologic effects of the hydantoins may occur.

Precipitant drug	Object drug	Description
Antacids Antineoplastics Barbiturates Carbamazepine Charcoal Diazoxide Ethanol (chronic ingestion) Folic Acid Influenza vaccine Loxapine Nitrofurantoin Pyridoxine Rifampin Sucralfate Theophylline	Hydantoins	Decreased pharmacological effects of the hydantoins may occur.
Acetaminophen Amiodarone Carbamazepine Cardiac glycosides Corticosteroids Cyclosporine Dicumarol Disopyramide Dopamine Doxycycline Estrogens Furosemide Haloperidol Levodopa Levonorgestrel Mebendezole Methadone Metyrapone Mexiletine Oral contraceptives Phenothiazines Quinidine Sulfonylureas Theophylline Valproic acid	Hydantoins	The effectiveness of these agents may be decreased by the hydantoins.

5. Lamotrigine

Precipitant drug	Object drug	Description
Acetaminophen	Lamotrigine	Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects. With chronic administration of acetaminophen, if an interaction is suspected, it may be necessary to adjust the dose of lamotrigine.
Carbamazepine	Lamotrigine	Lamotrigine concentration is decreased by approximately 40 percent. Carbamazepine-exposed levels may be increased.
Oral Contraceptives	Lamotrigine	Co-administration of ethinyl estradiol/ levonorgestrel with lamotrigine increased the clearance of lamotrigine approximately 20-fold. Similar effects may be seen with hormone replacement therapy.

Precipitant drug	Object drug	Description
Inducers/Inhibitors of glucuronidation	Lamotrigine	Inducers/inhibitors of glucuronidation may affect the clearance of lamotrigine and dosage may need to be adjusted according to clinical response.
Oxcarbazepine	Lamotrigine	Co-administration of these agents decreased serum concentrations of lamotrigine by 29%. Lamotrigine dose may need to be adjusted.
Primidone Phenobarbital	Lamotrigine	Lamotrigine concentration is decreased approximately 40 percent.
Phenytoin	Lamotrigine	Lamotrigine concentration is decreased approximately 40 percent.
Rifamycins	Lamotrigine	Lamotrigine plasma levels may be reduced. The dosage of lamotrigine should be adjusted as needed.
Succinimides (e.g., ethosuximide)	Lamotrigine	Lamotrigine serum concentrations may be reduced, decreasing the therapeutic effects. The dosage of lamotrigine should be adjusted as needed.
Valproic acid	Lamotrigine	The addition of valproic acid increased lamotrigine steady-state concentration more than two-fold. Trough steady-state valproic acid concentration decreased by approximately 25 percent when lamotrigine was added in one study. Another study showed no change in valproic acid concentrations.
Lamotrigine	Topiramate	Co-administration of these agents increased serum concentrations of topiramate by 15%.

6. **Levetiracetam**

Precipitant drug	Object drug	Description
Probenecid	Levetiracetam	The maximum steady-state plasma concentration of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057.

7. **Oxcarbazepine**

Precipitant drug	Object drug	Description
Carbamazepine	Oxcarbazepine	Concurrent use of carbamazepine and oxcarbazepine decreased MHD 1 concentration by ≈ 40 percent.
Phenobarbital	Oxcarbazepine	Administration of phenobarbital with oxcarbazepine decreased MHD 1 concentrations ≈25 percent while phenobarbital concentrations increased ≈14 percent.
Phenytoin	Oxcarbazepine	Co-administration of phenytoin with oxcarbazepine (600 to 1800mg/day) caused a 30 percent decrease in MHD 1 AUC. Higher doses of oxcarbazepine (> 1200 to 2400mg/day) increased phenytoin concentrations up to 40 percent. A decrease in phenytoin dose may be required when given with oxcarbazepine in doses > 1200mg/day.
Valproic Acid	Oxcarbazepine	Concurrent use of valproic acid and oxcarbazepine decreased MHD concentrations by approximately 18%.
Verapamil	Oxcarbazepine	Concurrent use of these agents resulted in a 20% decrease in MHD concentrations.
Oxcarbazepine	Felodipine	The AUC of felodipine decreased by 28 percent when repeatedly administered in combination with oxcarbazepine.
Oxcarbazepine	Lamotrigine	Oxcarbazepine administration reduced serum concentrations

Precipitant drug	Object drug	Description
		of lamotrigine 29%. The dose of lamotrigine may need to be adjusted.
Oxcarbazepine	Oral contraceptives	The mean AUC of ethinyl estradiol decreased by 48 to 52 percent, and the mean AUC of levonorgestrel decreased by 32 to 52 percent when administered in combination with oxcarbazepine.

8. Pregabalin

Precipitant drug	Object drug	Description
Pregabalin	Ethanol Lorazepam Oxycodone	Additive effects on cognitive and gross motor functioning were seen when pregabalin was coadministered with these drugs. No clinically important effects on respiration were seen.
Pregabalin	Thiazolidinediones	Because the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, take care when coadministering pregabalin and these agents.

9. Primidone

Precipitant drug	Object drug	Description
Carbamazepine	Primidone	Concomitant use of primidone and carbamazepine may result in decreased levels of primidone and its metabolite phenobarbital, as well as carbamazepine serum concentrations.
Hydantoins (e.g. phenytoin)	Primidone	Hydantoins may increase serum primidone and its metabolites. Patients on concomitant treatment with hydantoins and primidone should be monitored closely following any alteration in hydantoin therapy.
Succinimides (e.g. ethosuximide, methsuximide)	Primidone	Co-administration of primidone and a succinimide may result in lower primidone and phenobarbital serum concentrations.
Valproic Acid	Primidone	Plasma primidone concentrations may be elevated, increasing the pharmacologic and adverse effects. Primidone dosage may need to be decreased in some patients.
Primidone	Anticoagulants (e.g., warfarin sodium)	Primidone reduces the effect of anticoagulants. Anticoagulation dosage should be monitored and tailored as needed.
Primidone	Beta-blockers (e.g., propranolol)	Pharmacokinetic effects of certain beta-blockers may be reduced. A higher beta-blocker dose should be considered during co-administration of primidone.
Primidone	Corticosteroids (e.g., prednisone)	Decreased effect of corticosteroid may be observed. This combination should be avoided if possible.
Primidone	Doxycycline	Co-administration may decrease doxycycline half-life and serum levels, possibly resulting in a decreased therapeutic effect. These effects may persist for weeks following primidone discontinuation. An alternate tetracycline should be considered.
Primidone	Estrogens Oral contraceptives	AUC of estrogen may be decreased. Contraceptive failure has been reported. Alternate contraception methods are recommended.
Primidone	Ethanol	Impaired hand-eye coordination, additive CNS effects, and death have been reported upon acute ingestion. Chronic

Precipitant drug	Object drug	Description
		ethanol ingestion may manifest as drug tolerance. Concomitant use should be avoided.
Primidone	Felodipine	Pharmacologic effects of felodipine may be decreased. Patients receiving long-term treatment with both drugs may require higher doses of felodipine.
Primidone	Methadone	The actions of methadone may be reduced. Patients receiving chronic methadone treatment may experience opiate withdrawal symptoms. A higher dose of methadone may be required during co-administration with primidone.
Primidone	Metronidazole	Therapeutic failure of metronidazole has been observed. Higher initial metronidazole doses may be needed in patients also receiving primidone.
Primidone	Nifedipine	Decreased serum nifedipine concentrations, possibly reducing efficacy, have been observed. Dose should be titrated according to response. A larger nifedipine dose may be needed.
Primidone	Quinidine	Primidone appears to produce decreased quinidine serum concentrations and a decreased quinidine elimination half-life.
Primidone	Theophyllines	Decreased theophylline levels, possibly resulting in reduced therapeutic effects, have been observed. Increased theophylline dosages may be required with use of primidone.

10. Succinimides

Precipitant drug	Object drug	Description
Succinimides	Hydantoins	Serum hydantoin levels may be increased.
Succinimides	Primidone	Lower primidone and phenobarbital levels may occur.
Valproic acid	Succinimides	Both increases and decreases in succinimide levels have occurred.

11. Tiagabine

Precipitant drug	Object drug	Description
Carbamazepine	Tiagabine	Tiagabine clearance is 60 percent greater in patients taking carbamazepine, phenytoin, phenobarbital, or primidone with or without other enzyme-inducing antiepilepsy drugs (AEDs). Dose should be adjusted accordingly.
Phenobarbital		
Phenytoin		
Primidone		
Highly protein-bound drugs	Tiagabine	Tiagabine is 96 percent bound to plasma protein. Therefore, it has the potential to interact with other highly protein-bound drugs. Such an interaction can potentially lead to higher free fractions of either drug.
Valproate	Tiagabine	Tiagabine causes a slight decrease (approximately 10 percent) in steady-state valproate concentrations. Valproate significantly decreased tiagabine binding in vitro from 96.3 percent to 94.8 percent, which resulted in an increase of approximately 40 percent in the free tiagabine. The clinical relevance is unknown.

12. Topiramate

Precipitant drug	Object drug	Description
Carbamazepine	Topiramate	Carbamazepine may increase the metabolism of topiramate, causing a 40 percent decrease in serum concentrations. Dose should be adjusted as needed.
Carbonic anhydrase	Topiramate	Because topiramate is also a carbonic anhydrase inhibitor,

Precipitant drug	Object drug	Description
inhibitors (e.g., acetazolamide)		concomitant use may increase the risk for renal stone formation. Concurrent use should be avoided.
Hydantoins (e.g., phenytoin)	Topiramate	Hydantoins may increase the metabolism of topiramate, causing a 48 percent decrease in serum concentration. Topiramate may decrease the metabolism of phenytoin causing a 25 percent increase in serum concentrations in some patients. Dose should be adjusted as needed.
HCTZ	Topiramate	Co-administration increased topiramate Cmax by 27% and AUC by 29%. Topiramate dose may need to be adjusted.
Lamotrigine	Topiramate	Co-administration produced a 15 percent increase in topiramate concentration.
Metformin	Topiramate	Co-administration caused decreased topiramate plasma clearance; metformin Cmax and AUC to increase by 18 percent and 25 percent, respectively; and clearance to decrease 20 percent. The clinical significance of these effects is not known.
Pioglitazone	Topiramate	Topiramate's active hydroxy-metabolite had a decrease in Cmax and AUC by 13% and 16% respectively; as well as a 60% decrease in Cmax and AUC of active keto-metabolite. Monitor carefully. Pioglitazone AUC decreased by 15%.
Valproic acid	Topiramate	Coadministration caused a 14 percent decrease in topiramate serum concentrations and an 11 percent decrease in valproic acid serum concentrations. Co-administration has been associated with hyperammonemia with and without encephalopathy.
Topiramate	Alcohol, CNS depressants	Use topiramate with extreme caution because of the potential to cause CNS depression, as well as other cognitive and/ or neuropsychiatric adverse reactions.
Topiramate	Amitriptyline	Amitriptyline plasma concentrations may increase. Amitriptyline dose should be adjusted as needed.
Topiramate	Oral contraceptives, estrogen	Topiramate reduced the ethinyl estradiol AUC by 18 to 30 percent and plasma concentrations by 15 to 25 percent. Oral contraceptive efficacy may be reduced. Alternate methods of contraception or an increased estrogen dose should be considered.
Topiramate	Digoxin	Serum digoxin AUC was decreased by 12 percent when given with topiramate. The clinical relevance of this observation has not been established.
Topiramate	Lithium	Lithium AUC and Cmax decreased by 20 percent.
Topiramate	Risperidone	Concurrent administration produced a 25 percent decrease in exposure to risperidone. Close monitoring is recommended.

13. Valproic Acid Derivatives

Precipitant drug	Object drug	Description
Aspirin	Valproic Acid	Aspirin use causes a decrease in protein binding and inhibition of metabolism of valproate.
Carbapenem antibiotics	Valproic Acid	Coadministration may result in subtherapeutic valproic acid levels.
Chlorpromazine	Valproic Acid	Valproate elimination half-life and trough levels may increase; clearance may decrease.
Cholestyramine	Valproic Acid	Serum concentrations and bioavailability of valproic acid may be reduced, resulting in a decrease in therapeutic effects. Administer valproic acid at least 3 hours before, but not within 3 hours after cholestyramine.

Precipitant drug	Object drug	Description
Felbamate	Valproic Acid	Concomitant use of felbamate caused an increase in mean valproate peak concentration.
Rifampin	Valproic Acid	Oral clearance of valproate is increased.
Topiramate	Valproic Acid	Possible increased metabolism of both agents. Coadministration has been associated with hyperammonemia with and without encephalopathy.
Valproic Acid	Amitriptyline	Plasma clearance of amitriptyline decreased.
Valproic Acid	Nortriptyline	Plasma clearance of nortriptyline decreased.
Valproic Acid	Carbamazepine	Serum levels of carbamazepine decreased.
Valproic Acid	Clonazepam	Concomitant use may induce absence status in patients with a history of absence-type seizures.
Valproic Acid	Diazepam	Valproate displaces diazepam from its plasma albumin-binding sites and inhibits its metabolism.
Valproic Acid	Ethosuximide	Metabolism of ethosuximide is inhibited.
Valproic Acid	Lamotrigine	The elimination half-life of lamotrigine is increased.
Valproic Acid	Phenobarbital	Valproate inhibits the metabolism of phenobarbital. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity.
Valproic Acid	Primidone	Primidone, which is metabolized to a barbiturate, may be involved in an interaction similar to phenobarbital.
Valproic Acid	Phenytoin	Valproate displaces phenytoin from its plasma albumin-binding sites and inhibits its hepatic metabolism. The dosage of phenytoin should be adjusted as required by the clinical situation.
Valproic Acid	Tolbutamide	The unbound fraction of tolbutamide may be increased, but the clinical relevance is unknown.
Valproic Acid	Warfarin	The unbound fraction of warfarin may be increased.
Valproic Acid	Zidovudine	The clearance of zidovudine is decreased, but its half-life is unaffected.

14. Zonisamide

Precipitant drug	Object drug	Description
CYP3A4 Inducers	Zonisamide	Serum concentrations of zonisamide are increased.
CYP3A4 Inhibitors	Zonisamide	Serum concentrations of zonisamide are decreased.

Adverse Effects

1. Carbamazepine

The most serious adverse effects seen with carbamazepine involve the hemopoietic system, skin, liver, and cardiovascular system. Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based case-control study demonstrate that the risk of developing these reactions is five to eight times greater than in the general population. The overall risk of these reactions in the untreated general population is low, however, approximately six patients per one million per year for agranulocytosis, and two patients per one million per year for aplastic anemia. Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of carbamazepine, data are not available to accurately estimate their incidence or outcome. The vast majority of the cases of leukopenia, however, have not progressed to the more serious

conditions of aplastic anemia or agranulocytosis. Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed while monitoring patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest recommended dosage.

In a double-blind, placebo-controlled trial of three weeks' duration treating bipolar I disorder, the most commonly observed adverse reactions (at least five percent and twice placebo) seen in association with the use of carbamazepine include: ataxia, dizziness, somnolence, pruritus, dry mouth, nausea, vomiting, amblyopia, and speech disorders.

Equetro only: Carbamazepine- and placebo-treated patients from two double-blind, placebo-controlled studies were enrolled in a six-month, open-label study. The most common adverse reactions, with an incidence of five percent or more, include: amnesia, anxiety, ataxia, depression, dizziness, manic depressive reaction, somnolence, pruritus, rash, constipation, diarrhea, dyspepsia, nausea, accidental injury, asthenia, back pain, chest pain, headache, infection, and pain.

2. Felbamate

Before prescribing felbamate, the physician should be thoroughly familiar with the details of this prescribing information.
Felbamate should not be used by patients until there has been a complete discussion of the risks and the patient, parent, or guardian has provided written informed consent.

Aplastic anemia: The use of felbamate is associated with a marked increase in the incidence of aplastic anemia. Accordingly, felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable in light of the benefits conferred by its use. Ordinarily, a patient should not be placed on or continued on felbamate without consideration of appropriate expert hematologic consultation. Among felbamate treated patients, aplastic anemia (pancytopenia in the presence of a bone marrow largely depleted of hematopoietic precursors) occurs at an incidence that may be more than a 100-fold greater than that seen in the untreated population (i.e., 2 to 5 per million persons per year). The risk of death in patients with aplastic anemia generally varies as a function of its severity and etiology; current estimates of the overall

case fatality rate are in the range of 20% to 30%, but rates as high as 70% have been reported in the past. There are too few felbamate associated cases, and too little known about them to provide a reliable estimate of the syndrome's incidence or its case fatality rate or to identify the factors, if any, that might conceivably be used to predict who is at greater or lesser risk. In managing patients on felbamate, it should be borne in mind that the clinical manifestation of aplastic anemia may not be seen until after a patient has been on felbamate for several months (eg, onset of aplastic anemia among felbamate exposed patients for whom data are available has ranged from 5 to 30 weeks). However, the injury to bone marrow stem cells that is held to be ultimately responsible for the anemia may occur weeks to months earlier. Accordingly, patients who are discontinued from felbamate remain at risk for developing anemia for a variable, and unknown, period afterwards. It is not known whether or not the risk of developing aplastic anemia changes with duration of exposure. Consequently, it is not safe to assume that a patient who has been on felbamate without signs of hematologic abnormality for long periods of time is without risk. It is not known whether the dose of felbamate affects the incidence of aplastic anemia. It is not known whether or not concomitant use of antiepileptic drugs or other drugs affects the incidence of aplastic anemia. Aplastic anemia typically develops without premonitory clinical or laboratory signs, the full blown syndrome presenting with signs of infection, bleeding, or anemia. Accordingly, routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but, it will, in some cases, allow the detection of the hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.

Hepatic failure: Evaluation of post marketing experience suggests that acute liver failure is associated with the use of felbamate. The reported rate in the US has been about 6 cases of liver failure leading to death or transplant per 75,000 patient years of use. This rate is an underestimate because of under reporting, and the true rate could be considerably greater than this. For example, if the reporting rate is 10%, the true rate would be 1 case per 1250 patient years of use. Of the cases reported, about 67% resulted in death or liver transplantation, usually within 5 weeks of the onset of signs and symptoms of liver failure. The earliest onset of severe hepatic dysfunction followed subsequently by liver failure was 3 weeks after initiation of felbamate. Although some reports described dark urine and nonspecific prodromal symptoms (eg, anorexia, malaise, and gastrointestinal symptoms), in other reports it was not clear if any prodromal symptoms preceded the onset of jaundice. It is not known whether or not the risk of developing hepatic failure changes with duration of exposure. It is not known whether the dosage of felbamate affects the incidence of hepatic failure. It is not known whether concomitant use of other drugs affects the incidence of hepatic failure. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction.

The most common adverse reactions seen in association with felbamate in adults during monotherapy are anorexia, vomiting, insomnia, nausea, and headache.

The most common adverse reactions seen in association with felbamate in adults during adjunctive therapy are anorexia, vomiting, insomnia, nausea, dizziness, somnolence, and headache.

The most common adverse reactions seen in association with felbamate in children during adjunctive therapy are anorexia, vomiting, insomnia, headache, and somnolence.

3. Gabapentin

The most commonly observed adverse events associated with the use of gabapentin in adults and not seen at an equivalent frequency among placebo-treated patients are dizziness, somnolence, and peripheral edema.

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients greater than 12 years of age and not seen at an equivalent frequency among placebo-treated patients are somnolence, dizziness, ataxia, fatigue, and nystagmus.

The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients three to 12 years of age and not seen at an equal frequency among placebo-treated patients are emotional lability (primarily behavioral problems); hostility, including aggressive behaviors; thought disorders, including concentration problems and change in school performance; and hyperkinesia (primarily restlessness and hyperactivity).

4. Hydantoins

Ethotoin: Isolated cases of lymphadenopathy and systemic lupus erythematosus have been reported in patients taking hydantoin compounds, and lymphadenopathy has occurred with ethotoin. Withdrawal of therapy has resulted in remission of the clinical and pathological findings. Therefore, if a lymphoma-like syndrome develops, the drug should be withdrawn and the patient closely observed for regression of signs and symptoms before resuming treatment. Ataxia and gum hypertrophy have occurred only rarely, usually only in patients receiving an additional hydantoin derivative. It is of interest to note that ataxia and gum hypertrophy have subsided in patients receiving other hydantoins when ethotoin was given as a substitute antiepileptic. Occasionally, vomiting or nausea after ingestion of ethotoin has been reported, but the incidence of gastric distress is reduced if the drug is administered after meals. Other side effects have included chest pain, nystagmus, diplopia, fever, dizziness, diarrhea, headache, insomnia, fatigue, numbness, and skin rash.

Phenytoin: The most common manifestations encountered with phenytoin therapy are referable to the central nervous system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion. Dizziness, insomnia, transient nervousness, motor twitching, and headaches have also been observed. There have also been rare reports of phenytoin-induced dyskinesias, including chorea, dystonia, tremor, and asterixis. Coarsening of the facial features, enlargement of the lips, and gingival hyperplasia may also occur.

5. Lamotrigine

Serious rashes requiring hospitalization and discontinuation of lamotrigine, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have occurred in association with lamotrigine therapy. The risk of serious rash is detailed more fully below.

The most commonly observed (greater than or equal to five percent) adverse reactions seen in association with lamotrigine and not seen at an equivalent frequency among placebo-treated patients are dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting are dose related. These occurred more commonly in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine. Clinical data suggest a higher incidence of rash, including serious rash, in patients also receiving concomitant valproate than in patients not receiving valproate.

Serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8/1,000) in children (younger than 16 years of age) receiving lamotrigine as adjunctive therapy for epilepsy and 0.3% (3/1,000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8/1,000) in adult patients receiving lamotrigine as initial monotherapy and 0.13% (1.3/1,000) in adult patients receiving lamotrigine as adjunctive therapy. In a prospectively followed cohort of 1,983 children with epilepsy taking adjunctive lamotrigine, there was 1 rash-related death. In worldwide post marketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adults and children, but those numbers are too few to permit a precise estimate of the rate. Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash associated with lamotrigine. There are suggestions, yet to be proven, that the risk of rash may also be increased by coadministration of lamotrigine with valproate (includes valproic acid and divalproex sodium), exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine. However, cases have been reported in the absence of these factors. Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within 2 to 8 weeks of treatment

initiation. However, isolated cases have been reported after prolonged treatment (eg, 6 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash. Although benign rashes also occur with lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, ordinarily discontinue lamotrigine at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

6. Levetiracetam

In well-controlled clinical studies, the most frequently reported adverse reactions associated with the use of levetiracetam in combination with other AEDs and not seen at an equivalent frequency among placebo-treated patients were somnolence, asthenia, infection, and dizziness. In addition to the adverse experiences listed above, the following events have been reported in patients receiving marketed levetiracetam worldwide: suicidal behavior, pancreatitis, weight loss, hepatic failure, alopecia, and hematological events such as leukopenia, neutropenia, pancytopenia, and thrombocytopenia. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.

7. Oxcarbazepine

The most common adverse reactions (greater than or equal to five percent) in all clinical studies seen in association with oxcarbazepine and occurring substantially more frequently than in placebo-treated patients were as follows: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, amnesia, anxiety, confusion, headache, insomnia, nystagmus, nervousness, vertigo, constipation and abnormal gait.

8. Pregabalin

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormally" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (five percent or more and twice the rate of that seen in placebo).

There have been post marketing reports of angioedema in patients. Specific symptoms include swelling of the face, mouth, and neck. Some of these reported incidents were life-threatening with respiratory compromise requiring emergency treatment. Caution should be exercised when prescribing pregabalin in patients who have had previous episodes of angioedema or are currently taking other drugs associated with angioedema (e.g. angiotensin converting enzyme inhibitors).

There have been reports of hypersensitivity reactions after initiation of therapy, weight gain, ophthalmic effects, creatine kinase elevation, decreased platelet count, and prolonged PR intervals.

9. Primidone

The most frequently occurring early side effects are ataxia and vertigo. These tend to disappear with continued therapy or with reduction of initial dosage. Occasionally, the following have been reported: nausea, anorexia, vomiting, fatigue, hyperirritability, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, and morbilliform skin eruptions. Granulocytopenia, agranulocytosis, and red-cell hypoplasia and aplasia, have been reported rarely. Persistent or severe side effects may necessitate withdrawal of the drug.

10. Succinimides

The most commonly-observed CNS adverse effects with these agents include drowsiness, ataxia, dizziness, irritability, nervousness, headache, blurred vision, myopia, photophobia, hiccoughs, euphoria, dream-like state, lethargy, hyperactivity, fatigue and insomnia. The most common dermatologic adverse effects are pruritus, urticaria, Stevens-Johnson syndrome, pruritic erythematous rashes, skin eruptions, erythema multiforme, systemic lupus erythematosus, alopecia and hirsutism. Gastrointestinal effects, such as nausea, vomiting, vague gastric upset, cramps, anorexia, diarrhea, weight loss, epigastric and abdominal pain and constipation are also somewhat common.

11. Tiagabine

The most commonly observed adverse reactions in placebo-controlled, parallel-group, add-on epilepsy trials associated with the use of tiagabine in combination with other AEDs not seen at an equivalent frequency among placebo-treated patients are dizziness/light-headedness, asthenia/lack of energy, somnolence, nausea, nervousness/irritability, tremor, abdominal pain, and thinking abnormally/difficulty with concentration or attention.

12. Topiramate

The most commonly observed adverse reactions associated with the use of topiramate at dosages of 200 to 400mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that are seen at greater frequency in topiramate-treated patients and did not appear to be dose related are as follows: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, and diplopia. The most common dose-related adverse reactions at dosages of 200 to 1,000mg/day are fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease.

Adverse reactions associated with the use of topiramate at dosages of 5 to 9mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that are seen at greater frequency in topiramate-treated patients are fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease.

13. Valproic Acid Derivatives

Adverse reactions reported by greater than or equal to five percent of divalproex sodium-treated or oral valproic acid-treated patients and for which the incidence was greater than in the placebo group include: headache, asthenia, fever, nausea, vomiting, abdominal pain, diarrhea, anorexia, dyspepsia, constipation, somnolence, tremor, dizziness, diplopia, amblyopia, ataxia, nystagmus, emotional lability, abnormal thinking, amnesia, flu syndrome, infection, bronchitis, rhinitis, alopecia, and weight loss.

Hepatotoxicity: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Experience has indicated that children younger than two years of age are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When divalproex sodium is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for the appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

Teratogenicity: Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of valproate products in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is contemplated. An information sheet describing the teratogenic potential of valproate is available for patients.

Pancreatitis: Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use and after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and anorexia

can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

14. Zonisamide

The most commonly observed adverse reactions associated with the use of zonisamide in controlled clinical trials that are not seen at an equivalent frequency among placebo-treated patients are somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability.

Dosage and Administration

Table 4. Dosing Guidelines for the Antiepileptic Agents Included in this Review.

Agent	Adult Dosing	Pediatric Dosing
Carbamazepine	*Epilepsy (age 12 and older)* – Start 200mg BID, increase by 200mg/day at weekly intervals until desired response is achieved. Maximum dose should generally not exceed 1000mg/day in ages 12 to 15 or 1200mg/day over age 15. Usual maintenance dose is 800-1200mg/day. *Trigeminal neuralgia* – Day one, total daily dose of 200mg. Increase by up to 200mg/day only as needed to achieve freedom from pain. Maximum dose is 1200mg/day. Control is maintained in most patients at 400-800mg daily. Some patients may be maintained on as little as 200mg daily, while others may require as much as 1,200mg daily. Attempts should be made every three months to reduce the dose to the minimum effective level or even to discontinue the drug. *Bipolar* – Start 200mg BID, increase by 200mg/day at weekly intervals until desired response is achieved. Doses higher than 1,600mg/day have not been studied.	*Epilepsy (age six to 12)* – Start 100mg BID, increase by 100mg/day at weekly intervals until desired response is achieved. Maximum dose should generally not exceed 1000mg/day. Usual maintenance dose is 400-800mg/day. *(under age six)* - Start 10 to 20mg/kg/day. Increase weekly to achieve optimal clinical response. Optimal clinical response is generally achieved below 35mg/kg/day.
Divalproex Sodium	*Mania* - Start 750mg daily in divided doses (25mg/kg/day for the ER formulation). Increase to the lowest therapeutic dose which produces the desired clinical effect or the desired plasma concentration. The maximum recommended dosage is 60mg/kg/day. *Migraine* - Start 250mg BID (ER formulation: 500mg QD for 7 days then increase to 1g QD). Some patients may benefit from doses up to 1000mg/day. Clinical trials show no benefit with higher doses.	*Epilepsy* - Divalproex capsules and delayed-release tablets are indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. See adult dosing at left for dosing information.

Agent	Adult Dosing	Pediatric Dosing
	Epilepsy – Start 10 to 15mg/kg/day, increase by 5 to 10mg/kg/week to achieve optimal clinical response. Optimal clinical response is generally achieved at daily doses less than 60mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine if they are in the usually accepted therapeutic range (50 to 100mcg/mL).	
Ethosuximide	*Epilepsy* – Start 500mg/day. Maintenance dose must be individualized according to patient's response. Subsequent dose schedules can be based on effectiveness and plasma level determinations. Doses greater than 1.5g/day should be administered only under the strictest supervision of the physician.	*Epilepsy (age three – six)* – Start 250mg/day. *(six years and older)* – Start 500mg/day. Maintenance dose must be individualized according to patient's response. Optimal dose for most children is 20mg/kg/day, which should result in plasma levels within the accepted therapeutic range of 40 to 100mcg/mL. Subsequent dose schedules can be based on effectiveness and plasma level determinations. Doses greater than 1.5g/day should be administered only under the strictest supervision of the physician.
Ethotoin	*Epilepsy* - Initial daily dose should be 1g or less, with subsequent gradual dosage increases over a period of several days. The optimum dosage must be determined on the basis of individual response. The usual adult maintenance dosage is 2 to 3g daily taken in 4 to 6 divided doses. Less than 2g daily has been found ineffective in most adults.	*Epilepsy* - Pediatric dosage depends upon the age and weight of the patient. The initial dosage should not exceed 750mg daily. The usual maintenance dose in children ranges from 500mg to 1g daily, although occasionally 2 or (rarely) 3g daily may be necessary.
Felbamate	*Epilepsy (14 years and older)* - Felbamate is not indicated as a first-line antiepileptic treatment. Add at 1200mg/day in divided doses three or four times daily while reducing present AEDs by 20 percent in order to control plasma concentrations of concurrent phenytoin, valproic acid, phenobarbital, and carbamazepine and its metabolites. Further reductions of the concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Increase the dosage of felbamate by 1200mg/day increments at weekly intervals to 3600mg/day. Most side effects seen during felbamate adjunctive therapy resolve as the dosage of concomitant AEDs is decreased.	*Lennox-Gastaut syndrome (ages two to 14 years):* Adjunctive therapy - Felbamate should be added at 15mg/kg/day in divided doses three or four times daily while reducing present AEDs by 20 percent in order to control plasma levels of concurrent phenytoin, valproic acid, phenobarbital, and carbamazepine and its metabolites. Further reductions of the concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Increase the dosage of felbamate by 15mg/kg/day increments at weekly intervals to 45mg/kg/day. Most side effects seen during felbamate adjunctive therapy resolve as the dosage of concomitant AEDs is decreased.
Gabapentin	*Postherpetic neuralgia* - Start as a single 300mg dose on day one, 600mg/day on day two (divided twice daily), and 900mg/day on day three (divided 3 times daily). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800mg (divided three times daily). Additional benefit of using doses greater than 1800mg/day was not demonstrated.	*Epilepsy (age three-12 years)* - Effectiveness in pediatric patients below the age of three years has not been established. Starting dose should range from 10 to 15mg/kg/day in three divided doses, and the effective dose reached by upward titration over a period of approximately three days. The effective dose of gabapentin in patients five years of age and older is 25 to 35mg/kg/day and given in

Agent	Adult Dosing	Pediatric Dosing
	Epilepsy (12 years and older) - The effective dose of gabapentin is 900 to 1800mg/day and given in divided doses (three times a day) using 300 or 400mg capsules or 600 or 800mg tablets. The starting dose is 300mg three times a day. If necessary, the dose may be increased using 300 or 400mg capsules or 600 or 800mg tablets three times a day up to 1800mg/day. Dosages up to 2400mg/day have been well tolerated in long-term clinical studies. Doses of 3600mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the three-times-a-day schedule should not exceed 12 hours.	divided doses (three times a day). The effective dose in pediatric patients ages three and four years is 40mg/kg/day and given in divided doses (three times a day). Gabapentin may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50mg/kg/day have been well-tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy.
Lamotrigine	*Note* – The risk of non-serious rash is increased when the recommended initial dose and/or the rate of dose escalation of lamotrigine is exceeded. *Epilepsy, adjunctive therapy with valproate* – Start dose 25mg every other day weeks one and two. Titrate to 25mg/day weeks three and four. Maintenance dose 100 to 200mg/day. *Adjunctive therapy with other AEDs* – Start dose 50mg every other day weeks one and two. Titrate to 100mg/day weeks three and four. Maintenance dose 300 to 500mg/ day (in two divided doses). To achieve maintenance, dosages may be increased by 100mg/ day every one to two weeks. *Conversion to monotherapy (age 16 years and older)* – A four step regimen for conversion from concurrent therapy with valproate to monotherapy is included in the prescribing information. *Bipolar disorder* - Target dose is 200mg/day (100mg/day in patients taking valproate, which decreases lamotrigine clearance, and 400mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, which increase lamotrigine clearance). No additional benefit was seen at 400mg/day compared with 200mg/day.	*Epilepsy, adjunctive therapy (age two to 12 years)* – Start dose range from 0.15 to 0.6mg/kg/day weeks one and two. Titrate to 0.3 to 1.2mg/kg/day weeks three and four. Dose is dependent on concurrent AEDs. The smallest available strength of lamotrigine chewable tablets is 2mg, and only whole tablets should be administered. If the calculated dose cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet. *(age 12 and older)* – see adult dosing.
Levetiracetam	*Epilepsy, adjunctive therapy* – Start 500mg BID. Titrate at additional 1000mg/day every two weeks to a maximum recommended daily dose of 3000mg. There is no evidence that doses greater than 3000mg/day confer	Not approved for pediatric use.

Agent	Adult Dosing	Pediatric Dosing
	additional benefit. *Patients with impaired renal function* – Dosing must be individualized according to the patient's renal function status based on creatinine clearance estimation.	
Methsuximide	*Epilepsy* - Optimum dosage must be determined by trial. Suggested schedule is 300mg/day week one. Dosage may be increased at weekly intervals by 300mg/day for three weeks to a daily dosage of 1.2g. Methsuximide may be administered in combination with other anticonvulsants when other forms of epilepsy coexist with absence (petit mal).	*Epilepsy* – Due to inter-patient variability, therapy must be individualized according to clinical response. Optimal dosage is that minimum required for sufficient seizure control with minimal side effects. The smaller capsule (150mg) facilitates administration to small children.
Oxcarbazepine	*Epilepsy, adjunctive therapy* – Start 300mg BID. Titrate, if clinically indicated, by a maximum of 600mg/day at approximately weekly intervals to maximum of 1200mg BID. Daily dosages above 1200mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate 2400mg/day, primarily due to CNS effects. *Conversion to monotherapy* - Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with 600mg/day while simultaneously initiating the reduction of the dose of the concomitant AEDs to complete withdrawal over three to six weeks, while the maximum dose of oxcarbazepine should be reached in approximately two to four weeks. Patients should be observed closely during this transition phase. *Initiation of monotherapy* - Patients not currently being treated with AEDs may have monotherapy initiated with oxcarbazepine. Start 300mg BID. Increase by 300mg/day every third day to a dosage of 1200mg/day. A dosage of 2400mg/day has been shown to be effective in patients converted from other AEDs to oxcarbazepine monotherapy.	*Epilepsy, adjunctive therapy (age 4 to 16 years)* – Start 8 to 10mg/kg, generally not to exceed 600mg/day, given in a twice daily regimen. The target maintenance dose should be achieved over two weeks, dependent upon patient weight: 20 to 29kg = 900mg/day 29.1 to 39kg - 1200mg/day 39kg = 1800mg/day. Children younger than two years of age have not been studied in controlled clinical trials.
Phenytoin	*Epilepsy* – Start 100mg TID. Adjust dosage to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 100mg TID to QID, although an increase to 200mg TID may be made, if necessary. If seizure control is established with divided doses, 300mg once daily may be considered. When a change in dosage form or brand is made, levels should be monitored.	*Epilepsy* – Start 5mg/kg/day in two or three equally divided doses; individualize to maximum of 300mg daily. Recommended daily maintenance dosage is usually 4 to 8mg/kg. Children over six years old and adolescents may require the minimum adult dose (300mg/day).

Agent	Adult Dosing	Pediatric Dosing
Pregabalin	*Neuropathic pain associated with diabetic peripheral neuropathy* – Start 50mg three times a day (150mg/day). Titrate to 300mg/day within one week based on efficacy and tolerability. Maximum recommended dose of pregabalin is 300mg/day in patients with creatinine clearance (CLcr) of at least 60mL/min. Dose should be adjusted for patients with reduced renal function. Doses of 600mg/day have not been shown to confer additional significant benefit and are less well tolerated. *Epilepsy* – Doses of 150 to 600mg/day have been shown to be effective as adjunctive therapy in the treatment of partial-onset seizures in adults. The total daily dose should be divided and given two or three times daily. The efficacy and adverse reaction profiles of pregabalin have been shown to be dose related. In general, it is recommended that patients be started on a total daily dose no greater than 150mg/day (75 mg two times a day, or 50mg three times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600mg/day. *Postherpetic neuralgia* – Recommended dose is150 to 300mg/day in patients with CLcr of at least 60mL/min. Start 75mg two times a day, or 50mg three times a day (150mg/day). Increase to 300mg/day within one week based on efficacy and tolerability. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function. Patients who do not experience sufficient pain relief following two to four weeks of treatment with 300mg/day and who are able to tolerate pregabalin may be treated with up to 300mg two times a day or 200mg three times a day (600mg/day). In view of the dose-dependent adverse effects and the higher rate of treatment discontinuation caused by adverse reactions, dosing above 300mg/day should be reserved only for those patients who have ongoing pain and are tolerating 300mg daily. *Fibromyalgia* – Recommended dose is 300 – 450mg/day (for patients with a CLcr greater than 60mL/min). Dosing should begin at 75mg BID (150mg/day) and may be increased to 150mg BID (300mg/day) within one week based on efficacy and tolerability.	*Epilepsy* – Not approved for pediatric use. *Neuropathic pain* – No pediatric dosing information in the labeling.

Agent	Adult Dosing	Pediatric Dosing
	Patients who do not experience sufficient benefit may increase to 225mg BID (450mg/day). There is no evidence that doses above 450mg/day confers additional benefit and is not recommended.	
Primidone	*Epilepsy, first line/initial therapy* – Patients eight years of age and older who have received no previous treatment may be started on primidone according to the following regimen using either 50mg or scored 250mg primidone tablets: Days one to three - 100 to 125mg at bedtime. Days four to six - 100 to 125mg twice daily (morning and evening). Days seven to nine - 100 to 125mg three times daily (morning, noon, evening). Day 10 to maintenance - 250mg three times daily (morning, noon, evening). The usual maintenance dosage is 250mg TID or QID. If required, dose may be increased to five or six 250mg tablets daily, but daily doses should not exceed 500mg four times daily. In some cases, serum blood level determinations of primidone may be necessary for optimal dosage adjustment. Clinically effective serum level is 5 to 12mcg/mL. *Conversion from other AEDs* – In patients already on other anticonvulsants, start at 100 to 125mg at bedtime and gradually increase to maintenance level as the other drug is gradually decreased. This regimen should be continued until satisfactory dosage level is achieved for the combination, or the other medication is completely withdrawn. When therapy with primidone alone is the objective, the transition from concomitant therapy should not be completed in less than two weeks.	*Epilepsy (under eight years of age)* – The following regimen may be used: Days one to three - 50mg at bedtime. Days four to six - 50mg twice daily. Days seven to nine - 100mg twice daily. Day 10 to maintenance - 125mg three times daily to 250mg three times daily. For children under eight years of age the usual maintenance dosage is 125 to 250mg three times daily, or 10 to 25mg/kg/day in divided doses.
Tiagabine	*Epilepsy, concomitant antiepilepsy therapy* – The blood level obtained after a given dose depends on whether the patient also is receiving a drug that induces the metabolism of tiagabine. Dosing should take the presence of concomitant medications into account. *Patients taking enzyme-inducing antiepilepsy drugs (AEDs)* – The following dosing recommendations apply to patients who are already taking enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, primidone, phenobarbital). Start 4mg daily. Total daily dose may be increased by 4 to 8mg at weekly	*Epilepsy (children 12 to 18 years of age)* - Start 4mg daily. Modification of concomitant AEDs is not necessary unless clinically indicated. The total daily dose of tiagabine may be increased by 4mg at the beginning of week two. Thereafter, the total daily dose may be increased by 4 to 8mg at weekly intervals until clinical response is achieved, or up to 32mg/day. The total daily dose should be given in divided doses two to four times daily. Dosages above 32mg/day have been tolerated in a small number of adolescent patients for a relatively short duration.

Agent	Adult Dosing	Pediatric Dosing
	intervals until clinical response is achieved, or up to 56mg/day. Dosages above 56mg/day have not been systematically evaluated in adequate and well-controlled clinical trials.	
Topiramate	*Epilepsy(17 years of age and older)* – The recommended total daily dose of topiramate as adjunctive therapy in adults with partial seizures is 200 to 400mg/day in two divided doses, and 400mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25 to 50mg/day followed by titration to an effective dose in increments of 25 to 50mg/week. Titrating in increments of 25mg/week may delay the time to reach an effective dose. Daily doses above 1600mg have not been studied. *Migraine prophylaxis* – Start 25mg in the evening for one week. Titrate by an additional 25mg/day each week to 50mg BID.	*Epilepsy (two to 16 years of age)* – Start approximately 5 to 9mg/kg/day in two divided doses. Begin titration at 25mg (or less, based on a range of 1 to 3mg/kg/day) nightly for the first week. Then increase the dosage at one or two week intervals by increments of 1 to 3mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Guide dose titration by clinical outcome.
Valproic Acid	*Epilepsy, initial first line therapy or conversion to monotherapy or adjunctive therapy* – Start 10 to 15mg/kg/day. Increase by 5 to 10mg/kg/week to achieve optimal clinical response; generally achieved at daily doses below 60mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in therapeutic range (50 to 100mcg/mL).	*Epilepsy* – See adult dosage recommendations.
Zonisamide	*Note* – Because of its long half-life, up to two weeks may be required to achieve steady-state levels upon reaching a stable dose or following dosage adjustment. The prescriber may wish to prolong the duration of treatment at the lower doses in order to fully assess the effects at steady state, noting that many of the side effects of zonisamide are more frequent at doses of 300mg/day and above. *Epilepsy, adjunctive therapy* – Start 100mg daily. After two weeks, may be increased to 200mg/day for at least two weeks. It can be increased to 300mg/day and 400mg/day, with the dose stable for at least two weeks to achieve steady state at each level. Although doses of 100 to 600mg/day are effective, there is no suggestion of increasing response above 400mg/day. There is little experience with doses greater than 600mg/day.	*Epilepsy* – Safety and efficacy in pediatric patients younger than 16 years of age have not been established.

Agent	Adult Dosing	Pediatric Dosing
	Patients with renal or hepatic disease – Patients with renal or hepatic disease should be treated with caution and may require slower titration and more frequent monitoring.	

Efficacy

Table 5 summarizes many of the significant clinical trials involving the drugs in this review.

Table 5. Clinical Outcomes Data

Drug	Condition	Duration	Results
Depakote ER® versus placebo[19]	Migraine prophylaxis	12 weeks	The Depakote® sample received 500 to 1000mg per day and saw a reduction of 1.2 headaches per four weeks compared to a reduction of 0.6 headaches per four weeks in the placebo sample.
Depakote ER® versus Depakote[20]	Seizure control	12 weeks	The Depakote ER® group received 500mg QD and was 93 percent seizure-free, while the Depakote® sample received 250 to 500mg BID-TID and was 95 percent seizure-free.
Depakote®versus lithium versus placebo[21]	Bipolar disorder	1 year	The primary outcome measured was time to any mood (manic or depressive) episode. The median times to 50 percent survival without any mood episode, based on four-week intervals, were 40 weeks for divalproex sodium, 24 weeks for lithium and 28 weeks for placebo.
Topamax® versus carbamazepine and valproate[22]	Seizure control	1 year	Two treatment groups were studied. One compared TPM 100mg/day or 200mg/ day to CBZ 600mg/day. The other compared that same TPM doses to VPA 1250mg/day. Time to first seizure was comparable between the groups. The proportion of seizure-free patients at six months was 49 percent for TPM 100mg/day and 44 percent for all other groups.
Topamax® versus placebo[23]	Migraine prophylaxis	26 weeks	468 patients received one of three daily doses of topiramate or placebo. The authors concluded that topiramate is effective in migraine prevention with significant benefits displayed within the first month of treatment and maintained for 26 weeks.
Valproate versus lamotrigine versus topiramate[31]	Seizure control	2 – 7 years	716 patients were followed to 2 primary endpoints. In the time to treatment failure, valproic acid was significantly more effective than topiramate, but showed no significant difference from lamotrigine. Time to 12-month remission showed that valproic acid was significantly better than lamotrigine, but not significantly different from topiramate.
Pregabalin versus placebo[32]	Fibromyalgia	8 weeks	529 patients with fibromyalgia were followed to primary endpoint of comparison of end point mean pain scores. Pregabalin at 450mg/day significantly reduced the average severity of pain compared with placebo. Significantly more patients in the pregabalin group had ≥ 50% improvement in pain at the end point. Pregabalin at 300 – 450mg/day was associated with

Drug	Condition	Duration	Results
			significant improvements in sleep quality, fatigue, and global measures of change. Dizziness and somnolence were the most frequent adverse events.
Pregabalin versus placebo[33]	Fibromyalgia	6 weeks (open label) 26 weeks (double blind)	633 patients (279 pregabalin and 287 placebo) were followed to determine the time to loss of therapeutic response (LTR). Time to LTR was significantly longer for patients treated with pregabalin. 61% of placebo patients (vs. 32% of pregabalin patients) had lost therapeutic response. Most adverse effects were mild or moderate in intensity.
Lamotrigine versus sustained-release carbamazepine[34]	Epilepsy	40 weeks	Time to withdrawal from any cause did not differ between groups. The number of subjects who completed the 40-week period and were seizure free in the last 20 weeks was 48 (52%) in the LTG group and 52 (57%) in the CBZ group. Adverse events leading to withdrawal occurred in 13 (14%) subjects in the LTG group and 23 (25%) subjects in the CBZ group.
Pregabalin versus placebo[35]	Fibromyalgia	14 weeks	745 patients were randomized and had a baseline mean pain score=6.7. Differences from placebo in mean change from baseline to endpoint in pain score were: 300 mg/d, -0.71 (*P*=.0009); 450 mg/d, -0.98, 600 mg/d, -1.00 (each *P*<.0001). On the PGIC, 68% of 300-mg/d, 78% of 450-mg/d, and 66% of 600-mg/d patients reported at least minimal improvement *vs* 48% of placebo patients, representing a statistically significant superiority. Pregabalin 450 and 600 mg/d were associated with statistically significant improvements in total FIQ score: mean differences from placebo at endpoint were: 450 mg/d, -5.24 (*P*=.0041); 600 mg/d, -5.34 (*P*=.0034). Incidence of AEs increased with dosage. The most common AEs were dizziness (all pregabalin, 35.8%; placebo, 7.6%) and somnolence (18.0%; 3.8%).

TMP = topiramate, CBZ = carbamazepine, VPA = valproate, LTG = lamotrigine

Summary

Agent	Brand Name Examples	Generic Availability	FDA Approved Indications	Adverse Effects	Pregnancy Category
Carbamazepine IR	Tegretol®	Yes	Epilepsy, trigeminal neuralgia	Dizziness, drowsiness, unsteadiness, nausea, vomiting	D
Carbamazepine ER	Tegretol XR®	No			
	Carbatrol®	No	Epilepsy		D
	Equetro®	No	Bipolar disorder		D
Divalproex Sodium	Depakote®	No	Epilepsy, migraine prophylaxis, mania	Headache, asthenia, fever, nausea, vomiting, abdominal pain, diarrhea, anorexia, dyspepsia, constipation, somnolence, tremor, dizziness, diplopia, amblyopia, ataxia, nystagmus, emotional lability, abnormal thinking, amnesia, flu syndrome, infection, bronchitis, rhinitis, alopecia, weight loss	D
	Depakote ER®	No			D
Ethosuximide	Zarontin®	Yes	Epilepsy	Drowsiness, ataxia, dizziness	n/a
Ethotoin	Peganone®	No	Epilepsy	Lymphadenopathy, chest pain, nystagmus, diplopia, fever, dizziness, rash, diarrhea, headache, insomnia, fatigue, numbness	C
Felbamate	Felbatol®	No	Epilepsy	Anorexia, vomiting, insomnia, nausea, headache	C
Gabapentin	Neurontin®	Yes	Epilepsy, postherpetic neuralgia	Dizziness, somnolence, peripheral edema	C

Agent	Brand Name Examples	Generic Availability	FDA Approved Indications	Adverse Effects	Pregnancy Category
Lamotrigine	Lamictal®	Chewable tablet only	Epilepsy, bipolar disorder	Dizziness, ataxia, somnolence, rash headache, diplopia, blurred vision, nausea, vomiting	C
Levetiracetam	Keppra®	No	Epilepsy	Somnolence, asthenia, infection, dizziness	C
Methsuximide	Celontin®	No	Epilepsy	Drowsiness, ataxia, dizziness	n/a
Oxcarbazepine	Trileptal®	No	Epilepsy	Dizziness, tremor, somnolence, ataxia, diplopia, fatigue, nausea, vomiting, abnormal vision, abdominal pain, dyspepsia, abnormal gait	C
Phenytoin	Dilantin®	Yes (except Infatab®)	Epilepsy	Nystagmus, ataxia, slurred speech, decreased coordination, mental confusion, dizziness, insomnia, transient nervousness, motor twitching, headaches	C
Pregabalin	Lyrica®	No	Epilepsy, postherpetic neuralgia, diabetic peripheral neuropathy, fibromyalgia	Dizziness, edema, somnolence, dry mouth, blurred vision, weight gain, abnormal thinking	C
Primidone	Mysoline®	Yes	Epilepsy	Ataxia, vertigo	D

Agent	Brand Name Examples	Generic Availability	FDA Approved Indications	Adverse Effects	Pregnancy Category
Tiagabine	Gabitril®	No	Epilepsy	Dizziness, asthenia, somnolence, nausea, nervousness, tremor, abdominal pain, abnormal thinking, difficulty with concentration or attention	C
Topiramate	Topamax®	No	Epilepsy, migraine prophylaxis	Somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, diplopia	C
Valproic Acid	Depakene®	Yes	Epilepsy, migraine prophylaxis, mania	Headache, asthenia, fever, nausea, vomiting, abdominal pain, diarrhea, anorexia, dyspepsia, constipation, somnolence, tremor, dizziness, diplopia, amblyopia, ataxia, nystagmus, emotional lability, abnormal thinking, amnesia, flu syndrome, infection, bronchitis, rhinitis, alopecia, weight loss	D
Zonisamide	Zonegran®	Yes	Epilepsy	Somnolence, anorexia, dizziness, headache, nausea, agitation, irritability	C

IR = Immediate-release
ER=Extended-release

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ND Medicaid Anticonvulsant Utilization by Generic Name
12/01/06 – 11/30/07

ND Medicaid Anticonvulsant Utilization by Generic Name 12/01/06 - 11/30/07			
Generic Name	**Rx Num**	**Total Claim Cost**	**Average Price/Script**
LAMOTRIGINE	3116	$940,012.92	$301.67
DIVALPROEX SODIUM	4675	$811,017.95	$173.48
TOPIRAMATE	2576	$720,305.41	$279.62
OXCARBAZEPINE	2313	$545,307.79	$235.76
LEVETIRACETAM	1518	$465,609.98	$306.73
GABAPENTIN	2572	$285,616.08	$111.05
PREGABALIN	1871	$253,489.45	$135.48
CARBAMAZEPINE	2595	$177,893.65	$68.55
FELBAMATE	184	$70,940.91	$385.55
PHENYTOIN	1314	$54,192.54	$41.24
ZONISAMIDE	313	$51,722.10	$165.25
TIAGABINE HCL	103	$31,520.08	$306.02
PRIMIDONE	144	$9,306.11	$64.63
ETHOSUXIMIDE	86	$9,141.01	$106.29
ETHOTOIN	27	$8,830.77	$327.07
VALPROIC ACID	43	$6,259.48	$145.57
METHSUXIMIDE	26	$3,774.42	$145.17
FOSPHENYTOIN SODIUM	1	$180.00	$180.00
TOTAL	23477	$4,445,120.65	$189.34

ND Medicaid Anticonvulsant Utilization by NDC
12/01/06 – 11/30/07

Label Name	Rx Num	Total Claim Cost
CARBAMAZEPINE 100 MG TAB CHW	273	$9,501.63
CARBAMAZEPINE 100 MG/5 ML SUS	340	$15,461.33
CARBAMAZEPINE 200 MG TABLET	560	$17,123.57
CARBATROL 100 MG CAPSULE SA	33	$3,459.33
CARBATROL 200 MG CAPSULE SA	147	$17,290.46
CARBATROL 300 MG CAPSULE SA	167	$17,409.02
CELONTIN 300 MG KAPSEAL	26	$3,774.42
CEREBYX 50 MG PE/ML VIAL	1	$180.00
DEPAKOTE 125 MG SPRINKLE CAP	840	$142,952.69
DEPAKOTE 125 MG TABLET EC	214	$13,710.28
DEPAKOTE 250 MG TABLET EC	896	$116,687.47
DEPAKOTE 500 MG TABLET EC	1154	$268,790.53
DEPAKOTE ER 250 MG TAB SA	456	$40,358.73
DEPAKOTE ER 500 MG TAB SA	1104	$225,928.35
DILANTIN 100 MG CAPSULE	10	$517.09
DILANTIN 100 MG KAPSEAL	292	$13,479.95
DILANTIN 125 MG/5 ML SUSP	37	$2,453.58
DILANTIN 30 MG KAPSEAL	67	$1,528.84
DILANTIN 50 MG INFATAB	215	$6,734.53
ETHOSUXIMIDE 250 MG CAPSULE	38	$3,473.01
ETHOSUXIMIDE 250 MG/5 ML SYRP	22	$1,906.60
FELBATOL 400 MG TABLET	55	$19,910.20
FELBATOL 600 MG TABLET	66	$21,113.44
FELBATOL 600 MG/5 ML SUSP	63	$29,917.27
GABAPENTIN 100 MG CAPSULE	352	$15,122.15
GABAPENTIN 300 MG CAPSULE	958	$85,266.43
GABAPENTIN 400 MG CAPSULE	383	$42,454.01
GABAPENTIN 600 MG TABLET	582	$89,534.70
GABAPENTIN 800 MG TABLET	222	$43,143.84
GABITRIL 12 MG TABLET	25	$3,009.05
GABITRIL 16 MG TABLET	12	$2,638.78
GABITRIL 2 MG TABLET	31	$11,706.91
GABITRIL 4 MG TABLET	34	$14,037.21
KEPPRA 1,000 MG TABLET	91	$45,485.26
KEPPRA 100 MG/ML ORAL SOLN	403	$85,769.00

Label Name	Rx Num	Total Claim Cost
KEPPRA 250 MG TABLET	145	$25,950.22
KEPPRA 500 MG TABLET	687	$232,704.39
KEPPRA 750 MG TABLET	189	$75,212.61
LAMICTAL 100 MG TABLET	1182	$313,182.72
LAMICTAL 150 MG TABLET	401	$102,423.69
LAMICTAL 200 MG TABLET	689	$204,438.33
LAMICTAL 25 MG DISPER TABLET	31	$18,255.08
LAMICTAL 25 MG TABLET	606	$218,435.25
LAMICTAL 5 MG DISPER TABLET	19	$8,953.35
LAMICTAL TB START KIT (ORANGE)	20	$4,629.16
LAMOTRIGINE 25 MG DISPER TABS	112	$50,331.57
LAMOTRIGINE 5 MG DISPER TABLET	55	$19,348.77
LYRICA 100 MG CAPSULE	247	$39,639.49
LYRICA 150 MG CAPSULE	313	$43,634.55
LYRICA 200 MG CAPSULE	102	$17,169.46
LYRICA 225 MG CAPSULE	5	$680.16
LYRICA 25 MG CAPSULE	60	$7,510.19
LYRICA 300 MG CAPSULE	134	$16,024.70
LYRICA 50 MG CAPSULE	341	$41,479.22
LYRICA 75 MG CAPSULE	667	$87,043.94
MYSOLINE 250 MG TABLET	1	$186.99
MYSOLINE 50 MG TABLET	10	$1,255.90
NEURONTIN 250 MG/5 ML SOLN	68	$9,290.32
NEURONTIN 300 MG CAPSULE	2	$203.00
OXCARBAZEPINE 150 MG TABLET	25	$2,926.48
OXCARBAZEPINE 300 MG TABLET	58	$10,498.91
OXCARBAZEPINE 600 MG TABLET	37	$10,422.99
PEGANONE 250 MG TABLET	27	$8,830.77
PHENYTOIN 125 MG/5 ML SUSP	118	$5,382.57
PHENYTOIN SOD 100 MG CAPSULE	583	$24,523.56
PRIMIDONE 250 MG TABLET	110	$6,941.00
PRIMIDONE 50 MG TABLET	24	$942.30
TEGRETOL 100 MG TABLET CHEW	70	$5,565.73
TEGRETOL 100 MG/5 ML SUSP	57	$9,172.10
TEGRETOL 200 MG TABLET	43	$5,419.43
TEGRETOL XR 100 MG TABLET SA	273	$10,489.67
TEGRETOL XR 200 MG TABLET SA	306	$25,830.59

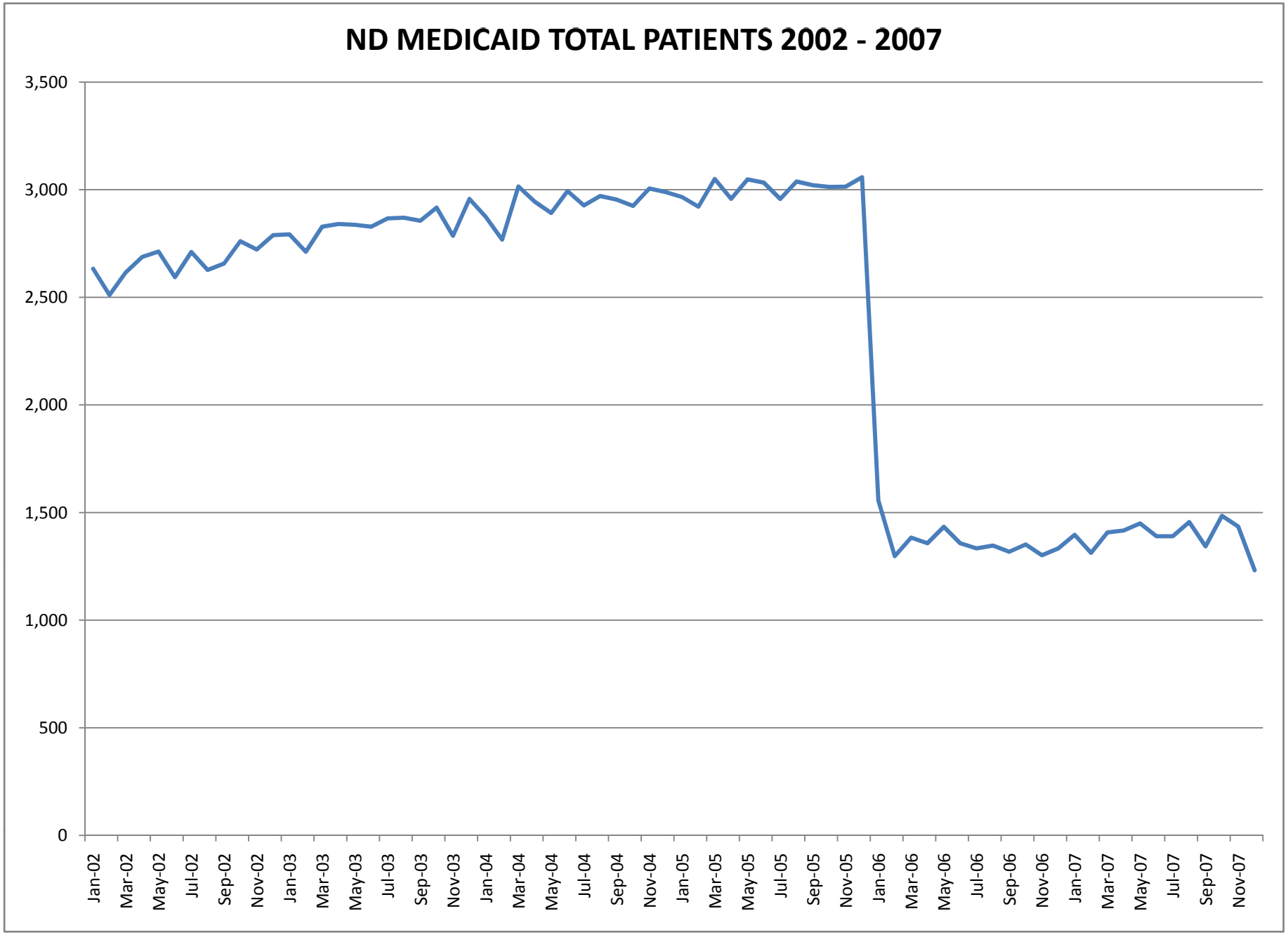
Label Name	Rx Num	Total Claim Cost
TEGRETOL XR 400 MG TABLET SA	326	$41,173.89
TOPAMAX 100 MG TABLET	863	$281,132.27
TOPAMAX 15 MG SPRINKLE CAP	67	$19,895.19
TOPAMAX 200 MG TABLET	284	$116,889.89
TOPAMAX 25 MG SPRINKLE CAP	76	$34,647.28
TOPAMAX 25 MG TABLET	757	$145,177.07
TOPAMAX 50 MG TABLET	526	$122,189.70
TRILEPTAL 150 MG TABLET	335	$46,459.11
TRILEPTAL 300 MG TABLET	805	$172,727.75
TRILEPTAL 300 MG/5 ML SUSP	393	$78,087.64
TRILEPTAL 600 MG TABLET	658	$223,524.61
VALPROIC ACID 250 MG CAPSULE	43	$6,259.48
ZARONTIN 250 MG CAPSULE	22	$3,139.80
ZARONTIN 250 MG/5 ML SYRUP	4	$621.60
ZONEGRAN 100 MG CAPSULE	24	$5,638.64
ZONISAMIDE 100 MG CAPSULE	243	$46,622.35
ZONISAMIDE 25 MG CAPSULE	49	$4,146.48
ZONISAMIDE 50 MG CAPSULE	21	$953.27
TOTAL 2690 RECIPIENTS	23477	$4,445,120.65

ND Medicaid Anticonvulsant Utilization
Patients with Seizure Diagnosis
12/01/06 – 11/30/07

Label Name	Rx Num	Total Claim Cost
CARBAMAZEPINE 100 MG TAB CHW	73	$2,365.75
CARBAMAZEPINE 100 MG/5 ML SUS	97	$3,911.17
CARBAMAZEPINE 200 MG TABLET	132	$4,312.91
CARBATROL 100 MG CAPSULE SA	28	$3,124.08
CARBATROL 200 MG CAPSULE SA	64	$7,851.66
CARBATROL 300 MG CAPSULE SA	74	$7,040.49
CELONTIN 300 MG KAPSEAL	13	$1,664.95
DEPAKOTE 125 MG SPRINKLE CAP	312	$48,620.39
DEPAKOTE 125 MG TABLET EC	43	$3,210.92
DEPAKOTE 250 MG TABLET EC	187	$21,916.70
DEPAKOTE 500 MG TABLET EC	228	$51,024.99
DEPAKOTE ER 250 MG TAB SA	53	$5,941.96
DEPAKOTE ER 500 MG TAB SA	230	$49,760.83
DILANTIN 100 MG CAPSULE	121	$4,883.19
DILANTIN 125 MG/5 ML SUSP	27	$1,399.38
DILANTIN 30 MG KAPSEAL	17	$468.53
DILANTIN 50 MG INFATAB	68	$1,366.33
ETHOSUXIMIDE 250 MG CAPSULE	25	$2,460.86
ETHOSUXIMIDE 250 MG/5 ML SYRP	21	$1,890.25
FELBATOL 400 MG TABLET	28	$12,120.71
FELBATOL 600 MG TABLET	17	$3,502.49
FELBATOL 600 MG/5 ML SUSP	52	$22,060.00
GABAPENTIN 100 MG CAPSULE	5	$246.05
GABAPENTIN 300 MG CAPSULE	90	$9,548.13
GABAPENTIN 400 MG CAPSULE	20	$1,345.44
GABAPENTIN 600 MG TABLET	24	$4,537.37
GABITRIL 16 MG TABLET	5	$1,518.75
GABITRIL 4 MG TABLET	6	$1,127.10
KEPPRA 1,000 MG TABLET	50	$26,485.54
KEPPRA 100 MG/ML ORAL SOLN	277	$55,431.81
KEPPRA 250 MG TABLET	65	$12,746.99
KEPPRA 500 MG TABLET	317	$117,580.29
KEPPRA 750 MG TABLET	58	$23,461.10
LAMICTAL 100 MG TABLET	339	$125,175.32

Label Name	Rx Num	Total Claim Cost
LAMICTAL 150 MG TABLET	66	$20,549.99
LAMICTAL 200 MG TABLET	152	$59,467.37
LAMICTAL 25 MG DISPER TABLET	4	$2,460.78
LAMICTAL 25 MG TABLET	181	$96,112.85
LAMICTAL 5 MG DISPER TABLET	11	$6,598.33
LAMICTAL TB START KIT (ORANGE)	1	$208.71
LAMOTRIGINE 25 MG DISPER TABS	67	$32,319.19
LAMOTRIGINE 5 MG DISPER TABLET	37	$15,089.80
LYRICA 100 MG CAPSULE	17	$2,782.15
LYRICA 150 MG CAPSULE	25	$3,420.39
LYRICA 25 MG CAPSULE	10	$1,178.87
LYRICA 300 MG CAPSULE	10	$725.90
LYRICA 50 MG CAPSULE	36	$4,568.98
LYRICA 75 MG CAPSULE	27	$3,331.62
MEBARAL 50 MG TABLET	1	$179.95
MEPHOBARBITAL 100 MG TABLET	6	$628.55
MEPHOBARBITAL 50 MG TABLET	11	$1,869.45
NEURONTIN 250 MG/5 ML SOLN	57	$8,289.78
OXCARBAZEPINE 150 MG TABLET	7	$984.31
OXCARBAZEPINE 300 MG TABLET	11	$2,264.11
OXCARBAZEPINE 600 MG TABLET	4	$1,256.45
PEGANONE 250 MG TABLET	15	$3,077.09
PHENYTOIN 125 MG/5 ML SUSP	91	$3,790.26
PHENYTOIN SOD 100 MG CAPSULE	253	$10,650.67
PRIMIDONE 250 MG TABLET	17	$1,121.85
TEGRETOL 100 MG TABLET CHEW	3	$179.53
TEGRETOL 100 MG/5 ML SUSP	23	$3,059.19
TEGRETOL 200 MG TABLET	7	$589.57
TEGRETOL XR 100 MG TABLET SA	82	$4,274.63
TEGRETOL XR 200 MG TABLET SA	77	$7,150.23
TEGRETOL XR 400 MG TABLET SA	90	$11,690.45
TOPAMAX 100 MG TABLET	148	$61,498.15
TOPAMAX 15 MG SPRINKLE CAP	47	$14,622.92
TOPAMAX 200 MG TABLET	46	$21,965.75
TOPAMAX 25 MG SPRINKLE CAP	32	$10,908.85
TOPAMAX 25 MG TABLET	201	$51,750.22
TOPAMAX 50 MG TABLET	59	$14,475.63

Label Name	Rx Num	Total Claim Cost
TRILEPTAL 150 MG TABLET	131	$20,165.44
TRILEPTAL 300 MG TABLET	192	$47,947.93
TRILEPTAL 300 MG/5 ML SUSP	229	$50,167.24
TRILEPTAL 600 MG TABLET	84	$32,474.61
VALPROIC ACID 250 MG CAPSULE	204	$18,537.59
ZARONTIN 250 MG CAPSULE	2	$283.31
ZONISAMIDE 100 MG CAPSULE	125	$21,539.94
ZONISAMIDE 25 MG CAPSULE	49	$4,146.48
ZONISAMIDE 50 MG CAPSULE	21	$953.27
TOTAL 448 Recipients	6135	$1,321,410.76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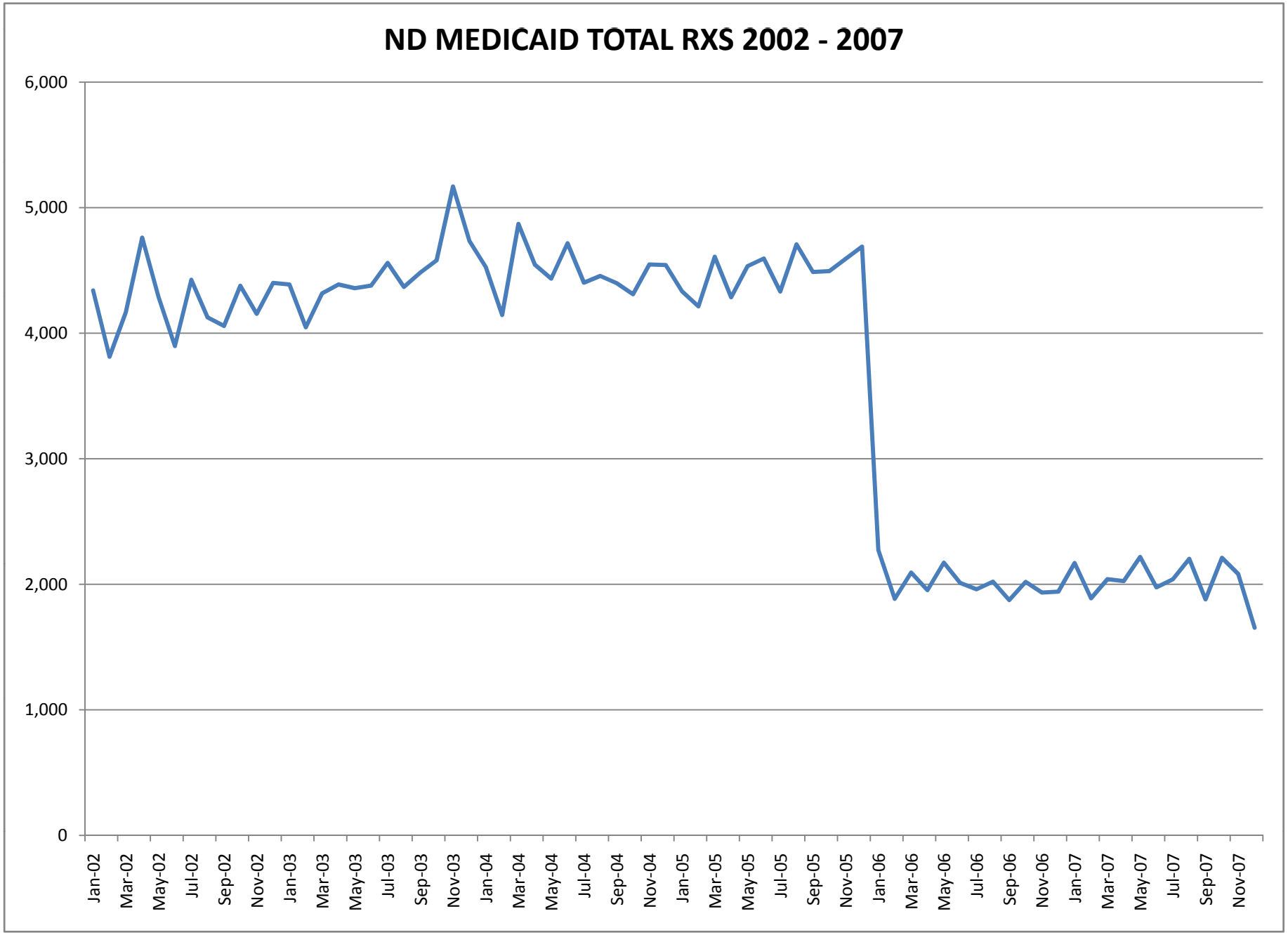
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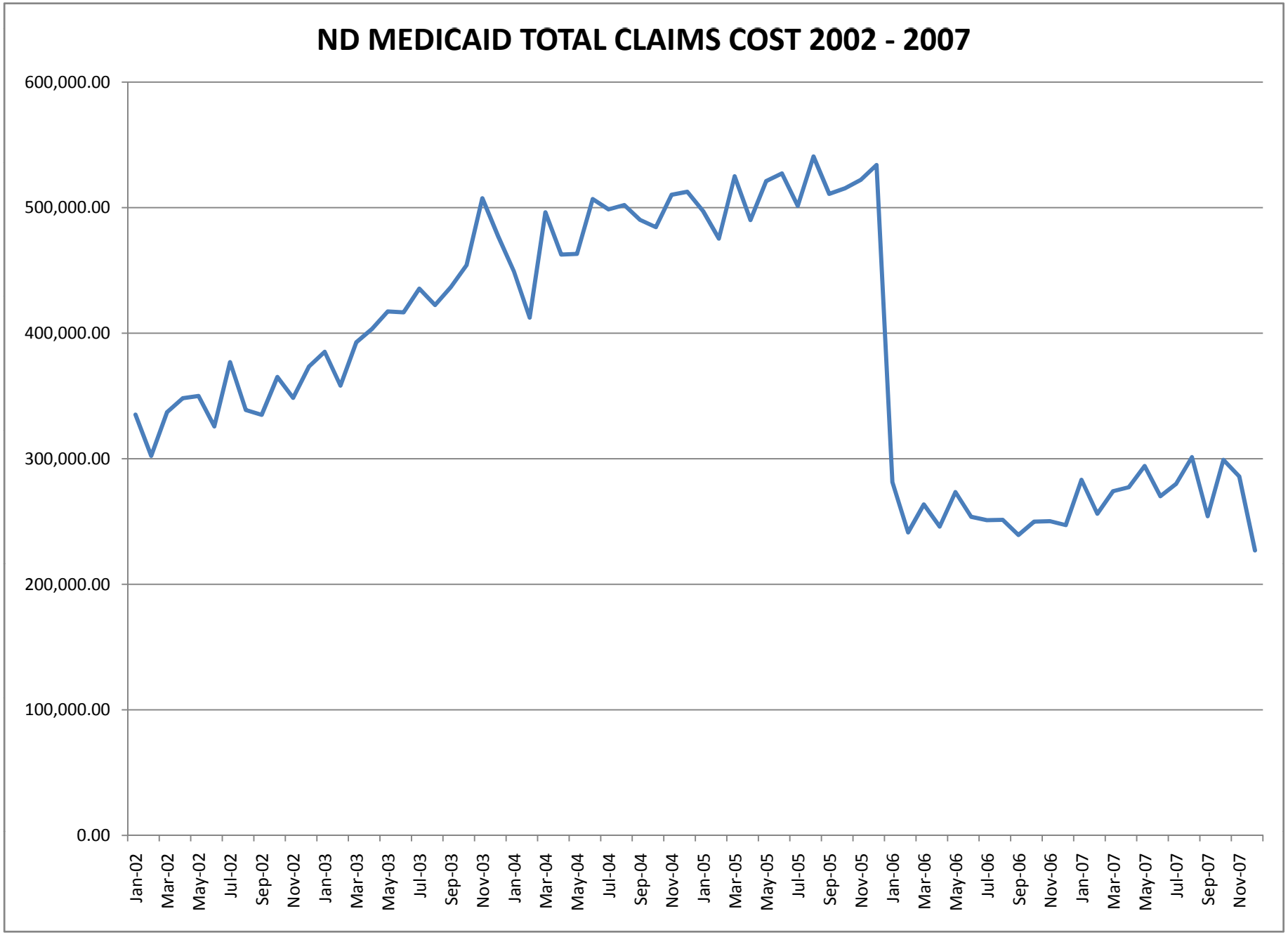
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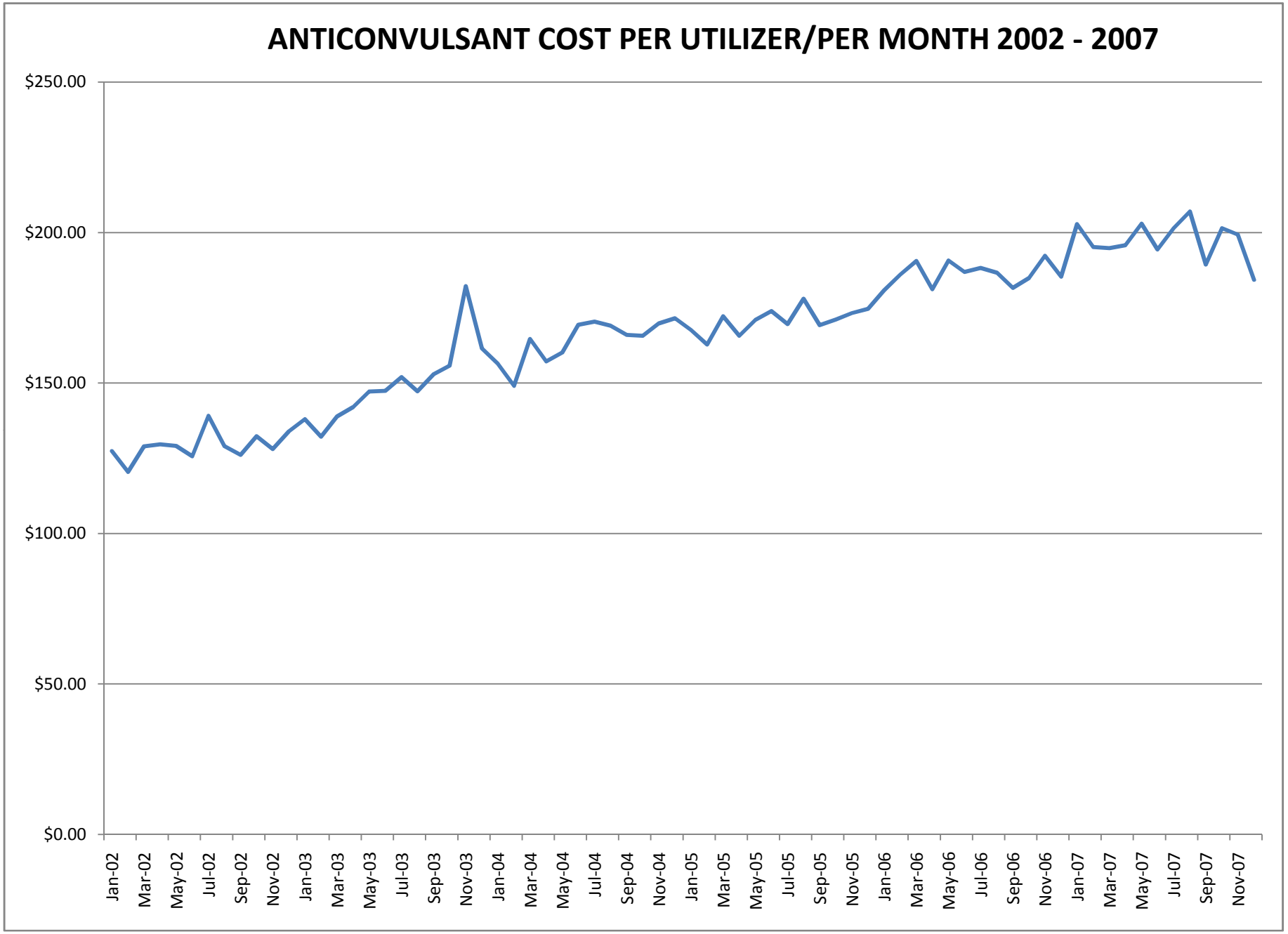
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