# *Therapeutic Class Overview*
# *Anticonvulsants*

**Therapeutic Class**
**Overview/Summary:** The anticonvulsants are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. Some anticonvulsants are also FDA-approved for the prevention of migraines, and management of bipolar disorders, fibromyalgia, neuropathic pain and other non-seizure related conditions. The specific FDA-approved indications for each of these agents are outlined in Table 1.[1-45] Seizure disorders are classified into four major categories: partial seizures (seizures beginning locally), generalized seizures (bilaterally symmetrical and without local onset), unilateral seizures (seizures that are predominantly unilateral) and unclassified epileptic seizures (seizures that are unclassifiable because of incomplete data). Partial seizures are subdivided into those with elementary symptomatology, those with complex symptomatology, and those that are secondarily generalized. Partial seizures with elementary symptomatology include those with motor symptoms (e.g., Jacksonian seizures) or with autonomic symptoms. Partial seizures with complex symptomatology are also known as temporal lobe or psychomotor seizures. Generalized seizures include tonic-clonic (grand mal) seizures, absence (petit mal) seizures, myoclonic seizures and akinetic seizures. Two or more seizures that occur sequentially without full recovery of consciousness between the seizures or seizures that last more than 30 minutes are known as status epilepticus.[46]

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life.[47] Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid. Over the past decade, many new chemical entities have become available in the United States. The newer antiepileptic drugs have better adverse event and drug interaction profiles, and they do not require serum concentration monitoring.[48-50] All of the anticonvulsants are FDA-approved for the treatment of various seizure disorders; however, these agents are primarily utilized in the treatment of partial, or focal, seizures and generalized tonic-clonic seizures. Currently there are several generic anticonvulsants available, and at least one generic agent is available within each anticonvulsant subclass.[1]

**Table 1. Current Medications Available in Therapeutic Class[1-45]**

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| **Barbiturates** | | | |
| Phenobarbital | Anticonvulsant (tablet), emergency control of certain acute convulsive episodes (injection), long term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures (injection), treatment of generalized and partial seizures (elixir), hypnotic, for short term treatment of insomnia (injection), preanesthetic (injection), sedative | Elixir:<br>20 mg/5 mL<br><br>Injection:<br>65 mg/mL<br>130 mg/mL<br><br>Tablet:<br>15 mg<br>16.2 mg<br>30 mg<br>32.4 mg<br>60 mg<br>64.8 mg<br>97.2 mg<br>100 mg | √ |
| Primidone (Mysoline®*) | Control of grand mal, psychomotor, and focal epileptic seizures, used alone or | Tablet:<br>50 mg | √ |


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catamaran

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | concomitantly with other anticonvulsants | 250 mg | |
| **Benzodiazepines** | | | |
| Clobazam (Onfi®) | Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients two years of age or older | Tablet:<br>5 mg<br>10 mg<br>20 mg | - |
| Clonazepam (Klonopin®*) | Treatment of Lennox-Gastaut Syndrome (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy, treatment of panic disorder, with or without agoraphobia | Orally disintegrating tablet:<br>0.125 mg<br>0.25 mg<br>0.5 mg<br>1 mg<br>2 mg<br><br>Tablet:<br>0.5 mg<br>1 mg<br>2 mg | √ |
| Diazepam (Diastat®*) | Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity | Rectal gel:<br>2.5 mg<br>10 mg<br>20 mg | √ |
| **Hydantoins** | | | |
| Ethotoin (Peganone®) | Control of generalized tonic-clonic and complex partial seizures | Tablet:<br>250 mg | - |
| Phenytoin (Phenytek®*, Dilantin®*) | Control of status epilepticus of the grand mal type (injection), control of generalized tonic-clonic and complex partial seizures (chewable tablet, extended-release capsule, suspension), prevention and treatment of seizures occurring during or following neurosurgery | Chewable tablet:<br>50 mg<br><br>Extended-release capsule:<br>30 mg<br>100 mg<br>200 mg<br>300 mg<br><br>Injection:<br>50 mg/mL<br><br>Suspension:<br>125 mg/5 mL | √ |
| **Succinimides** | | | |
| Ethosuximide (Zarontin®*) | Control of absence epilepsy | Capsule:<br>250 mg<br><br>Syrup:<br>250 mg/5 mL | √ |
| Methsuximide (Celontin®) | Control of absence seizures that are refractory to other drugs | Capsule:<br>300 mg | - |


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| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| **Anticonvulsants, Miscellaneous** | | | |
| Carbamazepine (Carbatrol®*, Epitol®*, Equetro®, Tegretol®*, Tegretol XR®*) | Generalized tonic-clonic seizures, mixed seizure patterns, partial seizures with complex symptomatology, acute treatment of manic or mixed episodes associated with bipolar disorder (Equetro®), trigeminal neuralgia | Chewable tablet:<br>100 mg<br><br>Extended-release capsule:<br>100 mg<br>200 mg<br>300 mg<br><br>Extended-release tablet:<br>100 mg<br>200 mg<br>400 mg<br><br>Suspension:<br>100 mg/5 mL<br><br>Tablet:<br>200 mg | √ |
| Divalproex (Depakote®*, Depakote ER®*) | Adjunctive therapy in patients with multiple seizure types, that include absence seizures (extended-release, delayed-release), monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), acute treatment of manic or mixed episodes associated with bipolar disorder (extended-release), prophylaxis of migraine headaches (extended-release, delayed-release) | Capsule (sprinkle):<br>125 mg<br><br>Delayed-release tablet:<br>125 mg<br>250 mg<br>500 mg<br><br>Extended-release tablet:<br>250 mg<br>500 mg | √ |
| Ezogabine (Potiga®) | Adjunctive therapy in the treatment of partial onset seizures | Tablet:<br>50 mg<br>200 mg<br>300 mg<br>400 mg | - |
| Felbamate (Felbatol®*) | Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use | Suspension:<br>600 mg/5 mL<br><br>Tablet:<br>400 mg<br>600 mg | √ |
| Gabapentin (Neurontin®*) | Adjunctive therapy in the treatment of partial seizures, postherpetic neuralgia | Capsule:<br>100 mg<br>300 mg<br>400 mg | √ |


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| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | | Solution:<br>250 mg/5 mL<br><br>Tablet:<br>600 mg<br>800 mg | |
| Lacosamide (Vimpat®) | Adjunctive therapy in the treatment of partial seizures | Injection:<br>200 mg/20 mL<br><br>Solution:<br>10 mg/mL<br><br>Tablet:<br>50 mg<br>100 mg<br>150 mg<br>200 mg | - |
| Lamotrigine (Lamictal®*, Lamictal CD®*, Lamictal ODT® Lamictal XR®*) | Adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome (chewable and orally disintegrating tablets), monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drugs, maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (chewable and orally disintegrating tablets) | Chewable tablet:<br>2 mg<br>5 mg<br>25 mg<br><br>Extended-release tablet:<br>25 mg<br>50 mg<br>100 mg<br>200 mg<br>250 mg<br>300 mg<br><br>Orally disintegrating tablet:<br>25 mg<br>50 mg<br>100 mg<br>200 mg<br><br>Tablet:<br>25 mg<br>50 mg<br>100 mg<br>150 mg<br>200 mg<br>250 mg | √ |
| Levetiracetam (Keppra®*, Keppra XR®*) | Adjunctive therapy in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy (injection, tablets), adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures | Extended-release tablet:<br>500 mg<br>750 mg<br><br>Injection: | √ |


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| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | (injection, tablets), | 500 mg/5 mL<br><br>Solution:<br>100 mg/mL<br><br>Tablet:<br>250 mg<br>500 mg<br>750 mg<br>1,000 mg | |
| Oxcarbazepine (Oxtellar XR®, Trileptal®*) | Monotherapy and adjunctive therapy in the treatment of partial seizures | Extended-release tablet:<br>150 mg<br>300 mg<br>600 mg<br><br>Suspension:<br>300 mg/5 mL<br><br>Tablet:<br>150 mg<br>300 mg<br>600 mg | √ |
| Perampanel (Fycompa®) | Adjunctive therapy in the treatment of partial onset seizures† | Tablet:<br>2 mg<br>4 mg<br>6 mg<br>8 mg<br>10 mg<br>12 mg | - |
| Pregabalin (Lyrica®) | Adjunctive therapy in the treatment of partial seizures, fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, postherpetic neuralgia | Capsule:<br>25 mg<br>50 mg<br>75 mg<br>100 mg<br>150 mg<br>200 mg<br>225 mg<br>300 mg<br><br>Solution:<br>20 mg/mL | - |
| Rufinamide (Banzel®) | Adjunctive therapy for seizures associated with Lennox–Gastaut syndrome | Suspension:<br>40 mg/mL<br><br>Tablet:<br>200 mg<br>400 mg | - |
| Tiagabine (Gabitril®*) | Adjunctive therapy in the treatment of partial seizures | Tablet:<br>2 mg<br>4 mg<br>12 mg<br>16 mg | √ |


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| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Topiramate (Topamax®*, Trokendi XR®) | Adjunctive therapy in patients with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome, monotherapy (initial) in patients with partial onset or primary generalized tonic-clonic seizures, prophylaxis of migraine headaches | Capsule (sprinkle):<br>15 mg<br>25 mg<br><br>Tablet:<br>25 mg<br>50 mg<br>100 mg<br>200 mg<br><br>Extended-release capsule:<br>25 mg<br>50 mg<br>100 mg<br>200 mg | √ |
| Valproic acid (Depakene®* Stavzor®) | Adjunctive therapy in patients with multiple seizure types, that include absence seizures, monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), prophylaxis of migraine headaches (delayed-release) | Capsule:<br>250 mg<br><br>Delayed-release capsule:<br>125 mg<br>250 mg<br>500 mg<br><br>Solution:<br>250 mg/5 mL | √ |
| Vigabatrin (Sabril®) | Adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss (tablet), monotherapy for pediatric patients (one month to two years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss (solution) | Solution (powder):<br>500 mg<br><br>Tablet:<br>500 mg | - |
| Zonisamide (Zonegran®*) | Adjunctive therapy in the treatment of partial seizures | Capsule:<br>25 mg<br>50 mg<br>100 mg | √ |

*Generic available in at least one dosage form or strength.
† With or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

**Evidence-based Medicine**

- Hancock et al conducted a meta-analysis of 14 randomized controlled trials which included infants and children with infantile spasms. Treatment with vigabatrin was associated with a complete cessation of spasms in 7/20 (35%) patients compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo.[51]


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- Another meta-analysis by Hancock et al included trials that evaluated the safety and efficacy of felbamate, lamotrigine, rufinamide and topiramate in the treatment of Lennox-Gastaut Syndrome (LGS). While all of these agents demonstrated some efficacy, the optimum treatment of LGS remained uncertain as no single drug was highly efficacious. Felbamate, lamotrigine, rufinamide and topiramate may be helpful as add-on therapy.[52]
- The results of a study by Ng et al demonstrated that the mean percent reduction in weekly drop seizures was 41.2% with clobazam 0.25 mg/kg/day ($P$=0.0120), 49.4% with clobazam 0.5 mg/kg/day ($P$=0.0015) and 68.3% with clobazam 1.0 mg/kg/day ($P$<0.0001) compared to 12.1% for placebo.[53]
- In a study by Porter et al, treatment with ezogabine 600, 900 and 1,200 mg reduced the total monthly seizure frequency from baseline by 23, 29 and 35% compared to 13% with placebo ($P$<0.001 for all).[54] In a second study of patients with drug-resistant partial epilepsy, ezogabine 1,200 mg daily reduced the total monthly seizure frequency from baseline by 44.3% compared to 17.5% with placebo ($P$<0.001).[55]
- Perampanel is approved as adjunctive therapy in patients with partial onset seizures. In one study perampanel 8 or 12 mg significantly reduced seizure frequency compared to placebo ($P$=0.0261 and $P$=0.0158 for 8 and 12 mg, respectively); however, there was no significant difference in the proportion of patients who achieved a seizure reduction >50% from baseline compared to the placebo group.[56] Similar results were reported in a second study ($P$<0.001 and $P$=0.011 for 8 and 12 mg, respectively); however, more patients treated with perampanel 8 or 12 mg had a reduced seizure frequency >50% from baseline compared to placebo ($P$=0.002 and $P$<0.001 for 8 and 12 mg, respectively).[57] In a third study, treatment with perampanel 4 or 8 mg significantly reduced seizure frequency compared to placebo ($P$=0.003 and $P$<0.001 for 4 mg and 8 mg, respectively). Moreover, a greater proportion of patients treated with perampanel 4 or 8 mg achieved a reduction in seizure frequency >50% from baseline compared to placebo ($P$=0.013 and $P$<0.001 for 4 and 8 mg, respectively).[58]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
    - The 2012 National Institute for Clinical Excellence guideline recommends carbamazepine and lamotrigine as first-line treatment of children, young people, and adults with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated antiepileptic also proves inadequate. Sodium valproate is recommended first-line for the treatment of children, young people, and adults with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered to all patients if first-line therapies are inadequate.[46]
    - Vigabatrin (oral solution) is Food and Drug Administration (FDA)-approved for the management of infantile spasm. According to the 2012 American Academy of Neurology medical management of infantile spasms guideline, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone (ACTH) and vigabatrin. Evidence suggests that ACTH may be preferred over vigabatrin for short-term management.[59]
    - Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are FDA-approved for the management of Lennox Gastaut Syndrome. Sodium valproate is recognized as first-line, with lamotrigine recommended as adjunctive therapy if needed.[46]
    - Treatment guidelines recommend valproate and carbamazepine as potential beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine, topiramate, or gabapentin are unlikely beneficial in this clinical situation and oxcarbazepine may be considered for treatment. With regard to bipolar depression in adults, lamotrigine should be considered as a potential first-line option, and patients who do not respond to initial monotherapy should receive combination therapy with lithium.[60-64]
    - Divalproex, topiramate and valproic acid are FDA-approved for the prophylaxis of migraine headaches, and all should be offered for migraine prevention according to the 2012 guidelines from the American Academy of Neurology/American Headache Society.


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Furthermore, carbamazepine may be considered for migraine prevention as it is a possibly effective treatment, and lamotrigine is ineffective.[65]
  - According to the American Academy of Neurology, anticonvulsants, antidepressants, opioids and other pharmacologic agents (capsaicin, isosorbide dinitrate spray, and lidocaine patch) are potential treatment options for painful diabetic neuropathy. If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment.[66]
  - According to the American Academy of Neurology, first-line therapies for the management of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.[67]
  - The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.[68]
- Other Key Facts:
  - The majority of anticonvulsants are available in a generic formulation, and there is at least one generic agent available within each pharmacologic class.
  - Clobazam was most recently approved by the FDA in 2011; however, this agent has been available internationally for several years for the treatment of anxiety and epilepsy.
  - Ezogabine has a unique mechanism of action in that it may act as an anticonvulsant by reducing excitability through the stabilization of neuronal potassium channels in an “open” position.[34]
  - Perampanel is a first-in-class anticonvulsant that works as a highly selective, non-competitive AMPA-type glutamate receptor antagonist.[69]

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# *Therapeutic Class Review*
# *Anticonvulsants*

## Overview/Summary

The anticonvulsants encompass over 20 different chemical entities including barbiturates, benzodiazepines, hydantoins, succinimides and miscellaneous anticonvulsants. These agents are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. Some anticonvulsants are also FDA-approved for the prevention of migraines, and management of bipolar disorder, fibromyalgia, neuropathic pain and other non-seizure related conditions. The specific FDA-approved indications for each of these agents are outlined in Table 2a, 2b, 2c, 2d, and 2e.[1,2] Seizure disorders are classified into four major categories: partial seizures (seizures beginning locally), generalized seizures (bilaterally symmetrical and without local onset), unilateral seizures (seizures that are predominantly unilateral) and unclassified epileptic seizures (seizures that are unclassifiable because of incomplete data). Partial seizures are subdivided into those with elementary symptomatology, those with complex symptomatology and those that are secondarily generalized. Partial seizures with elementary symptomatology include those with motor symptoms (e.g., Jacksonian seizures) or with autonomic symptoms. Partial seizures with complex symptomatology are also known as temporal lobe or psychomotor seizures. Generalized seizures include tonic-clonic (grand mal) seizures, absence (petit mal) seizures, myoclonic seizures and akinetic seizures. Two or more seizures that occur sequentially without full recovery of consciousness between the seizures or seizures that last more than 30 minutes are known as status epilepticus.

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life.[3] Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone (metabolized to phenobarbital) and valproic acid. Over the past decade, many new chemical entities have become available in the United States. Some advantages of the newer antiepileptic drugs are better adverse event and drug interaction profiles, and they do not require serum concentration monitoring.[4-6] All of the anticonvulsants are FDA-approved for the treatment of various seizure disorders; however, these agents are primarily utilized in the treatment of partial, or focal, seizures and generalized tonic-clonic seizures.

The 2012 National Institute for Clinical Excellence guideline recommends carbamazepine and lamotrigine as first-line treatment of children, young people and adults with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated antiepileptic also proves inadequate. Furthermore, sodium valproate is recommended first-line for the treatment of children, young people, and adults with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered to all patients if first-line therapies are inadequate.[7] The roles of ezogabine and perampanel, the two newest anticonvulsants to be approved by the FDA, are not addressed within the most recent guidelines. Two clinically unique seizure disorders are infantile spasms and Lennox-Gastaut Syndrome (LGS). Infantile spasms is an age-specific convulsive disorder of infancy and early childhood that is typically associated with electroencephalographic pattern of hypsarrhythmia, and also developmental regression.[8] Typically, LGS is an ill-defined syndrome that is associated with severe seizures in childhood. Patients with LGS present in the first seven years of life, with some experiencing seizures prior to the age of one.[9] Vigabatrin (oral solution) is FDA-approved for the management of infantile spasm. According to the 2012 American Academy of Neurology medical management of infantile spasms guideline, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone (ACTH) and vigabatrin. Furthermore, evidence suggests that ACTH may be preferred over vigabatrin for short-term management.[10] Previous guidelines support these recommendations.[11] Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are FDA-approved


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for the management of LGS. Sodium valproate is recognized as first-line, with lamotrigine recommended as adjunctive therapy if needed.[7]

Carbamazepine, divalproex and valproic acid are FDA-approved for the treatment of acute manic and/or mixed episodes associated with bipolar disorders. Lamotrigine is FDA-approved for maintenance therapy of bipolar disorder, specifically to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. Treatment guidelines recommend valproate and carbamazepine as potential beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine, topiramate or gabapentin are unlikely beneficial in this clinical situation and oxcarbazepine may be considered for treatment. Lamotrigine should be considered as a potential first-line option for the treatment of bipolar depression in adults. For patients who do not respond to initial monotherapy, combination therapy with lithium is recommended.[12-16]

Divalproex, topiramate, and valproic acid are FDA-approved for the prophylaxis of migraine headaches, and all should be offered for migraine prevention according to the 2012 guidelines from the American Academy of Neurology/American Headache Society. Furthermore, carbamazepine may be considered for migraine prevention as it is a possibly effective treatment, while lamotrigine is ineffective.[17] Pregabalin is the only anticonvulsant FDA-approved for the management of diabetic peripheral neuropathy (DPN). According to the American Academy of Neurology, anticonvulsants, antidepressants, opioids and other pharmacologic agents (capsaicin, isosorbide dinitrate spray and lidocaine patch) are potential treatment options for painful diabetic neuropathy. If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment.[18] Pregabalin, and gabapentin, are the only anticonvulsants FDA-approved for the management of postherpetic neuralgia (PHN). According to the American Academy of Neurology, first-line therapies for the management of PHN include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.[19] Pregabalin is also the only anticonvulsant FDA-approved for the management of fibromyalgia.

The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.[20] Carbamazepine is the only anticonvulsant FDA-approved for the management of trigeminal neuralgia. Carbamazepine should be offered to patients experiencing pain associated with trigeminal neuralgia. Oxcarbazepine and lamotrigine are also potential treatment options to consider.[21] Included in the review are certain anticonvulsants from the following pharmacologic classes: barbiturates, benzodiazepines, hydantoins, succinimides, and miscellaneous anticonvulsants. Currently there are several generic agents available, and at least one generic agent is available within each subclass of anticonvulsant. Of note, the barbiturate Mebaral® (mephobarbital) was discontinued in March 2012.[22]

## Medications

**Table 1. Medications Included Within Class Review[1,23-66]**

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| **Barbiturates** | | |
| Phenobarbital | Barbiturates | √ |
| Primidone (Mysoline®*) | Barbiturates | √ |
| **Benzodiazepines** | | |
| Clobazam (Onfi®) | Benzodiazepine | - |
| Clonazepam (Klonopin®*) | Benzodiazepine | √ |
| Diazepam (Diastat®*) | Benzodiazepine | √ |
| **Hydantoins** | | |
| Ethotoin (Peganone®) | Hydantoins | - |
| Phenytoin (Phenytek®*, Dilantin®*) | Hydantoins | √ |
| **Succinimides** | | |
| Ethosuximide (Zarontin®*) | Succinimides | √ |


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| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| Methsuximide (Celontin®) | Succinimides | - |
| **Anticonvulsants, Miscellaneous** | | |
| Carbamazepine (Carbatrol®*, Epitol®*, Equetro®, Tegretol®*, Tegretol XR®*) | Anticonvulsants | √ |
| Divalproex (Depakote®*, Depakote ER®*) | Anticonvulsants | √ |
| Ezogabine (Potiga®) | Anticonvulsants | - |
| Felbamate (Felbatol®*) | Anticonvulsants | √ |
| Gabapentin (Neurontin®*) | Anticonvulsants | √ |
| Lacosamide (Vimpat®) | Anticonvulsants | - |
| Lamotrigine (Lamictal®*, Lamictal CD®*, Lamictal ODT® Lamictal XR®) | Anticonvulsants | √ |
| Levetiracetam (Keppra®*, Keppra XR®*) | Anticonvulsants | √ |
| Oxcarbazepine (Oxtellar XR®, Trileptal®*) | Anticonvulsants | √ |
| Perampanel (Fycompa®) | Anticonvulsants | - |
| Pregabalin (Lyrica®) | Anticonvulsants | - |
| Rufinamide (Banzel®) | Anticonvulsants | - |
| Tiagabine (Gabitril®*) | Anticonvulsants | √ |
| Topiramate (Topamax®*, Trokendi XR®) | Anticonvulsants | √ |
| Valproic acid (Depakene®*, Stavzor®) | Anticonvulsants | √ |
| Vigabatrin (Sabril®) | Anticonvulsants | - |
| Zonisamide (Zonegran®*) | Anticonvulsants | √ |

*Generic available in at least one dosage form or strength.

## Indications

**Table 2a. Food and Drug Administration-Approved Indications-Barbiturates**[1,48-50,56]

| Indication | Phenobarbital | Primidone |
|---|---|---|
| **Seizure-related Indications** | | |
| Anticonvulsant | √ (tablet) | |
| Control of grand mal, psychomotor, and focal epileptic seizures, used alone or concomitantly with other anticonvulsants | | √ |
| Emergency control of certain acute convulsive episodes | √ (injection) | |
| Long term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures | √ (injection) | |
| Treatment of generalized and partial seizures | √ (elixir) | |
| **Other** | | |
| Hypnotic, for short term treatment of insomnia | √ (injection) | |
| Preanesthetic | √ (injection) | |
| Sedative | √ | |

**Table 2b. Food and Drug Administration-Approved Indications-Benzodiazepines**[1,25,28,45]

| Indication(s) | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| **Seizure-related Indications** | | | |
| Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients two years of age or older | √ | | |
| Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity | | | √ |
| Treatment of Lennox-Gastaut Syndrome (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy | | √ | |


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| Indication(s) | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| **Other** | | | |
| Treatment of panic disorder, with or without agoraphobia | | √ | |

**Table 2c. Food and Drug Administration-Approved Indications-Hydantoins**[1,47,51-54]

| Indication(s) | Ethotoin | Phenytoin |
|---|---|---|
| **Seizure-related Indications** | | |
| Control of status epilepticus of the grand mal type | | √ (injection) |
| Control of generalized tonic-clonic and complex partial seizures | √ | √ (chewable tablet, extended-release capsule, suspension) |
| Prevention and treatment of seizures occurring during or following neurosurgery | | √ (chewable tablet, extended-release capsule, injection) |

**Table 2d. Food and Drug Administration-Approved Indications-Succinimides**[1,24,33,34]

| Indication(s) | Ethosuximide | Methsuximide |
|---|---|---|
| **Seizure-related Indications** | | |
| Control of absence epilepsy | √ | |
| Control of absence seizures that are refractory to other drugs | | √ |


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**Table 2e. Food and Drug Administration-Approved Indications-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Indication(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Seizure-related Indications** | | | | | | | | | | | | | | | | | |
| Adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss | | | | | | | | | | | | | | | | √ (tab) | |
| Adjunctive therapy in patients with multiple seizure types, that include absence seizures | | √ (ER, DR) | | | | | | | | | | | | | √ | | |
| Adjunctive therapy in patients with partial onset or primary generalized tonic-clonic seizures | | | | | | | | | | | | | | √ | | | |
| Adjunctive therapy in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy | | | | | | | | √ (inj, tab) | | | | | | | | | |
| Adjunctive therapy in the treatment of partial seizures | | | | | √ | √ | √ | √ | | | √ | | √ | | | | √ |
| Adjunctive therapy in the treatment of partial onset seizures | | | √‡ | | | | | | | √† | | | | | | | |
| Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures | | | | | | | √ | √ (inj, soln, tab) | | | | | | | | | |
| Adjunctive therapy for seizures | | | | | | | √ | | | | | √ | | √ | | | |


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| Indication(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| associated with Lennox-Gastaut syndrome | | | | | | | (chew, ODT) | | | | | | | | | | |
| Generalized tonic-clonic seizures | √ | | | | | | | | | | | | | | | | |
| Mixed seizure patterns | √ | | | | | | | | | | | | | | | | |
| Monotherapy and adjunctive therapy in the treatment of partial seizures | | | | | | | | | √ | | | | | | | | |
| Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures | | √ | | | | | | | | | | | | | √ | | |
| Monotherapy for pediatric patients (one month to two years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss | | | | | | | | | | | | | | | | √ (soln) | |
| Monotherapy (initial) in patients with partial onset or primary generalized tonic-clonic seizures | | | | | | | | | | | | | | √ | | | |
| Monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drugs | | | | | | | √ | | | | | | | | | | |
| Patients who respond inadequately to alternative | | | | √ | | | | | | | | | | | | | |


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| Indication(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use | | | | | | | | | | | | | | | | | |
| Partial seizures with complex symptomatology | √ | | | | | | | | | | | | | | | | |
| **Other** | | | | | | | | | | | | | | | | | |
| Acute treatment of the manic episodes associated with bipolar disorder | | √ (DR) | | | | | | | | | | | | | √ (DR) | | |
| Acute treatment of manic or mixed episodes associated with bipolar disorder | √* | √ (ER) | | | | | | | | | | | | | | | |
| Fibromyalgia | | | | | | | | | | | √ | | | | | | |
| Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy | | | | | | | √ (chew, ODT) | | | | | | | | | | |
| Neuropathic pain associated with diabetic peripheral neuropathy | | | | | | | | | | | √ | | | | | | |
| Neuropathic pain associated with spinal cord injury | | | | | | | | | | | √ | | | | | | |
| Postherpetic neuralgia | | | | | √ | | | | | | √ | | | | | | |
| Prophylaxis of migraine headaches | | √ (DR, | | | | | | | | | | | | √ | √ (DR) | | |


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| Indication(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ER) | | | | | | | | | | | | | | | |
| Trigeminal neuralgia | √ | | | | | | | | | | | | | | | | |

Cap=capsule, Chew=chewable tablet, DR=delayed-release, ER=extended release, Inj= injection, ODT=orally disintegrating tablet, Soln=oral solution, Tab=tablet
*This is the sole indication of Equetro®. No other carbamazepine-containing products have this indication.
† With or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.
‡who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity.


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## Pharmacokinetics

**Table 3a. Pharmacokinetics-Barbiturates**[1,48-50,56]

| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Phenobarbital | Bioavailability: nd (food: nd)<br>Cmax: nd<br>Tmax: nd | Vd: nd<br>Protein binding: nd | Method: liver<br>Metabolites: inactive metabolites not specified | Route: renal (Percent not reported)<br>fecal (percent not reported)<br>Half-life: 53 to 118 hours (adults), 60 to 180 hours (pediatrics)<br>Cl: nd |
| Primidone | Bioavailability: 90 to 100% (food: nd)<br>Cmax: nd<br>Tmax: nd | Vd: 0.4 to 1.0 L/kg<br>Protein binding: 20 to 30% | Method: liver<br>Metabolites (active): phenobarbital, phenylethyl-malonamide | Route: renal (minimal)<br>Half-life: 3.3 to 7.0 hours (29 to 150 hours for metabolites)<br>Cl: nd |

Cl=clearance, Cmax=maximum concentration, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

**Table 3b. Pharmacokinetics-Benzodiazepines**[1,25,28,45]

| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Clobazam | Bioavailability: 87%<br>(food: no effect)<br>Cmax: nd<br>Tmax: 0.5 to 4.0 hours | Vd: 100 L<br>Protein binding: 80 to 90% | Method: liver (extensive)<br>Metabolites (active): N-des-methylclobazam (norclobazam) | Route: renal (82%)<br>fecal (11%)<br>Half-life: 36 to 42 hours (71 to 82 hours for metabolites)<br>Cl: nd |
| Clonazepam | Bioavailability: 90%<br>(food: nd )<br>Cmax: nd<br>Tmax: 1 to 4 hours | Vd: 3.2 L/kg<br>Protein binding: 85% | Method: liver (extensive)<br>Metabolites: none | Route: renal (0.5 to 1.0%)<br>Half-life: 30 to 40 hours<br>Cl: nd |
| Diazepam | Bioavailability: 90% (relative to injection)<br>(food:)<br>Cmax:<br>Tmax: 1.5 hours | Vd: 1 L/kg<br>Protein binding: 95 to 98% | Method: liver (extensive)<br>Metabolites (active): N-desmethyl-diazepam, N-methyloxazepam | Route: renal (75%)<br>Half-life: 0.83 to 2.25 days (40 to 194 hours for metabolites)<br>Cl: nd |

Cl=clearance, Cmax=maximum concentration, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

**Table 3c. Pharmacokinetics-Hydantoins**[1,47,51-54]

| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Ethotoin | Bioavailability: extent unknown (food: nd)<br>Cmax: 15 to 50 µg/mL (adult)<br>14.4 to 34 µg/mL (pediatric)<br>Tmax: 2 hours (oral) | Vd: nd<br>Protein binding: minimal (percent not reported) | Method: liver (extensive)<br>Metabolites (inactive): A 5-hydroxy-5-phenylhydantoin metabolite, N-deethyl, P-hydroylethotoin | Route: renal (percent not reported)<br>Half-life: 2 to 12 hours<br>Cl: nd |
| Phenytoin | Bioavailability: 20 to 90%<br>(food: increased | Vd: 0.5 to 1.0 L/kg<br>Protein | Method: liver<br>Metabolites: none | Route: bile (extensive) renal (extent unknown) |


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| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| | absorption)<br>Cmax: nd<br>Tmax: 1.5 to 3.0 hours (oral) | binding: 88 to 93% | | Half-life: 14 hours (chewable tablet)<br>22 hour (suspension)<br>Cl: nd |

Cl=clearance, Cmax=maximum concentration, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

**Table 3d. Pharmacokinetics-Succinimides**[1,24,33,34]

| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Ethosuximide | Bioavailability: nd (food: nd)<br>Cmax: nd<br>Tmax: nd | Vd: nd<br>Protein binding: nd | Method: nd<br>Metabolites: nd | Route: nd<br>Half-life: nd<br>Cl: nd |
| Methsuximide | Bioavailability: nd (food: nd)<br>Cmax: nd<br>Tmax: nd | Vd: nd<br>Protein binding: nd | Method: nd<br>Metabolites (active): N-desmethylsuximide | Route: nd<br>Half-life: 1.4 hours (25.6 to 38 hours for metabolite)<br>Cl: nd |

Cl=clearance, Cmax=maximum concentration, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

**Table 3e. Pharmacokinetics-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Carbamazepine | Bioavailability: 70 to 79% (tablet)<br>95.9% (solution)<br>(food: increased bioavailability)<br>Cmax: nd<br>Tmax: 4 to 5 hours (IR)<br>6 hours (chewable tablet)<br>3 to 12 hours (ER)<br>1.5 hours (suspension) | Vd: 0.8 to 2 L/kg<br>Protein binding: 76% | Method: liver (98%)<br>Metabolites (active): 9 hydroxymethyl-10-carbamoyl acridan, carbamazepine-10,11-epoxide | Route: renal (72%) fecal (28%)<br>Half-life: 12 to 17 hours (6.1 hours for metabolites)<br>Cl: 3.85 L/hour |
| Divalproex | Bioavailability: 90% (ER)<br>(food: no significant effect)<br>Cmax: nd<br>Tmax: 4 to 8 hours (IR)<br>3.3 to 4.8 hours (sprinkle capsule)<br>4 to 17 hours (ER) | Vd: 0.14 to 0.23 L/kg<br>Protein binding: nd | Method: nd<br>Metabolites: nd | Route: renal (70 to 80%) bile (7%)<br>Half-life: nd<br>Cl: 0.9 L/hour |
| Ezogabine | Bioavailability: 60% (food: none)<br>Cmax: nd<br>Tmax: 0.5 to 2.0 hours | Vd: 2 to 3 L/kg<br>Protein binding: 80% | Method: liver (extensive)<br>Metabolites: NAMR (active) | Route: renal (85%)<br>Half-life: 7 to 11 hours<br>Cl: 0.4 to 0.6 L/kg/hour |
| Felbamate | Bioavailability: nd (food: none)<br>Cmax: nd<br>Tmax: nd | Vd: 0.7 to 1.0 L/kg<br>Protein binding: 22 to 25% | Method: nd<br>Metabolites: nd | Route: renal (90%)<br>Half-life: 20 to 23 hours<br>Cl: 2.75 L/hour |


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| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Gabapentin | Bioavailability: 60% (food: 14% increase in AUC and Cmax)<br>Cmax: 8,536 ng/mL (600 mg TID)<br>Tmax: 2 hours | Vd: 58 L<br>Protein binding: <3% | Method: not metabolized<br>Metabolites: not applicable | Route: 76 to 81% (renal) 10 to 23% (fecal)*<br>Half-life: 5 to 7 hours<br>Cl: nd |
| Lacosamide | Bioavailability: 100% (food: none)<br>Cmax: nd<br>Tmax: 1 to 4 hours | Vd: 0.6 L/kg<br>Protein binding: <15% | Method: nd<br>Metabolites (inactive): O-desmethyl-lacosamide | Route: renal (95%) fecal (<0.5%)<br>Half-life: 13 hours (15 to 23 hours for metabolites)<br>Cl: nd |
| Lamotrigine | Bioavailability: 98% (IR) (food: none)<br>Cmax: 0.58 to 4.63 mg/L (oral)<br>Tmax: 1.4 to 4.8 hours (adults; IR) 4 to 11 hours (adults; ER) 1.6 to 5.2 hours (pediatrics; IR) | Vd: 0.9 to 1.3 L/kg (adults) 1.5 L/kg (pediatrics)<br>Protein binding: 55% | Method: liver (extensive)<br>Metabolites: nd | Route: renal (94%) fecal (2%)<br>Half-life: 12.6 to 58.8 hours (adults)<br>Cl: nd |
| Levetiracetam | Bioavailability: 100% (food: minor)<br>Cmax: 23.1 µg/L<br>Tmax: 1 hour (IR) 4 hours (ER) | Vd: 0.7 L/kg<br>Protein binding: <10% | Method: liver (insignificant)<br>Metabolites (inactive): ucb L057 | Route: renal (66%)<br>Half-life: 6 to 8 hours (8.4 hours for metabolites)<br>Cl: 0.96 mL/min/kg |
| Oxcarbazepine | Bioavailability: percent not reported (rapid) (food: none)<br>Cmax: nd<br>Tmax: 4.5 hours (tablet) 6 hours (suspension) | Vd: 49 L<br>Protein binding: 40 to 60% | Method: liver (rapid and extensive)<br>Metabolites: 10-monohydroxy-carbazepine (active), two isomeric 10,11-diols (inactive) | Route: renal (95 to 96%) fecal (<4%)<br>Half-life: 1 to 2.5 hours (8 to 11 hours for metabolites)<br>Cl: nd |
| Perampanel | Bioavailability: 100% (food: decrease in Cmax by 28 to 40% and approximately 2 to 3 hour increase in Tmax)<br>Cmax: nd<br>Tmax: <2.5 hours | Vd: nd<br>Protein binding: 95 | Method: oxidation and sequential glucuronidation<br>Metabolites: nd | Route: fecal (48%) renal (22%)<br>Half-life:105 hours<br>Cl: 12 mL/min |
| Pregabalin | Bioavailability: ≥90% (food: decrease in Cmax by 25 to 30% and approximately 3 hour increase in | Vd: 0.5 L/kg<br>Protein binding: none | Method: minor metabolism to an N-methylated derivative and an unidentified metabolite | Route: 90.0 to 99.0% (renal) <0.1% (fecal)<br>Half-life: 5.0 to 6.5 hours<br>Cl: nd |


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| Generic Name | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| | Tmax)<br>Cmax: nd<br>Tmax: 1.5 hours | | Metabolites: activity unknown | |
| Rufinamide | Bioavailability: 85%<br>(food: 34% increase)<br>Cmax: nd<br>Tmax: 4 to 6 hours | Vd: 50 L<br>Protein binding: 34% | Method: liver (extensive)<br>Metabolites (inactive): CGP 47292 | Route: renal (85%)<br>Half-life: 6 to 10 hours<br>Cl: nd |
| Tiagabine | Bioavailability: 90%<br>(food: slows absorption rate but not extent)<br>Cmax: nd<br>Tmax: 45 minutes | Vd: nd<br>Protein binding: 96% | Method: liver<br>Metabolites (inactive): 5-oxo-tigabine | Route: renal (25%) fecal (63%)<br>Half-life: 7 to 9 hours<br>Cl: 109 mL/minute |
| Topiramate | Bioavailability: 80%<br>(food: none)<br>Cmax: 1.7, 3.7, and 8 µg/mL following 100, 200, and 400 mg doses<br>Tmax: 1.5 to 4 hours | Vd: 0.6 to 0.8 L/lg<br>Protein binding: 9 to 41% | Method: liver (not extensive)<br>Metabolites: inactive metabolites not specified | Route: renal (70%)<br>Half-life: 21 hours<br>Cl: 20 to 30 mL/min |
| Valproic acid | Bioavailability: (food:)<br>Cmax: nd<br>Tmax: 2.0 to 4.8 hours (DR capsule)<br>1 to 4 hours (IR capsules)<br>1.2 hours (solution)<br>3.1 hours (rectal syrup) | Vd: 0.14 to 0.23 L/kg<br>Protein binding: 90% | Method: liver (extensive)<br>Metabolites (activity unknown): 2-propyl-3-keto-pentanoic acid, 2-propyl-hydroxypentanoic acids | Route: renal (70 to 80%) bile (7%)<br>Half-life: 6 to 17 (hours)<br>Cl: 0.9 L/hour |
| Vigabatrin | Bioavailability: 50 %<br>(food: none)<br>Cmax: nd<br>Tmax: 1 hour (tablet)<br>1.0 to 2.5 hours (solution) | Vd: 1.1 L/kg<br>Protein binding: not bound | Method: liver (minimal)<br>Metabolites: none | Route: renal (95%)<br>Half-life: 7.0 to 7.5 hours (adults)<br>5.7 hours (infants)<br>Cl: 0.74 mL/min/kg |
| Zonisamide | Bioavailability: nd<br>(food: no significant effect)<br>Cmax: 2 to 5 µg/mL<br>Tmax: 2 to 6 hours | Vd: 0.8 to 1.6 L/kg<br>Protein binding: 40 to 60% | Method: nd<br>Metabolites (activity not reported): 2-sulfamoylacetyl phenol, N-acetyl zonisamide | Route: renal (62%) fecal (3%)<br>Half-life: 63 hours (plasma)<br>105 hours (erythrocytes)<br>Cl: 2.34 L/hour |

*Animal data.
AUC=area under the curve, Cl=clearance, Cmax=maximum concentration, DR=delayed-release, ER=extended-release, IR=immediate-release, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution


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## Clinical Trials

Clinical trials evaluating the anticonvulsants in their respective Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[67-198]

Several clinical trials support the safety and efficacy of the anticonvulsant agents in the management of seizure disorders. At this time, there is insufficient evidence to suggest that one agent is more efficacious than another.[67-157]

Vigabatrin is the only anticonvulsant that is FDA-approved for the treatment of infantile spasms. Data from clinical trials support the role of vigabatrin and steroids as first-line drugs for the treatment of infantile spasms. Hancock et al conducted a meta-analysis of 14 randomized controlled trials which included infants and children with infantile spasms. Treatment with vigabatrin was associated with a complete cessation of spasms in 7/20 (35%) patients compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo.[68] Another meta-analysis by Hancock et al included trials that evaluated the safety and efficacy of felbamate, lamotrigine, rufinamide and topiramate in the treatment of Lennox-Gastaut Syndrome (LGS). While all of these agents demonstrated some efficacy, authors concluded that the optimum treatment of LGS remained uncertain as no trial demonstrated that treatment with any one drug was highly efficacious. Authors concluded that felbamate, lamotrigine, rufinamide, and topiramate may be helpful as add-on therapy.[147]

Clobazam was FDA-approved for adjunctive therapy of seizures associated with LGS in 2011. The results of a study by Ng et al demonstrated that the mean percentage decrease in average weekly rate of drop seizures was 41.2% for clobazam 0.25 mg/kg/day ($P$=0.0120), 49.4% for clobazam 0.5 mg/kg/day ($P$=0.0015) and 68.3% for clobazam 1.0 mg/kg/day ($P$<0.0001) compared to 12.1% for placebo.[128] In another study of patients two to 26 years of age with LGS, the number of weekly drop seizures was reduced from 141 to 91 with low-dose clobazam (0.25 mg/kg/day) and from 207 to 32 with high-dose clobazam (1.0 mg/kg/day). The percent change from baseline was significant in both the low-dose (12%; $P$=0.0162) and high-dose treatment groups (85%; $P$<0.0001). Moreover, the reduction in drop seizure rates was significantly greater in the high-dose group compared to the low-dose group ($P$=0.0001). Significantly more patients in the high-dose group compared to the low-dose group had a reduction in weekly drop seizure rates of ≥25% (89 vs 56%; $P$=0.0025), ≥50% (83 vs 38%; $P$=0.0001), and ≥75% (67 vs 25%; $P$=0.0006).[129] In an open-label, extension study of patients enrolled in either of the above studies, the median percent reduction from baseline in weekly drop seizures was 71.1% at three months and 91.6% at 24 months of continued treatment. The median percent decreases in total seizures in these patients were 64.8% and 81.5% at three and 24 months, respectively.[130]

Another recently approved agent, ezogabine, has demonstrated improvements in seizure frequency in patients with partial-onset seizures. In a study by Porter et al, treatment with ezogabine 600, 900 and 1,200 mg reduced the total monthly seizure frequency from baseline by 23, 29 and 35% compared to 13% with placebo ($P$<0.001 for overall difference across all treatment arms).[73] In a second study of patients with drug resistant partial epilepsy, ezogabine 1,200 mg daily (divided in three daily doses) reduced the total monthly seizure frequency from baseline by 44.3% compared to 17.5% with placebo ($P$<0.001).[74]

Perampanel has been evaluated as adjunctive therapy in patients with partial onset seizures. In study 304, treatment with perampanel 8 mg or 12 mg resulted in a statistically significant reduction in seizure frequency when compared to placebo ($P$=0.0261 and $P$=0.0158 for 8 mg and 12 mg, respectively); however, there was no significant difference in the proportion of patients who achieved a seizure reduction of >50% from baseline compared to the placebo group.[91] In study 305, there was a similar reduction in seizure frequency compared to study 304 ($P$<0.001 and $P$=0.011 for 8 mg and 12 mg, respectively). In addition, a greater proportion of patients treated with perampanel 8 mg or 12 mg had a reduction in seizure frequency of >50% from baseline ($P$=0.002 and $P$<0.001 for 8 mg and 12 mg, respectively).[92] In study 306, patients treated with perampanel 4 mg or 8 mg once daily experienced a significant reduction in seizure frequency compared to placebo ($P$=0.003 and $P$<0.001 for 4 mg and 8 mg,


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respectively). Moreover, a greater proportion of patients treated with perampanel 4 mg or 8 mg achieved a reduction in seizure frequency of >50% from baseline compared to placebo (*P*=0.013 and *P*<0.001 for 4 and 8 mg, respectively). Treatment with perampanel 2 mg did not result in a significant decrease in either endpoint compared to placebo. (*P*=0.420 and *P* not reported, respectively).[93] In an extension study, patients who completed the double-blinded phases of studies 304, 305 and 306 could receive perampanel titrated up to 12 mg daily. Of the patients who had six months of data, 8.9% were seizure-free for the entire six months and 7.1% of patients with 12 months of data, remained seizure-free for the entire year.[94]

A meta-analysis of 23 clinical trials (n=2,927) demonstrated that anticonvulsants were effective in reducing the frequency of migraine attacks by approximately one to two attacks per month (weighted mean difference [WMD], -1.31; 95% confidence interval [CI], -1.99 to -0.63; *P* value not reported). In addition, patients receiving anticonvulsants were also more than twice as likely to reduce the number of their migraine attacks by ≥50% compared to placebo (relative risk [RR], 2.25; 95% CI, 1.79 to 2.84; number needed to treat [NNT], 3.9; 95% CI, 3.4 to 4.7; *P* value not reported). The majority of the trials involved topiramate or valproic acid.[174]

Clinical trials and meta-analyses demonstrated that carbamazepine, gabapentin, and pregabalin were effective in the management of chronic neuropathic pain.[166-169,172,173,177-199] In a meta-analysis of three head-to-head trials (n=120), there was no difference between gabapentin and tricyclic antidepressants for achieving pain relief for diabetic peripheral neuropathy and postherpetic neuralgia. Indirect analyses reported that gabapentin was worse than tricyclic antidepressants for achieving pain relief.[181] In a meta-analysis of five clinical trials, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve ≥30% reduction in pain was 8.5. Anxiety, depressed mood and fatigue were not improved with gabapentin or pregabalin treatment.[172]

Macritchie et al conducted a meta-analysis of ten clinical trials (n=932) comparing valproic acid to placebo, carbamazepine, haloperidol, lithium and olanzapine for the treatment of acute manic episodes in patients with bipolar disorders. Valproic acid was significantly more effective than placebo (relative risk reduction, [RRR] 38%; RR, 0.62; 95% CI, 0.51 to 0.77) in the treatment of mania and comparable to carbamazepine, haloperidol, and lithium (RRR, 34%; RR, 0.66; 95% CI, 0.38 to 1.16). Valproic acid was not as effective as olanzapine (failure to achieve clinical response; relative risk increase, 25%; RR, 1.25; 95% CI, 1.01 to 1.54; average of 2.8 point less change on the Mania Rating Scale; 95% CI, 0.83 to 4.79), but was associated with less sedation and weight gain.[163]

The antiepileptic drugs are available in many dosage forms, including immediate release, delayed-release, and extended-release capsules or tablets; sprinkle capsules; chewable tablets; orally disintegrating tablets; solutions or suspensions; and injections. There are limited studies comparing the efficacy and safety of one dosage form to another.[72,81,85]


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**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Treatment of Generalized Seizures** | | | | |
| Posner et al[67]<br><br>Ethosuximide<br><br>vs<br><br>lamotrigine<br><br>vs<br><br>sodium valproate<br><br>vs<br><br>placebo<br><br>Trials compared study drug as monotherapy or add-on therapy. | MA (5 RCTs)<br><br>Children and adolescents with absence seizures | N=total not reported<br><br>Duration not reported | Primary:<br>Proportion of patients seizure free, proportion with ≥50% reduction in seizure frequency, normalization of EEG and/or negative hyper-ventilation test, safety<br><br>Secondary:<br>Not reported | Primary:<br>Five small trials were found of which four were of poor methodological quality.<br><br>One short trial (n=29) compared lamotrigine with placebo using a response conditional design. Individual taking lamotrigine were significantly more likely to be seizure free than participants taking placebo.<br><br>Another trial compared lamotrigine with sodium valproate; however, the study lacked power to detect differences in efficacy.<br><br>Three studies compared ethosuximide, but because of diverse study designs and populations studied, the results were not pooled in a MA. None of these studies found a difference between valproate and ethosuximide with respect to seizure control, but CI were wide and the existence of important differences could not be excluded.<br><br>Secondary:<br>Not reported |
| Hancock et al[68]<br><br>Vigabatrin vs placebo (1 trial)<br><br>Vigabatrin low dose vs vigabatrin high dose (1 trial)<br><br>Vigabatrin vs hormonal treatment (ACTH, tetracosactide [synthetic ACTH*] or prednisolone) (3 trials) | MA (14 RCTs)<br><br>Infants and children (mean age 15 to 41 weeks) with infantile spasms | N=681<br><br>Duration varied | Primary:<br>Cessation of spasms, reduction in number of spasms, effects on relapse rates, effects on resolution of EEG, effect on subsequent epilepsy rates, adverse events and death | Primary:<br>Complete cessation of spasms was reported in 7/20 (35%) patients treated with vigabatrin compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo. Of the seven patients who responded to vigabatrin, four patients relapsed. Both patients who were successfully treated with placebo relapsed. Overall, only three patients treated with vigabatrin and no patient treated with placebo remained spasm free within the four week study period. Resolution of EEG was noted in 5/7 patients who had responded to vigabatrin, and 1/2 patients who had responded to placebo. Other primary end points were not reported in this study. No adverse events severe enough to warrant stopping treatment and no deaths were reported in this study (*P* values were not reported). |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Vigabatrin vs hydrocortisone (1 trial)<br><br>Valproate vs placebo (1 trial)<br><br>MA also evaluated various corticosteroid regimens (4 trials), nitrazepam* vs ACTH (1 trial), sulthiame* vs placebo (1 trial) and methysergide vs α-methylparatyrosine* (1 trial).<br><br>Only the results for studies evaluating the anticonvulsants were included in this summary. | | | Secondary:<br>Not reported | In a study comparing low vs high doses of vigabatrin, 8/75 patients receiving low-dose vigabatrin were spasm free and had resolution of their EEG as compared to 24/67 patients treated with high-dose vigabatrin. A large number of patients were lost to follow-up (15 in the low-dose group and 22 in the high-dose group; *P* values were not reported).<br><br>Combining results from three studies, 45/81 patients randomized to vigabatrin had cessation of their spasms compared to 57/77 patients randomized to hormonal treatment. In one study, the median time to achieve cessation of spasms was 11.5 days for vigabatrin and three days for hormonal treatment. Another study reported a range of one to 14 days for vigabatrin and two to 12 days for ACTH for complete cessation of spasms. Overall 19/52 patients receiving vigabatrin remained spasm free compared to 22/55 patients receiving hormonal treatment. Resolution of EEG occurred in 30/45 patients responding to vigabatrin and 40/49 patients responding to ACTH. For the subgroup of infants with no identified underlying etiology for infantile spasms, mean composite scores for psychomotor development were higher in infants receiving hormone treatment than in those receiving vigabatrin ($P$=0.025). Seizures at follow-up were reported in 27/81 patients receiving vigabatrin compared to 33/77 patients receiving hormonal treatment. Therapy was stopped in three patients in each group due to adverse events while deaths occurred in three patients receiving vigabatrin and two patients receiving hormonal treatment. Unless noted; *P* values were not reported.<br><br>When vigabatrin was compared to hydrocortisone in 22 infants with infantile spasms due to tuberous sclerosis, 11/11 patients treated with vigabatrin were spasm free as compared to 5/11 patients treated with hydrocortisone. The average time to cessation of spasms was 4/13 days in the vigabatrin and hydrocortisone arms, respectively; *P* values were not reported).<br><br>In a small crossover study comparing valproate to placebo (n=17), patients receiving valproate had a lower mean spasm index compared to placebo when valproate was administered first ($P$<0.04). There was no significant difference between valproate and placebo during the second levels of treatment. No other outcomes were reported. |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Secondary:<br>Not reported |
| **Treatment of Partial Seizures** | | | | |
| Koch et al[69]<br><br>Carbamazepine monotherapy<br><br>vs<br><br>oxcarbazepine monotherapy | MA (3 RCT)<br><br>Adults with partial-onset seizures | N=723<br><br>Duration not reported | Primary:<br>Time to treatment withdrawal and safety<br><br>Secondary:<br>Not reported | Primary:<br>Only one trial used adequate outcome measures of efficacy; therefore, the results pertaining to efficacy are based on a single trial, whereas the results pertaining to adverse events are based on all three trials.<br><br>There was no overall difference in time to treatment withdrawal between oxcarbazepine and carbamazepine (HR, 1.04; 95% CI, 0.78 to 1.39). Further analyses showed no significant difference in treatment withdrawal for unacceptable adverse events between oxcarbazepine and carbamazepine (HR, 0.85; 95% CI, 0.59 to 1.24). There was no significant difference in treatment withdrawal for inadequate seizure control for oxcarbazepine vs carbamazepine (HR, 1.33; 95% CI, 0.82 to 2.15; *P* values were not reported).<br><br>Oxcarbazepine ad carbamazepine appeared to be similarly effective and well tolerated although the CI around estimates were wide and did not rule out the possibility of important differences. Significantly more patients on oxcarbazepine than carbamazepine developed nausea and/or vomiting (HR, 1.33; 95% CI, 0.82 to 2.15; *P* value not reported).<br><br>Secondary:<br>Not reported |
| Mattson et al[70] (abstract)<br><br>Carbamazepine, dosing and frequency not specified<br><br>vs<br><br>valproate (divalproex sodium), dosing and | DB, MC, RCT<br><br>Adults with complex partial seizures and secondarily generalized tonic-clonic seizures | N=480<br><br>1 to 5 years | Primary:<br>Total number of seizures, number of seizures per month, time to first seizure, seizure rating score (not specified) and safety | Primary:<br>For the control of secondarily generalized tonic-clonic seizures, carbamazepine and valproate were comparably effective (*P* values not reported).<br><br>For complex partial seizures carbamazepine was favored over valproate with regards to the total number of seizures (2.7 vs 7.6; *P*=0.05), the number of seizures per month (0.9 vs 2.2; *P*=0.01), the time to first seizure (*P*<0.02), and the seizure-rating score (*P*=0.04).<br><br>Carbamazepine was also “superior” according to a composite score that combined scores for the control of seizures and for adverse effects (*P*<0.001). Valproate was |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| frequency not specified | | | Secondary:<br>Not reported | associated more frequently than carbamazepine with weight gain >5.5 kg (20 vs 8%; *P*<0.001), with hair loss or change in texture (12 vs 6%; *P*=0.02), and with tremor (45 vs 22%; *P*<0.001). Rash was more often associated with carbamazepine (11 vs 1%; *P*<0.001).<br><br>Secondary:<br>Not reported |
| Mattson et al[71] (abstract)<br><br>Carbamazepine, dosing and frequency not specified<br><br>vs<br><br>phenobarbital, dosing and frequency not specified<br><br>vs<br><br>phenytoin, dosing and frequency not specified<br><br>vs<br><br>primidone, dosing and frequency not specified | DB, MC, RCT<br><br>Adults with new onset partial and secondarily generalized tonic-clonic seizures | N=622<br><br>2 years | Primary:<br>Overall treatment success (not defined), control of partial or tonic-clonic seizures and safety<br><br>Secondary:<br>Not reported | Primary:<br>Overall treatment success was highest with carbamazepine or phenytoin, intermediate with phenobarbital, and lowest with primidone (*P*<0.002). Other *P* values were not reported.<br><br>Differences in failure rates of the drugs were explained primarily by the fact that primidone caused more intolerable acute toxic effects, such as dizziness, sedation, nausea and vomiting. In addition, decreased libido and impotence were more common in patients given primidone. Phenytoin caused more dysmorphic effects and hypersensitivity; *P* values were not reported.<br><br>Control of tonic-clonic seizures did not differ significantly with the various drugs. Carbamazepine provided complete control of partial seizures more often than primidone or phenobarbital (*P*<0.03; other *P* values were not reported).<br><br>Secondary:<br>Not reported |
| Ficker et al[72]<br><br>Carbamazepine IR (mean dose 759 mg at baseline) as monotherapy or with 1 | OL, PRO<br><br>Adults and adolescents (>12 years of age) with partial | N=466<br><br>3 months | Primary:<br>Safety and change in seizure frequency | Primary:<br>In adults the switch from carbamazepine IR to ER significantly improved nervous system adverse events (*P*<0.0001). The total score for adverse events also improved from baseline to end point (37.2 vs 31.7; *P*<0.0001), with the number of adults with toxic scores decreasing from 101 (24.1%) at baseline to 54 (12.9%) at end point (*P*<0.0001). |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| additional AED switched to carbamazepine ER (mean dose 781 mg at end point) (Carbatrol®) | epilepsy with or without secondary generalization | | Secondary:<br>Not reported | In adolescents, significant improvements in sedation and confusion were noted after the switch from carbamazepine IR to ER (*P*<0.01). The total adverse event score also improved from baseline to end point (26.7 vs 22.6; *P*<0.01).<br><br>Switching from carbamazepine IR to ER resulted in a reduction in mean monthly seizure count in observed cases at month three (-0.36; *P*=0.015; n=387) and at end point (-0.34; *P*=0.017; n=447).<br><br>Secondary:<br>Not reported |
| Porter et al[73]<br><br>Ezogabine 600, 900 or 1,200 mg/day, administered in 3 equal doses/day<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients 16 to 70 years of age who had inadequately controlled partial-onset seizures, ≥4 partial-onset seizures/month during an 8 week baseline phase with no 30 day seizure free period, while maintained on stable doses of 1 or 2 anticonvulsants (valproate, carbamazepine, phenytoin, topiramate, lamotrigine, | N=399<br><br>16 weeks (8 weeks of forced titration, followed by 8 weeks of main-tenance therapy) | Primary:<br>Percentage change from baseline in monthly seizure frequency<br><br>Secondary:<br>Proportion of patients experiencing ≥50% reduction in seizure frequency (responder rate), emergence of new seizure types, physician assessment of global clinical improvement, safety and tolerability | Primary:<br>The median percent change in monthly total seizure frequency from baseline was -23, -29 and -35% with ezogabine 600, 900 and 1,200 mg/day compared to -13% with placebo (*P*<0.001 for overall difference across all treatment arms).<br><br>Secondary:<br>Responder rates with ezogabine were 23, 32 and 33% for 600 (*P* value not reported), 900 (*P*=0.021) and 1,200 mg/day (*P*=0.016) compared to 16% with placebo.<br><br>Treatment with ezogabine was not associated with newly occurring seizure type(s) compared to treatment with placebo.<br><br>At the end of the trial, no change in clinical global improvement score was observed with placebo; however, there was a progressive improvement observed with all doses of ezogabine, with significant differences vs placebo with 600 (*P*=0.015), 900 (*P*=0.004) and 1,200 mg/day (*P*=0.005), respectively.<br><br>The most common treatment-emergent adverse events were somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia and diplopia. |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | gabapentin, oxcarbazepine, benzodiazepines or barbiturates) | | | |
| French et al[74]<br><br>Ezogabine 1,200 mg/day, administered in 3 equal doses/day<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients 18 to 75 years of age with drug resistant partial epilepsy characterized by simple or complex partial-onset seizures, a 28 day partial seizure frequency of ≥4 seizures over 8 weeks and currently receiving a stable dose of 1 to 3 background anticonvulsants with or without vagus nerve stimulator | N=306<br><br>18 weeks (6 weeks of forced titration, followed by 12 weeks of main-tenance therapy) | Primary: Percentage change from baseline in monthly seizure frequency, proportion of patients experiencing ≥50% reduction in seizure frequency (responder rate)<br><br>Secondary: Distribution of patients across seizure frequency reduction categories, proportion of seizure free patients, percent of treatment days without seizures, CGI-I, PGI-I, safety | Primary:<br>The median change in monthly total seizure frequency from baseline was -44.3% with ezogabine compared to -17.5% with placebo (*P*<0.001).<br><br>In the 256 patients entering the 12 week maintenance therapy phase, responder rates were 55.5 and 22.6% with ezogabine and placebo (*P*<0.001).<br><br>Secondary:<br>Distribution across seizure frequency reduction categories significantly favored ezogabine over placebo (*P*<0.001). A larger proportion of ezogabine-treated patients were in the 50 to <75% or 75 to 100% seizure free reduction categories, while a larger proportion of placebo-treated patients were in the no seizure reduction, <25% or 25 to <50% reduction categories.<br><br>For those patients who completed the trial, more ezogabine-treated patients were seizure free during the entire maintenance phase (5.2 vs 0.8%; *P*=0.087).<br><br>Median percentage of seizure free days was significantly greater with ezogabine compared to placebo (*P*<0.001).<br><br>Mean scores for CGI-I were better with ezogabine (2.7 vs 3.2; *P*=0.002), while both treatments achieved a mean score of 2.9 for PGI-I scores.<br><br>The proportion of patients discontinuing treatment due to a treatment-emergent adverse event was 26.8 vs 8.6% (*P* value not reported). The most commonly reported adverse events were dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia and blurred vision. |
| Brodie et al[75]<br><br>Ezogabine 600 or 900 | DB, MC, PC, PG, RCT | N=538<br><br>16 weeks | Primary: Percentage change from | Primary:<br>The median percent change in monthly total seizure frequency from baseline was -27.9 and -39.9% with ezogabine 600 (*P*=0.007) and 900 mg/day (*P*<0.001) |


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| mg/day, administered in 3 equal doses/day<br><br>vs<br><br>placebo | Patients 18 to 75 years of age diagnosed with localization-related epilepsy, which was refractory to stable doses of 1 to 3 anticonvulsants, experiencing ≥4 qualifying seizures/28 days without a seizure free period >21 days during an 8 week baseline phase | (4 weeks of forced titration, followed by 12 weeks of main-tenance therapy) | baseline in monthly seizure frequency, proportion of patients experiencing ≥50% reduction in seizure frequency (responder rate)<br><br>Secondary:<br>Safety | compared to placebo (-15.9%).<br><br>Responder rates were significantly greater with ezogabine (600 mg/day, 38.6%; *P*<0.001, 900 mg/day, 47.0%; *P*<0.001) compared to placebo (18.9%).<br><br>Secondary:<br>The most commonly reported adverse events (>10%) were dizziness, somnolence, headache and fatigue. |
| Marson et al[76] (abstract)<br><br>Gabapentin, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | MA (5 RCTs)<br><br>Patients with drug-resistant partial epilepsy | N=997<br><br>Duration not reported | Primary:<br>Proportion with ≥50% reduction in seizure frequency, treatment withdrawal for any reason and safety<br><br>Secondary:<br>Not reported | Primary:<br>The overall OR for ≥50% reduction in seizure frequency with gabapentin compared to placebo was 1.93 (95% CI, 1.37 to 2.71; *P* value not reported), indicating that gabapentin was significantly more effective than placebo in reducing seizure frequency. Dose regression analysis showed increasing efficacy with increasing dose, with 28.5% of patients responding to 1,800 mg of gabapentin compared to placebo (NNT, 6.7; 95% CI, 3.0 to 10.5; *P* value not reported).<br><br>The overall OR for treatment withdrawal for any reason for gabapentin compared to placebo was 1.05 (95% CI, 0.68 to 1.61; *P* value not reported).<br><br>Gabapentin was associated with significantly more dizziness, fatigue, and somnolence than placebo (*P* values not reported).<br><br>Secondary:<br>Not reported |


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| Chung et al[77]<br><br>Lacosamide 400 mg/day in 2 divided doses plus 1 to 3 marketed concomitant AEDs<br><br>vs<br><br>lacosamide 600 mg/day in 2 divided doses plus 1 to 3 marketed concomitant AEDs<br><br>vs<br><br>placebo in 2 divided doses plus 1 to 3 marketed concomitant AEDs | DB, MC, PC, PG, RCT<br><br>Patients 18 to 65 years of age with simple or complex partial-onset seizures, with or without secondary generalization; history of partial-onset seizures for at least the last 2 years despite prior therapy with ≥2 AEDs; during the 8-week baseline period, patients must have had ≥4 partial-onset seizures per 28 days on average, with no seizure-free period ≥21 days; in the 4 weeks before enrollment, patients must have been on a stable dosage regimen of 1 or 2 AEDs, with or without VNS | N=405<br><br>26 weeks (8-week baseline monitoring plus 6-week dose titration period plus 12-week main-tenance period)<br><br>(Patients who completed the main-tenance period had the option to enter a long-term OL extension trial of lacos-amide.) | Primary:<br>Change in seizure frequency (analyzed by reduction in seizure frequency per 28 days from baseline to maintenance) and responder rate (≥50% reduction in seizure frequency from baseline to maintenance)<br><br>Secondary:<br>Proportion of patients achieving seizure-free status throughout the study for patients completing the maintenance period and proportion of seizure-free days during the maintenance | Primary:<br>An ANCOVA analysis revealed a statistically significant median percent reduction in seizure frequency in both the lacosamide 400 mg/day (37%; *P*=0.008) and 600 mg/day (38%; *P*=0.006) groups compared to the placebo group (21%).<br><br>Statistically significant differences in 50% responder rates vs placebo (18%) were seen in the lacosamide 400 mg/day (38%; *P*<0.001) and 600 mg/day (41%; *P*<0.001) groups.<br><br>Secondary:<br>For patients who completed the maintenance phase, nine patients were seizure free throughout the 12-week period: 4/160 (2.5%) in the lacosamide 400 mg/day group and 5/62 (8.1%) in the lacosamide 600 mg/day group; no placebo group patients were seizure free during this period.<br><br>Both the 400 and 600 mg/day lacosamide groups had reported significant and clinically relevant increases in the percentage of seizure-free days during the maintenance phase compared to placebo, but details were not described at length. |


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| Halász et al[78]<br><br>Lacosamide 200 mg/day in 2 divided doses plus 1 to 3 marketed concomitant AEDs<br><br>vs<br><br>lacosamide 400 mg/day in 2 divided doses plus 1 to 3 marketed concomitant AEDs<br><br>vs<br><br>placebo in 2 divided doses plus 1 to 3 marketed concomitant AEDs | DB, MC, PC, PG, RCT<br><br>Patients18 to 65 years of age with simple or complex partial-onset seizures, with or without secondary generalization; history of partial-onset seizures for at least the last 2 years despite prior therapy with ≥2 AEDs; during the 8-week baseline period, patients must have had ≥4 partial-onset seizures per 28 days on average, with no seizure-free period ≥21 days; in the 4 weeks before enrollment, patients must have been on a stable dosage regimen of 1 or 2 AEDs, with or | N=485<br><br>24 weeks (8-week baseline monitoring plus 4-week titration period plus 12-week maint-enance period)<br><br>(Patients who completed the main-tenance period had the option to enter a long-term OL, ES of lacos-amide.) | Primary:<br>Change in seizure frequency (analyzed by reduction in seizure frequency per 28 days from baseline to maintenance) and responder rate (≥50% reduction in seizure frequency from baseline to maintenance)<br><br>Secondary:<br>Percent change in seizure frequency per 28 days, number and proportion of patients achieving seizure-free status throughout the study for patients completing the | Primary:<br>The ANCOVA analysis showed statistically significant reductions in seizure frequency over placebo in the lacosamide 200 mg/day (14.4%; 95% CI, 2.2 to 25.1; *P*=0.02) and lacosamide 400 mg/day (15.0%; 95% CI, 1.4 to 26.8; *P*=0.03) treatment groups.<br><br>PP analysis showed a greater median percent reduction in seizure frequency per 28 days from baseline to the maintenance period for lacosamide 200 mg/day (35.3%; *P*=0.04), and lacosamide 400 mg/day (44.9%; *P*=0.01) compared to placebo (25.4%).<br><br>The 50% responder rate for lacosamide 400 mg/day (40.5%) was statistically significant (*P*=0.01) over placebo (25.8%); the rate for lacosamide 200 mg/day (35.0%) was numerically higher than placebo, but not statistically significant (*P*=0.07).<br><br>In the PP population, compared to placebo (27.5%), the 50% responder rates were 35.0% for lacosamide 200 mg/day (*P*=0.19) and 46.3% for lacosamide 400 mg/day (*P*<0.01).<br><br>Secondary:<br>In completers of the maintenance period, 5 (36.7%) of 137 patients in the lacosamide 200 mg/day group and 3 (2.4%) of 123 patients in the lacosamide 400 mg/day group were seizure free throughout the 12 weeks, compared to 3 (2.1%) of 143 patients in the placebo group.<br><br>A 5% increase in the percentage of seizure-free days during the maintenance period over placebo was observed for lacosamide 400 mg/day (95% CI 1.5 to 8.5; *P*=0.01). |


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| | without VNS | | maintenance period and proportion of seizure-free days during the maintenance period | |
| Ben-Menachem et al[79]<br><br>Lacosamide 200 mg/day in 2 divided doses plus 1 or 2 marketed concomitant AEDs<br><br>vs<br><br>lacosamide 400 mg/day in 2 divided doses plus 1 or 2 marketed concomitant AEDs<br><br>vs<br><br>lacosamide 600 mg/day in 2 divided doses plus 1 or 2 marketed concomitant AEDs<br><br>vs<br><br>placebo in 2 divided doses plus 1 or 2 marketed concomitant AEDs | DB, MC, PC, PG, RCT<br><br>Patients 18 to 65 years of age with simple or complex partial-onset seizures, with or without secondary generalization; history of partial-onset seizures ≥2 years despite prior therapy with ≥2 AEDs; during the 8-week baseline period, patients must have had ≥4 partial-onset seizures per 28 days on average, with no seizure-free period ≥21 days; in the 4 weeks before enrollment, | N=418<br><br>26 weeks (8-week baseline monitoring plus 6-week dose titration period plus 12-week main-tenance period)<br><br>(Patients who completed the main-tenance period had the option to enter a long-term OL extension trial of lacos- | Primary:<br>Change in seizure frequency (analyzed by reduction in seizure frequency per 28 days from baseline to maintenance) and responder rate (≥50% reduction in seizure frequency from baseline to maintenance)<br><br>Secondary:<br>Percent change in seizure frequency, achievement of seizure-free status, proportion of seizure-free | Primary:<br>The ANCOVA analysis showed statistically significant reductions in seizure frequency over placebo in the lacosamide 400 mg/day (28.4%; *P*=0.0023) and lacosamide 600 mg/day (21.3%; *P*=0.0084) treatment groups; the reduction in the lacosamide 200 mg/day group was 14.6% and not significant (*P*=0.1010).<br><br>PP analysis showed a greater treatment difference between placebo and all lacosamide treatment groups with reductions in seizure frequency over placebo for lacosamide 200 mg/day (21.5%; *P*=0.0112), 400 mg/day (39.3%; *P*<0.0001) and 600 mg/day (31.6%; *P*=0.0002).<br><br>From the logistic regression analysis, the proportion of patients with at least a 50% reduction of seizure frequency during maintenance (and statistically significant when compared to placebo at 21.9%) was 41.1% for lacosamide 400 mg/day (*P*=0.0038) and 38.1% for lacosamide 600 mg/day (*P*=0.0141); the 50% responder rate in the lacosamide 200 mg/day group was 32.7% and not significant (*P*=0.0899).<br><br>PP analysis showed a greater treatment difference between placebo and all lacosamide treatment groups with respect to the 50% responder rate: 21.2% for placebo, 38.1% for lacosamide 200 mg/day (*P*=0.0214), 49.4% for lacosamide 400 mg/day (*P*=0.0002) and 49.2% for lacosamide 600 mg/day(*P*=0.0004).<br><br>Secondary:<br>Some patients experienced an increase in seizure frequency during the trial; however, lacosamide did not appear to increase seizure frequency defined as ≥25% overall as compared to placebo (20% for placebo, 15% for lacosamide 200 mg/day, 21% for 400 mg/day, 20% for 600 mg/day). |


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| | patients must have been on a stable dosage regimen of 1 or 2 AEDs, with or without VNS | amide). | days and CGIC score | At the end of the maintenance phase, the median change from baseline in the percentage of seizure-free days was 3% for the placebo group, 6% for the lacosamide 200 mg/day group, 12% for the lacosamide 400 mg/day group and 12 % for the lacosamide 600 mg/day group.<br><br>The CGIC analysis showed an improvement (by ratings of "very much improved" or "much improved") from baseline to maintenance in a greater percentage of patients in the treatment groups compared to the placebo group: lacosamide 200 mg/day (35%), 400 mg/day (40%) and 600 mg/day (38%) vs placebo (25%). |
| Ramaratnam et al[80]<br><br>Lamotrigine, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | MA (11 RCTs; 8 of which were XO)<br><br>Patients of any age with drug-resistant partial epilepsy (n=199 children and n=1,044 adults) | N=1,243<br><br>Duration not reported | Primary:<br>Proportion with ≥50% reduction in seizure frequency, treatment withdrawal for any reason, safety and effects on cognition<br><br>Secondary:<br>Not reported | Primary:<br>The overall OR for ≥50% reduction in seizure frequency with lamotrigine compared to placebo was 2.71 (95% CI, 1.87 to 3.91; *P* value not reported), indicating that lamotrigine was significantly more effective than placebo in reducing seizure frequency.<br><br>The overall OR for treatment withdrawal for any reason for lamotrigine compared to placebo was 1.12 (95% CI, 0.78 to 1.61; *P* value not reported).<br><br>Lamotrigine was associated with significantly more ataxia, diplopia, dizziness, and nausea than placebo (*P* values not reported).<br><br>The limited data available precludes any conclusions about effects on cognition.<br><br>Secondary:<br>Not reported |
| Naritoku et al[81]<br><br>Lamotrigine XR QD, dosing not specified, in addition to current AED therapy<br><br>vs | DB, PG, RCT<br><br>Patients >12 years of age with partial epilepsy and taking 1 to 2 baseline AEDs | N=239<br><br>Treatment duration 19 weeks | Primary:<br>Change in weekly partial seizure frequency<br><br>Secondary:<br>Proportion of patients with | Primary:<br>Lamotrigine XR was more effective than placebo with respect to median percent reduction from baseline in weekly partial seizure frequency (46.6 vs 24.5% for the entire 19-week treatment phase; 29.8 vs 15.6% for the seven-week escalation phase; and 58.4 vs 26.8% for the 12-week treatment phase; all *P*<0.05).<br><br>Secondary:<br>The proportion of patients with ≥50% reduction in partial seizure frequency (44.0 vs 20.8%; *P*=0.0002) and time to ≥50% reduction in partial seizure frequency |


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| placebo, in addition to current AED therapy | | | ≥50% reduction in partial seizure frequency, time to ≥50% reduction in partial seizure frequency and safety | (*P*<0.0001) also favored lamotrigine XR over placebo.<br><br>A similar pattern of results was observed for secondarily generalized seizures.<br><br>The most common adverse events were headache (16 vs18%) and dizziness (19 vs 5%) (*P* values were not reported). |
| Biton et al[82]<br><br>Lamotrigine XR 200 mg, 300 mg or 500 mg daily (dose based on coadministration with other AEDs)<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Patients ≥13 years of age with a confident diagnosis of epilepsy with primary generalized tonic-clonic seizures for >24 weeks before baseline phase, historical or PRO electro-encephalo-graphic evidence of either spike-and-wave discharges consistent with primary generalized tonic-clonic seizures or at least 2 EEGs | N=153<br><br>19 weeks<br><br>All patients completing the mainten-ance phase had the option of entering a 52 week OL continua-tion phase during which they received lamotrigine XR | Primary:<br>Percent change from baseline in weekly primary generalized tonic-clonic seizure frequency during DB treatment (escalation and maintenance)<br><br>Secondary:<br>Percent change from baseline in weekly primary generalized tonic-clonic seizure frequency during escalation phase only and maintenance phase only, percent of | Primary:<br>Median percent reduction from baseline in weekly frequency of primary generalized tonic-clonic seizures during DB treatment was 75.4% in the lamotrigine XR group compared to 32.1% in the placebo group (median difference 31.6%; *P*<0.0001).<br><br>Secondary:<br>A significant reduction from baseline in weekly frequency of primary generalized tonic-clonic seizures during the escalation phase was observed (25.7% difference between groups; *P*=0.0016).<br><br>A significant reduction from baseline in weekly frequency of primary generalized tonic-clonic seizures during the maintenance phase was observed (35.8% difference between groups; *P*=0.0016).<br><br>Lamotrigine XR reduced the median frequency of primary generalized tonic-clonic seizures during DB treatment regardless of concomitant AED.<br><br>A significantly higher proportion of patients in the lamotrigine XR group had a ≥50% reduction in primary generalized tonic-clonic seizure frequency during DB treatment (69.6 and 31.9% respectively; *P*<0.0001).<br><br>A significantly higher proportion of patients in the lamotrigine XR group had a ≥50% reduction in primary generalized tonic-clonic seizure frequency during the escalation phase (55.1 and 31.9% respectively, *P*<0.0001).<br><br>A significantly higher proportion of patients in the lamotrigine XR group had a |


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| | with no indication of focal abnormalities, documented history of primary generalized tonic-clonic seizures with or without other generalized seizure types with no focal onset and at least one primary generalized tonic-clonic seizure during the 8 consecutive weeks prior to the baseline phase, and at least 3 primary generalized tonic-clonic seizures during the 8-week baseline phase; patients had to be receiving a stable regimen of one or two AEDs for at least 4 weeks before the beginning of the baseline phase | | patients with ≥50% reduction and 100% reduction in primary generalized tonic-clonic seizure frequency during escalation and maintenance phases combined, the escalation phase alone and the maintenance phase alone, time to ≥50% reduction in primary generalized tonic-clonic seizure frequency during DB treatment, percentage of patients with improvement in investigator- and patient-rated status, safety | ≥50% reduction in primary generalized tonic-clonic seizure frequency during the maintenance phase (75.0% and 41.4% respectively; *P*<0.0001).<br><br>The time (weeks) to ≥50% reduction in primary generalized tonic-clonic seizure frequency during DB treatment was significantly shorter in the lamotrigine XR group compared to the placebo group (*P*<0.0001), beginning on day eight of the escalation phase.<br><br>The percent of patients with 100% reduction in primary generalized tonic-clonic seizure frequency was 20.3% for lamotrigine XR and 9.7% for placebo (*P*=0.0989) during the escalation plus maintenance phase, 21.7 and 12.5% respectively (*P*=0.1805) during the escalation phase only and 45.6 and 14.3% respectively (*P*<0.0001) during the maintenance phase only.<br><br>Significantly more patients in the lamotrigine XR group showed improvement in investigator-rated clinical status during DB treatment compared to placebo (84 and 51% respectively; *P*=0.0002).<br><br>Significant differences in responses in favor of lamotrigine XR were observed in seizure frequency (87 and 69% respectively; *P*=0.0420), seizure duration (82 and 54% respectively; *P*=0.0005) seizure intensity (85 and 58% respectively; *P*=0.0012), and adverse experiences (41 and 23% respectively; *P*=0.0197).<br><br>No significant differences between lamotrigine XR and placebo were observed for social, intellectual or motor functioning.<br><br>No significant difference in patient-reported improvement in clinical status was observed (87 and 74% respectively; *P* value not reported).<br><br>The proportion of patients with at least one adverse event during the study was 54% in the lamotrigine XR group and 57% in the placebo group.<br><br>Non-serious rash was reported in two patients in the lamotrigine XR group and four patients in the placebo group. No serious rashes were reported in either group. Adverse events of seizures were reported in one patient in the placebo |


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| | | | | group (convulsion) and two patients in the lamotrigine XR group (absence seizure in one patient and simple partial seizures on days one and seven of treatment in one patient with no history or electrographic evidence of partial seizures).<br><br>Adverse events led to premature withdrawal in one patient in the lamotrigine XR group and two patients in the placebo group. Two adverse events that led to premature withdrawal (non-serious rash in lamotrigine XR and placebo groups) were considered to be caused by study medication.<br><br>The only serious adverse event was confusional state in the lamotrigine XR group. This was not thought to be caused by study medication and lamotrigine XR was not discontinued. |
| Rosenow et al[83]<br><br>Lamotrigine 200 mg/day<br><br>vs<br><br>levetiracetam 2,000 mg/day<br><br>In patients <50 kg, target daily doses were reduced to 1,500 mg of levetiracetam and 150 mg of lamotrigine. After reaching the target dose, 2 dose adjustments by 500 mg (levetiracetam) or 50 mg (lamotrigine) were allowed depending on seizure control and tolerability. | DB, MC, PG, RCT<br><br>Patients newly diagnosed with focal, generalized or unclassified epilepsy (2 or more unprovoked seizures or first seizure with high risk for recurrence)<br><br>Patients already receiving 1 AED at enrolment were included and the AED was tapered over 3 weeks. | N=409<br><br>26 weeks | Primary:<br>Proportion of patients seizure-free at six weeks<br><br>Secondary:<br>Proportion of patients seizure-free at during the 16-week maintenance period, seizure-free time, QOLIE and safety | Primary:<br>In the ITT population, the proportion of patients who were seizure-free at six weeks was not significantly different between the lamotrigine and levetiracetam treatment groups (64.0 vs 67.5%, respectively; *P*=0.47). Similar results were reported in the PP population (79.8 vs 83.6%; *P*=0.51).<br><br>Secondary:<br>During the 16-week maintenance period, there was no statistically significant difference between the lamotrigine and levetiracetam treatment groups with regard to the proportion of seizure-free patients (55.7 vs 51.9%, respectively; *P*=0.49).<br><br>Over the complete 26-week study 47.8% of patients treated with lamotrigine remained seizure-free compared to 45.2% of patients treated with levetiracetam (*P*=0.62).<br><br>There was no statistically significant difference between the treatment groups with regard to the median time to first seizure (HR, 0.86; 95% CI, 0.61 to 1.22; *P*=0.40).<br><br>The change from baseline in QOLIE scores between the treatment groups was not statistically significant (*P*=0.69).<br><br>Adverse events were reported in a similar number of patients treated with lamotrigine or levetiracetam (70.6 vs 74.5%, respectively; *P*=0.38). Tiredness and |


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| | | | | aggression occurred significantly more frequently with levetiracetam (32.8 and 8.8%, respectively) compared to lamotrigine (16.4 and 2.5%, respectively; *P*<0.001 for both). There were 17 serious adverse events in the lamotrigine group compared to 24 serious adverse events in the levetiracetam group; however, the difference was not statistically significant (*P*=0.40). |
| Chaisewikul et al[84] (abstract)<br><br>Levetiracetam, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | MA of 4 PC, RCT (Cochrane Review 2001)<br><br>Patients with drug-resistant localization related (partial) epilepsy | N=1,023<br><br>16 to 24 weeks | Primary:<br>Proportion with ≥50% reduction in total seizure frequency, treatment withdrawal for any reason, safety and effects on cognition<br><br>Secondary:<br>Not reported | Primary:<br>The overall OR for ≥50% reduction in total seizure frequency with levetiracetam compared to placebo was 3.81 (95% CI, 2.78 to 5.22; *P* value not reported). Higher levetiracetam doses were associated with greater reductions in seizure frequency (~15% of patients taking 1,000 mg/day and 20 to 30% of patients taking 3,000 mg/day had a ≥50% reduction in seizure frequency).<br><br>Patients were not significantly more likely to have levetiracetam withdrawn compared to placebo (OR, 1.25; 95% CI, 0.87 to 1.80; *P* value not reported).<br><br>Levetiracetam was associated with significantly more dizziness and infection, whereas placebo was associated with significantly more accidental injury (*P* values not reported).<br><br>Cognitive effect outcomes suggest that levetiracetam had a positive effect on cognition (additional information not reported).<br><br>Secondary:<br>Not reported |
| Peltola et al[85]<br><br>Levetiracetam XR 1,000 mg QD, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | DB, MC, PC, PG,<br><br>Patients 12 to 10 years of age with partial-onset seizures refractory to 1 to 3 AEDs | N=158<br><br>Treatment duration 12 weeks | Primary:<br>Frequency of partial-onset seizures per week<br><br>Secondary:<br>Proportion of responders (≥50% reduction in partial-onset | Primary:<br>The reduction in median partial-onset seizures per week was 46.1% on levetiracetam XR and 33.4% on placebo. The estimated reduction with levetiracetam XR over placebo was 14.4% (*P*=0.038).<br><br>Secondary:<br>Thirty-four (43%) levetiracetam XR and 23 (29%) placebo patients experienced ≥50% reduction in partial-onset seizures per week. Eight (10.1%) patients receiving levetiracetam XR and one (1.3%) patient receiving placebo were free of partial-onset seizures during the 12-week treatment period. |


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| | | | seizures per week), proportion of patients who were seizure-free and safety | Forty-one (53%) levetiracetam XR and 43 (54%) placebo patients reported ≥1 adverse event. Adverse events reported with an incidence >5% and seen more often with levetiracetam XR than with placebo were dizziness, influenza, irritability, nasopharyngitis, nausea and somnolence. |
| Otoul et al[86]<br><br>Levetiracetam, in addition to current AED therapy<br><br>vs<br><br>gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate or zonisamide, in addition to current AED therapy | MA of PC, RCT (studies identified in the Cochrane Library 2002, number of trials not reported)<br><br>Patients with refractory partial epilepsy | N=not reported<br><br>Duration not reported | Primary:<br>Responder rate (efficacy measure) and withdrawal rate (mainly tolerability measure)<br><br>Secondary:<br>Not reported | Primary:<br>A fixed-effects model was used to estimate responder and withdrawal rate of levetiracetam and other new AEDs vs placebo. Because no head-to-head clinical trials comparing these new AEDs were found, adjusted indirect comparisons were made between levetiracetam and other AEDs using the MA results.<br><br>At doses tested, levetiracetam was more effective in terms of responder rate than gabapentin (OR, 2.64; 95% CI, 1.51 to 4.63) and lamotrigine (OR, 1.86; 95% CI, 1.04 to 3.34) and equally well tolerated; *P* values were not reported.<br><br>Levetiracetam had a significantly lower withdrawal rate than topiramate (OR, 0.52; 95% CI, 0.29 to 0.93) and oxcarbazepine (OR, 0.55; 95% CI, 0.33 to 0.92), with comparable efficacy; *P* values were not reported.<br><br>Although levetiracetam did not differ significantly from tiagabine and zonisamide, numerical trends favoring levetiracetam were obtained in response rate and in withdrawal rate.<br><br>Indirect comparisons based on MAs suggest that add-on therapy with levetiracetam has a favorable responder and/or withdrawal rate relative to several AEDs in patients with partial epilepsy with doses used in clinical trials. These MAs give only short-term efficacy and safety data.<br><br>Secondary:<br>Not reported |
| Cumbo et al[87]<br><br>Levetiracetam 500 mg/day | Case control, PG, PRO, RETRO | N=95<br><br>12 months | Primary:<br>Efficacy (percentage of patients who | Primary:<br>At 12 months, 71% (27/38) of levetiracetam-treated patients were responders, 11 of whom (29%) had become seizure-free, 7/11 were seizure-free from the start of therapy and the other four became seizure free after two months. Forty two |


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| vs<br><br>lamotrigine 25 mg/day<br><br>vs<br><br>phenobarbital 50 mg/day<br><br>All patients were AED-naïve and had concomitant cholinesterase inhibitor therapy for Alzheimer's disease. | Patients 60 to 90 years of age meeting the diagnostic criteria for probably Alzheimer's disease with mild to moderate disease, educational level ≥5 years, a diagnosis of partial epilepsy and a caregiver who can ensure compliance to treatment | | became seizure free or experienced a >50% decrease in seizure frequency over 12 months)<br><br>Secondary: Change from baseline in MMSE score, ADAS-Cog score and Cornell scale score | percent (16/38) had a >50% reduction in seizure frequency, and 16% (6/38) had no significant change from baseline. Five (13%) patients had no change in seizure frequency.<br><br>Fifty nine percent (17/29) of lamotrigine-treated patients were responders. Twenty four percent (7/29) became seizure-free, and there was a 50 to 99% decrease in seizure frequency was observed in 34% (10/29) patients. Three of the seven patients were seizure-free from the start of therapy, and four became seizure-free two months later.<br><br>The majority of phenobarbital-treated patients responded (64% [18/28]), with eight (29%) patients being seizure-free from the start of therapy. Thirty six percent (10/28) of patients had a 50 to 99% decrease in seizure frequency, and 11% (3/28) had a <50% reduction and six (21%) patients did not respond.<br><br>There was no significant difference in responder rate between the levetiracetam (71%), lamotrigine (59%) and phenobarbital (64%) (*P*=0.34). No patient experienced an increase in seizures.<br><br>Secondary:<br>Levetiracetam-treated patients had an improvement by a mean of +0.23 points compared to baseline, with a similar improvement observed in ADAS-Cog scores (-0.23). Phenobarbital-treated patients showed a significant worsening cognitive performance. Patients treated with lamotrigine showed a slight decline in MMSE and ADAS-Cog scores. |
| Schiemann-Delgado et al[88]<br><br>Levetiracetam 20 to 100 mg/kg/day<br><br>Levetiracetam was administered as adjunctive therapy. | ES, MC, OL<br><br>Children 4 to 16 years of age with partial-onset epilepsy, receiving a stable regimen of 1 or 2 AEDs | N=103<br><br>48 weeks | Primary: Cognitive and behavioral measures<br><br>Secondary: Seizure control, safety | Primary:<br>The increased mean change from baseline in Leiter-R AM Memory Screen composite score (week 24: 4.8 points; 95% CI, 2.1 to 4.5; week 48: 4.5 points; 95% CI, 1.1 to 7.9) indicated stability in cognitive functioning during long term administration, as these changes were similar to the changes observed at the end of the evaluation in the prior short term trial (levetiracetam, 5.2; placebo, 5.4). Of the other mean composite scores, Attention Score, Associated Memory score, Memory Span score, and Memory process score also increased from baseline to week 24 and 48. |


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| | | | | Child Behavior Checklist Syndrome scores improved from baseline at week 24 and 48 (change, -9.3±22.2 and -10.4±23.4).<br><br>Secondary:<br>Treatment provided in good and sustained seizure control (median percentage reduction from baseline in partial-onset seizure frequency per week during maintenance treatment, 86.4%). In addition, 24.7% of patients had continuous seizure freedom from all seizure types for ≥40 weeks.<br><br>Treatment was well tolerated; the most frequently reported CNS-related treatment-emergent adverse events included headache (24.3%), aggression (7.8%), and irritability (7.8%). Overall, 4.9% of patients discontinued because of treatment-emergent adverse events. |
| Castillo et al[89]<br><br>Oxcarbazepine, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | MA (2 RCTs)<br><br>Patients of any age with drug-resistant partial epilepsy (n=267 children ages 4 to 17 years and n=694 adults ages 15 to 65 years) | N=961<br><br>Treatment duration 16-26 weeks | Primary:<br>Proportion with ≥50% reduction in seizure frequency, treatment withdrawal for any reason and safety<br><br>Secondary:<br>Not reported | Primary:<br>The overall OR for ≥50% reduction in seizure frequency with oxcarbazepine compared to placebo was 2.96 (95% CI, 2.20 to 4.00; *P* value not reported), indicating that oxcarbazepine was significantly more effective than placebo in reducing seizure frequency.<br><br>The overall OR for treatment withdrawal for any reason for oxcarbazepine compared to placebo was 2.17 (95% CI, 1.59 to 2.97; *P* value not reported).<br><br>Oxcarbazepine was associated with significantly more ataxia, diplopia, dizziness, fatigue, nausea, and somnolence than placebo (*P* values not reported).<br><br>Secondary:<br>Not reported |
| Costa et al[90]<br><br>Oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, zonisamide, eslicarbazepine* or | MA (71 RCTs)<br><br>Patients >2 years of age with drug-refractory partial epilepsy | N=14,272<br><br>≥8 weeks | Primary:<br>Responder rate (≥50% reduction in seizure frequency) in the treatment period compared to | Primary:<br>*AEDs vs placebo:*<br>Responder rates for each AED was significantly higher compared to placebo with ORs between 2.08 (gabapentin) and 4.31 (topiramate). Significant heterogeneity was found only for oxcarbazepine and pregabalin.<br><br>Significant differences were found in the dose-subgroup analysis for oxcarbazepine and eslicarbazepine (*P*=0.02 and *P*=0.03 respectively) suggesting |


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| lacosamide<br><br>vs<br><br>matched placebo or other AED control | | | baseline, withdrawal rate<br><br>Secondary: Proportion of patients seizure-free during treatment period, withdrawal rate due to adverse events, proportion of patients experiencing ataxia, dizziness, fatigue, headache, nausea, or somnolence | a dose-response relationship for those AEDs. However, the data in the trials did not allow for a dose-response regression analysis.<br><br>Withdrawal rate from any cause was higher with oxcarbazepine, topiramate, pregabalin, zonisamide, tiagabine and lacosamide in comparison with placebo but not with lamotrigine, gabapentin, levetiracetam and eslicarbazepine. Significant heterogeneity was observed only with eslicarbazepine.<br><br>Significant differences were found in the dose-subgroup analysis for oxcarbazepine, gabapentin and zonisamide ($P<0.01$, $P=0.04$ and $P<0.01$ respectively).<br><br>*Each AED and other AEDs:*<br>Significant differences were found in the analysis of the responder rate based on relative measurements of treatment effects favoring topiramate in comparison to all other AEDs. Gabapentin and lacosamide were less efficacious compared other AEDs. A trend was found for eslicarbazepine. For eslicarbazepine, significant differences were found in the dose-subgroup analysis ($P=0.03$).<br><br>Significant differences were observed in the analysis of responder rate based on absolute estimates (NNT) adjusted for baseline risk. Topiramate and levetiracetam were more efficacious and gabapentin and tiagabine were less efficacious. This demonstrates the importance of considering baseline risk in the analysis. In particular, the OR for lacosamide was significantly difference from other AEDs but not the NNT, because responder rates in the placebo arm were higher in the lacosamide trials. Similar results were seen in the eslicarbazepine trials.<br><br>Oxcarbazepine and topiramate were associated with more withdrawals and gabapentin and levetiracetam with fewer withdrawals.<br><br>Secondary:<br>*AEDs vs placebo*<br>Significant differences on the percent of patients seizure-free were not found for topiramate, levetiracetam and eslicarbazepine, without evidence of heterogeneity. Data for this outcome was only available in 32 of the 63 studies. |


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| | | | | Withdrawal rate due to adverse events was higher for lamotrigine, topiramate, gabapentin, pregabalin, zonisamide, eslicarbazepine and lacosamide but not for tiagabine and levetiracetam. Data for this outcome was only available in 15 of 63 studies. Significant heterogeneity was found for lamotrigine, tiagabine and eslicarbazepine.<br><br>The incidence of the six pre-specified adverse events were higher among all AED's compared to placebo in general.<br><br>*Each AED and other AEDs*<br>No significant differences were observed between AEDs in the proportion of patients that were seizure-free. The data for this comparison is sparse.<br><br>Withdrawal rate due to adverse events was significantly less with levetiracetam compared to all other AEDs. There were no significant differences observed between other AEDs.<br><br>Comparisons between the AEDs for the six pre-specified events showed few differences. There were no significant differences for ataxia, headache was more frequent with lacosamide, dizziness was more frequent with pregabalin, fatigue was more frequent with topiramate and less frequent with lamotrigine, nausea was more frequent with oxcarbazepine and less frequent with gabapentin and levetiracetam, and somnolence was more frequent with oxcarbazepine and less frequent with tiagabine.<br><br>*Combined evidence from indirect and direct comparisons:*<br>Combined results for indirect and direct comparisons showed no difference in responder rate withdrawal rate or seizure-free rate between lamotrigine and gabapentin.<br><br>Combined analyses favored topiramate for responder rate and seizure free rate compared to lamotrigine and favored lamotrigine for withdrawal rate.<br><br>Combined analyses favored pregabalin for responder rate compared to |


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| | | | | lamotrigine. There were no differences observed in seizure-free rate or withdrawal rate.<br><br>Combined analyses showed no difference between lamotrigine and levetiracetam in responder rate, seizure-free rate or withdrawal rate. |
| French et al[91]<br>Study 304<br><br>Perampanel 8 mg QD<br><br>vs<br><br>perampanel 12 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥12 years of age with partial-onset seizures with or without secondary generalization who had failed ≥2 AEDs and were receiving 1 to 3 AEDs at baseline | N=388<br><br>19 weeks (6-week titration phase followed by 13-week mainten-ance phase) | Primary:<br>Percent change in seizure frequency, responder rate defined (percentage of patients with ≥50% reduction in seizure frequency from baseline<br><br>Secondary:<br>Percent change in frequency of complex partial seizures plus secondary generalized seizures and safety | Primary:<br>The median percent change in seizure frequency over the double-blind phase was -26.3 and -34.5% in the perampanel 8 mg (*P*=0.0261) and 12 mg (*P*=0.0158) treatment groups compared to -21.0% in the placebo group. The median differences compared to placebo were -13.5% (95% CI, -26.3 to -1.9) and -14.2% (95% CI, -25.0 to -2.7) for the perampanel 8 mg and 12 mg treatment groups, respectively.<br><br>The 50% responder rates were 37.6 (95% CI, 29.4 to 45.8; *P*=0.0760), 36.1 (95% CI, 27.9 to 44.3; *P*=0.0914) and 26.4% (95% CI, 18.6 to 34.3) for the perampanel 8 mg, 12 mg and placebo treatment groups, respectively. The NNT were nine and 10 patients for a response, and the absolute risks were 11.2 (95% CI, -0.2 to 22.5) and 9.7% (95% CI, -1.7 to 21.0) for the perampanel 8 mg and 12 mg treatment groups, respectively.<br><br>Secondary:<br>The percent change in complex partial plus secondary generalized seizures were -33.0 and -33.1% for the perampanel 8 mg (*P*=0.0020) and 12 mg (*P*=0.0081) groups compared to -17.9% in the placebo group.<br><br>Treatment-emergent adverse events occurred in 88.0, 91.8 and 82.6% of patients treated with perampanel 8 mg, 12 mg or placebo, respectively. Treatment-related adverse events occurred in 74.4, 80.6 and 47.9% of patients treated with perampanel 8 mg, 12 mg or placebo, respectively. The most commonly reported adverse events occurring more frequently with perampanel treatment compared to placebo were dizziness, somnolence, headache, ataxia and irritability. The incidence of treatment-emergent adverse events leading to dose reduction or interruption was highest in the perampanel 12 mg (33.6%) and 8 mg (22.6%) groups compared to the placebo group (5.0%). More patients discontinued treatment due to treatment-emergent adverse events in the perampanel 12 mg |


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| | | | | group (19.4%) compared to the perampanel 8 mg (6.8%) and placebo (6.6%) groups. Among all treatment groups, one death occurred during baseline following a convulsion. The investigators did not report which group the death occurred in.<br><br>Secondary:<br>None reported |
| French et al[92]<br>Study 305<br><br>Perampanel 8 mg QD<br><br>vs<br><br>perampanel 12 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥12 years of age with simple or complex partial-onset seizures, with or without secondary generalization despite 2 different AEDs in the previous 2 years and current regimen of 1 to 3 AEDs | N=386<br><br>19 weeks (6-week titration phase followed by 13-week mainten-ance phase) | Primary:<br>Responder rate (percentage of patients with ≥50% reduction in seizure frequency from baseline) and percent change in seizure frequency<br><br>Secondary:<br>Percent change in the frequency of complex partial plus secondarily generalized seizures | Primary:<br>The responder rates were 33.3 (*P*=0.002), 33.9 (*P*<0.001) and 14.7% for the perampanel 8 mg, 12 mg and placebo groups, respectively.<br><br>The median percent change in seizure frequency over the double-blind phase was -30.5 (*P*<0.001), -17.6 (*P*=0.011) and -9.7% for the perampanel 8 mg, 12 mg and placebo groups, respectively. The median difference in percent change in seizure frequency compared to placebo was -19.1 (95% CI, -29.2 to -8.4) and -13.7 (95% CI, -25.2 to -2.3) for the perampanel 8 mg and 12 mg groups, respectively.<br><br>Secondary:<br>The median percent change in seizure frequency per 28 days was -32.7% (*P*<0.001), -21.9% (*P*=0.005) and -8.1 for perampanel 8 mg, 12 mg and placebo, respectively.<br><br>The proportion of patients that achieved a 75 to 100% reduction in seizure frequency was 15.5 and 16.5% for the perampanel 8 mg and 12 mg groups, respectively, compared to 4.4% of the placebo group (*P* value not reported).<br><br>Treatment-related adverse events occurred in 69.0, 77.7 and 47.8% of the perampanel 8 mg, 12 mg and placebo groups, respectively. Serious treatment-emergent adverse events occurred in 7.8, 9.9 and 5.1% of the perampanel 8 mg, 12 mg and placebo groups, respectively. The most common adverse events that occurred more frequently in the perampanel groups compared to placebo were dizziness, somnolence and fatigue. The proportion of patients that experienced a treatment-emergent adverse event leading to discontinuation was higher in the perampanel 8 mg and 12 mg groups (9.3% and 19.0%, respectively) compared to the placebo group (4.4%). No deaths occurred during the study. |


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| Krauss et al[93]<br>Study 306<br><br>Perampanel 2 mg QD<br><br>vs<br><br>perampanel 4 mg QD<br><br>vs<br><br>perampanel 8 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥12 years of age with simple or complex partial-onset seizures, with or without secondary generalization, with uncontrolled partial-onset seizures despite treatment with 2 different AEDs in the previous 2 years and current regimen of one to three AEDs | N=706<br><br>19 weeks (6-week titration phase followed by 13-week mainten-ance phase) | Primary:<br>Percent change in seizure frequency, responder rate (percentage of patients with ≥50% reduction in seizure frequency from baseline)<br><br>Secondary:<br>Percent change in frequency of complex partial seizures plus secondarily generalized seizures, dose-response analysis of the percent change in seizure frequency | Primary:<br>The percent change in seizure frequency was -13.6 (*P*=0.420), -23.3 (*P*=0.003) and -30.8% (*P*<0.001) for the perampanel 2 mg, 4 mg and 8 mg groups, respectively, compared to -10.7% in the placebo group.<br><br>The responder rates were 20.6 (*P* value not significant), 28.5 (*P*=0.013) and 34.9% (*P*<0.001) for patients treated with perampanel 2 mg, 4 mg and 8 mg, respectively, compared to 17.9% in the placebo group.<br><br>Secondary:<br>The percent change in frequency of complex partial seizures plus secondarily generalized seizures was -20.5 (*P* value not reported), -31.2 (*P*=0.007) and -38.7% (*P*<0.001) for the perampanel 2 mg, 4 mg and 8 mg groups, respectively, compared to -17.6% in the placebo group.<br><br>Of patients who completed the maintenance period, the proportion of patients who were seizure-free during the maintenance period was 1.9, 4.4 and 4.8% for the perampanel 2 mg, 4 mg and 8 mg groups, compared to 1.2% for the placebo group (*P* values not reported).<br><br>Treatment-related adverse events were reported in 37.2, 44.8, 56.8 and 31.9% of the perampanel 2 mg, 4 mg, 8 mg and placebo groups, respectively. Serious treatment-related adverse events occurred in 3.3, 3.5, 3.6 and 4.9% of the perampanel 2 mg, 4 mg, 8 mg and placebo groups, respectively. Adverse events that occurred more frequently in the perampanel compared to placebo included dizziness and somnolence. |
| Krauss et al[94]<br>Extension study 307<br><br>Perampanel titrated to a maximum of 12 mg QD in 2 mg increments every 2 weeks | ES<br><br>Patients who completed the double-blind phase of studies 304, 305 and 306 | N=1,218<br><br>Up to 276 weeks | Primary:<br>Change in seizure frequency, responder rate (percentage of patients with ≥50% reduction from baseline in | Primary:<br>The percent change in seizure frequency was measured for each 13-week interval. In patients that had at least one year of treatment with perampanel (n=588), the median percent change in seizure frequency observed in the last 13-week interval was -47.2%. In patients with at least two years of treatment with perampanel (n=19), the median percent change in seizure frequency observed in the last 13-week interval was -56.0%.<br><br>The overall median percent changes in seizure frequency for weeks one to 13 |


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| | | | seizure frequency) and safety<br><br>Secondary:<br>None reported | (n=1,207), weeks 40 to 52 (n=731) and weeks 92 to 104 (n=59) were -29.1, -46.5% and -58.1%, respectively.<br><br>In patients that had received at least one year of treatment with perampanel, the responder rate at the end of one year was 47.6%. In patients that had received at least two years of treatment with perampanel, the responder rate at the end of two years was 63.2%.<br><br>The responder rates for weeks one to 13, weeks 40 to 52 and weeks 92 to 104 were 31.1, 46.9 and 62.7%, respectively. Of the patients that had six months of data, 16.4% were seizure-free for the last three months and 8.9% were seizure-free for all six months. Of the patients that had nine and 12 months of data, 7.6 and 7.1% were seizure-free for all nine and 12 month period, respectively.<br><br>The most commonly reported treatment-emergent adverse events included dizziness, somnolence, headache and fatigue. The proportion of patients with treatment-emergent adverse events was similar among patients taking one, two or three AEDs at baseline. Adverse events leading to withdrawal, dose reduction or dose interruption occurred in 13.2, 36.1 and 3.3% patients, respectively. Three deaths occurred during the study, none of which were determined to be related to study treatment.<br><br>Secondary:<br>Not reported |
| French et al[95]<br><br>Pregabalin 50, 150, 300 or 600 mg/day BID; in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | DB, MC, PC, PG, RCT<br><br>Patients with refractory partial seizures while on 1 to 3 AEDs; median baseline seizure rate was 10/month | N=453<br><br>12 weeks | Primary:<br>Seizure frequency<br><br>Secondary:<br>Responder rates (defined as ≥50% reduction in seizure frequency) and adverse events | Primary:<br>Seizure frequency reductions from baseline were dose-related and as follows: 7% with placebo, 12% with 50 mg/day, 34% with 150 mg/day, 44% with 300 mg/day and 54% with 600 mg/day ($P \leq 0.0001$ for all pregabalin doses compared to placebo).<br><br>Secondary:<br>Responder rates were dose-related and as follows: 14% with placebo, 15% with 50 mg/day, 31% with 150 mg/day, 40% with 300 mg/day and 51% with 600 mg/day ($P \leq 0.006$ for all pregabalin doses compared to placebo). |


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| | | | | Discontinuation rates due to adverse events were 5% with placebo, 7% with 50 mg/day, 1% with 150 mg/day, 14% with 300 mg/day and 24% with 600 mg/day.<br><br>Incidences of CNS adverse events were dose-related. Most common adverse events were dizziness (9 to 43% vs 9% with placebo) and somnolence (10 to 28% vs 11% with placebo). |
| Arroyo et al[96]<br><br>Pregabalin 150 or 600 mg/day TID, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | DB, MC, PC, RCT<br><br>Patients with refractory partial seizures (defined as failed at least one AED at maximally tolerated doses) and currently receiving 1 to 3 AEDs | N=287<br><br>12 weeks | Primary: Seizure frequency<br><br>Secondary: Responder rate, percentage of patients free of seizures during the last 28 days and median percentage change in seizure frequency | Primary:<br>Seizure reduction from baseline was greater with both doses of pregabalin compared to placebo (*P*=0.0007 with 150 mg/day and *P*≤0.0001 with 600 mg/day).<br><br>Seizure frequency was reduced by 20.6% with pregabalin 150 mg/day (-12.4; 95% CI, -20.5 to -4.3) and 47.8% with 600 mg/day (-32.3; 95% CI, -40.6 to -24.0) and increased by 1.8% with placebo.<br><br>Seizure frequency was significantly improved with pregabalin 600 mg/day compared to 150 mg/day (*P*≤0.0001).<br><br>Secondary:<br>Responder rate was significantly greater in the pregabalin 600 mg/day group (*P*≤0.001), but not in the 150 mg/day group (*P*=0.087) compared to placebo.<br><br>Median percentage of seizure frequency was reduced by 16.5% in the pregabalin 150 mg/day group and 42.6% in the 600 mg/day group, but increased by 1.3% in the placebo group.<br><br>Percentage of patients free of seizures during the last 28 days of the study was higher with pregabalin 600 mg/day (12% vs 1% with placebo; *P*=0.002) than 150 mg/day (7 vs 1% with placebo; *P*=0.065).<br><br>Dizziness (6.0 to 29.0% vs 7.3%) and somnolence (19.0 to 26.0% vs 8.0%) were reported with higher frequency in the pregabalin groups vs the placebo group. |
| Beydoun et al[97]<br><br>Pregabalin 600 mg/day BID or TID, in addition | DB, MC, PC, PG, RCT<br><br>Patients with | N=312<br><br>12 weeks | Primary: Seizure frequency | Primary:<br>Both regimens of pregabalin were more efficacious in reducing the frequency of partial-onset seizures compared to placebo (*P*≤0.0001). |


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| to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | medically refractory partial epilepsy, who have failed ≥2 AEDs at maximally tolerated doses | | Secondary: Responder rate, adverse events | The percentages of reduction in seizure frequency from baseline were as follows: 53.0% reduction for TID dosing, 44.3% reduction for BID dosing and 1.2% increase for placebo (RR, -7.7; 95% CI, -17.4 to 1.9 for the two pregabalin groups).<br><br>Secondary:<br>Responder rate was significantly higher in the pregabalin groups compared to placebo (49% for TID vs 43% for BID vs 9% for placebo; *P*≤0.001 for both compared to placebo), but not significantly different from one another (no *P* value reported).<br><br>Commonly reported adverse events include: dizziness (38 to 42% with pregabalin vs 12% with placebo), somnolence (23 to 30% vs 12%), ataxia (17 to 27% vs 6%), weight gain (15 to 20% vs 2%), amblyopia (10 to 17% vs 4%), asthenia (12 to 14% vs 5%), diplopia (10 to 14% vs 4%) and abnormal thinking (9 to 11% vs 1%). |
| Elger et al[98]<br><br>Pregabalin fixed-dose of 600 mg/day BID, in addition to current AED therapy<br><br>vs<br><br>pregabalin flexible-dose regimen of 150 and 300 mg/day for 2 weeks each, followed by 450 and 600 mg/day for 4 weeks each BID, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to | DB, MC, PC, PG, RCT<br><br>Patients receiving ≥1 AED and experiencing ≥4 partial seizures during 6-week baseline period and no 4-week seizure-free interval | N=341<br><br>12 weeks | Primary: Partial seizure frequency<br><br>Secondary: Responder rate, percentage of patients free of seizures during the last 28 days, adverse events | Primary:<br>Pregabalin fixed-dose (49.3%; *P*=0.0001) and flexible-dose (35.4%; *P*=0.0091) regimen resulted in greater percentage reduction in partial seizure frequency from baseline compared to placebo (10.6%).<br><br>Pregabalin fixed-dose was more effective than pregabalin flexible-dose in reducing the frequency of partial seizures (*P*=0.0337).<br><br>Secondary:<br>Responder rate was higher in the pregabalin fixed-dose group than in the pregabalin flexible-dose group (45.3 vs 31.3%; *P*=0.016).<br><br>No difference was observed between pregabalin treatment groups in percentages of patients free of seizures during the last 28 days (12.4% of fixed-dose group vs 12.2% of flexible-dose group vs 8.2% of placebo group).<br><br>Five most frequently reported treatment-related adverse events were dizziness, ataxia, weight gain, asthenia and somnolence. |


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| current AED therapy | | | | |
| Lozsadi et al[99]<br><br>Pregabalin 50 to 600 mg/day, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | MA (4 RCTs)<br><br>Patients 12 to 82 years of age with drug-resistant partial epilepsy | N=1,397<br><br>Treatment duration 12 weeks | Primary:<br>Proportion with ≥50% reduction in seizure frequency<br><br>Secondary:<br>Proportion of patients with a complete cessation of seizures, treatment withdrawal for any reason or due to adverse effects and safety | Primary:<br>The overall OR for ≥50% reduction in seizure frequency with pregabalin compared to placebo was 3.56 (95% CI, 2.60 to 4.87; *P* value not reported), indicating that pregabalin was significantly more effective than placebo in reducing seizure frequency. A dose response analysis suggested increasing effect with increasing dose.<br><br>Secondary:<br>Pregabalin was not significantly associated with seizure freedom (RR, 2.73; 95% CI, 0.72 to 10.33; *P* value not reported).<br><br>Patients were significantly more likely to have pregabalin withdrawn for any reason (RR, 1.43; 95% CI, 1.11 to 1.85; *P* value not reported) or due to adverse effects (RR, 2.47; 95% CI, 1.80 to 4.17; *P* value not reported) than placebo.<br><br>Pregabalin was associated with significantly more ataxia, dizziness, somnolence and weight gain than placebo (*P* values not reported). |
| Baulac et al[100]<br><br>Pregabalin 300 mg/day<br><br>vs<br><br>lamotrigine 300 mg/day<br><br>vs<br><br>placebo<br><br>Patients in the pregabalin group who had seizures during phase I (titration) had | DB, MC, PC, PG, RCT<br><br>Patients ≥18 years of age and ≥40 kg with a diagnosis of epilepsy with partial seizures refractory to treatment (i.e. failed treatment with at least 3 AEDs from at least 2 different AED classes | N=434<br><br>17 weeks | Primary:<br>Change in seizure frequency (assessed by response ratios in the pregabalin and placebo groups during phase I, change in seizure frequency in the pregabalin and lamotrigine groups in phase I and II | Primary:<br>Pregabalin did not achieve statistically significant superiority against placebo during phase I or against lamotrigine in phase I and II.<br><br>During phase I, response ratios and corresponding percent changes from baseline for pregabalin showed a non-significant trend toward greater reduction in seizures compared to placebo in the ITT population (*P*=0.052).<br><br>Over the full DB period, treatment differences favored pregabalin vs placebo (*P*=0.0008) and vs lamotrigine (*P*=0.0825).<br><br>Lamotrigine did not achieve a significantly better response than placebo during phase I (*P*=0.12).<br><br>Pregabalin showed clinically relevant improvements vs placebo regarding response ratio and percent change from baseline during phase II and during fixed- |


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| their dose titrated over 1 week to 600 mg/day and patients in the lamotrigine group having seizures in phase I had their dose increased to 400 mg/day without titration.<br><br>Patients were allowed to take one to 3 AEDs concurrently, one which must be an enzyme inducer. | each at or above the lowest recommended dose or the lowest adequate plasma concentration for a minimum of 3 months), and having at least 4 partial seizures during the 6-week baseline period and no 28-day period free of partial seizures | | combined<br><br>Secondary:<br>28-day seizure rates, proportion of responders (≥50% reduction in 28-day seizure rates), patients seizure-free for specified intervals, mean number of seizure-free days per 28-day period; response ratios were calculated by dividing the difference between 28-day seizure rates during DB treatment and baseline period by the sum of the baseline and treatment seizure rates, safety | doses phases I and II combined (*P*<0.001).<br><br>Lamotrigine showed clinically relevant improvement vs placebo during phase II and during fixed-dose phases I and II combined (*P*=0.023)<br><br>There were non-significant treatment differences favoring pregabalin over lamotrigine during phase II (*P*=0.091) and fixed-dose phases I and II combined (*P*=0.08) in the ITT analysis and in the PP analysis (*P*=0.10).<br><br>Secondary:<br>During phase I, pregabalin showed a median percent change treatment difference vs placebo of -13.6% in percent change from baseline in seizure frequency (*P*=0.024).<br><br>During all DB phases, the median percent change form baseline in seizure frequency with pregabalin compared to placebo and lamotrigine was -20.0% (*P*=0.001) and -9.7% (*P*=0.082) respectively.<br><br>For all ITT patients during phase I and II, the percentage of pregabalin responders was significantly greater than placebo (35.5 and 21.4% respectively, *P*=0.0069) and statistically greater than lamotrigine (35.5 and 24.1% respectively, *P*=0.041). Lamotrigine was not significantly better than placebo (*P*=0.66).<br><br>A ≥25% and ≥75% reduction in all partial seizures occurred in more patients in the pregabalin group (58% and 17% respectively) compared to placebo (43 and 6% respectively; *P*<0.01) but not for lamotrigine (50 and 9% respectively, *P*≥0.284 vs placebo).<br><br>Seizure-free rates for phases I and II combined were 1, 3, and 4% for placebo, lamotrigine and pregabalin respectively. Seizure-free rates for the last 28 days of treatment during phases I and II combined were 11, 11, and 12% for placebo, lamotrigine and pregabalin respectively. No significant differences between treatment groups were observed during any study period.<br><br>Most adverse effects were mild to moderate and consistent with known safety |


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| | | | | profiles of the study medications. Dizziness and headache were among the most common adverse events reported with pregabalin and lamotrigine.<br><br>The incidence of serious adverse effects ranged from 3 to 5% per treatment group. Sixteen patients experienced serious adverse events: four in the placebo group, five in the pregabalin group and seven in the lamotrigine group.<br><br>Investigators considered four serious adverse events to be related to a study drug: peripheral edema and ataxia/encephalopathy reported by pregabalin patients and two cases of grand mal seizures reported by lamotrigine patients.<br><br>There was one death during the study: a possible suicide in the pregabalin group. This was not considered to be related to study treatment.<br><br>In the pregabalin group, the most frequent adverse event-attributed withdrawals were due to dizziness, asthenia and abnormal thinking. In the lamotrigine group, the most frequent adverse event-attributed withdrawals were due to dizziness, asthenia and headache.<br><br>The frequency of spontaneously reported weight gain was higher in pregabalin patients (9%) compared to lamotrigine (2%) and placebo (1%). The percentage of patients with clinically significant weight gain (≥7% per the Food and Drug Administration) was higher for pregabalin (23%) than placebo (3%) or lamotrigine (1%). Three pregabalin patients withdrew due to weight gain. |
| Delahoy et al[101]<br><br>Pregabalin low-dose (150 mg/day), mid-dose (300 mg/day) or high-dose (600 mg/day<br><br>vs<br><br>gabapentin low-dose (900 mg/day), mid-dose | MA (8 RCTs)<br><br>Patients with partial epilepsy refractory to up to 3 established AEDs | N=1,911<br><br>12 weeks | Primary:<br>Responder rate (≥50% reduction from baseline in the number of seizures), change from baseline in seizure-free days over the past 28 days | Primary:<br>*Analysis using LOCF in ITT population:*<br>Each dose of pregabalin was significantly different from placebo in responder rate (*P* value not reported).<br><br>Patients who received adjunctive high-dose pregabalin were at least four times more likely to attain ≥50% reduction in baseline seizures compared to patients receiving placebo (RR, 4.63; 95% CI, 3.72 to 5.58).<br><br>Each dose of gabapentin was significantly different from placebo in responder rate (*P* value not reported) with the magnitude of difference increasing with dose. |


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| (1,200 mg/day) or high-dose (1,800 mg/day)<br><br>The analysis also estimated the efficacy of gabapentin at 2,400 mg/day by extrapolating the dose response equations. | | | Secondary:<br>Not reported | The risk for patients attaining a ≥50% reduction in seizures with gabapentin 2,400 mg was 2.82 times that of placebo, though a greater gradient for the dose-response curve was observed with pregabalin.<br><br>Overlapping 95% CI's were observed between pregabalin 300 mg and gabapentin 1,200 mg dose levels and between pregabalin 600 mg and gabapentin 1,800 mg dose level, statistical significance in favor of pregabalin at these levels for responder rate was indicated.<br><br>*Analysis of completers:*<br>Each dose of pregabalin and gabapentin was significantly different from placebo in responder rate with magnitude of effects increasing with dose.<br><br>The magnitude of effect in favor of pregabalin over gabapentin at all doses in the LOCF analysis of responder rate is only retained for the high-dose comparison (pregabalin 600 mg/day and gabapentin 1,800 mg/day) in the completer analysis.<br><br>*Analysis of responders:*<br>Each dose of gabapentin was significantly different compared to placebo in responder rate.<br><br>When the responder data are subject to indirect comparison using placebo as the common comparator, there were no significant differences between the pregabalin and gabapentin and any dose.<br><br>*Change from baseline in seizure-free days:*<br>Pregabalin and gabapentin were associated with a change from baseline in seizure-free days relative to placebo at all dose levels.<br><br>On average, patients receiving pregabalin experienced at least a two day increase in seizure-free days compared to placebo. Patients receiving gabapentin experienced at most a 1.5-day increase in seizure-free days compared to placebo. The dose-response curve is steeper for pregabalin with respect to mean difference in seizure-free days. |


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| | | | | Secondary:<br>Not reported |
| Kwan et al[102] (abstract)<br><br>Pregabalin 75 mg BID<br><br>vs<br><br>lamotrigine 50 mg BID | DB, MC, NI, PC, RCT<br><br>Adults with newly diagnosed partial seizures | N=660<br><br>52 weeks | Primary:<br>Proportion of patients who remained seizure free for six or more continuous months<br><br>Secondary:<br>Safety | Primary:<br>Fewer patients receiving pregabalin compared to patients receiving lamotrigine became seizure free for six or more continuous months (162 [52%] vs 209 [68%]; difference, -0·16, 95% CI, -0.24 to -0.09).<br><br>Secondary:<br>The overall incidence of adverse events was similar between the two treatments and consistent with that in previous trials; dizziness (55 [17%] vs 45 [14%] patients), somnolence (29 [9%] vs 14 [4%]), fatigue (27 [8%] vs 19 [6%]), and weight increase (21 [6%] vs 7 [2%]) were numerically more common with pregabalin compared to lamotrigine. |
| Uthman et al[103]<br><br>Pregabalin 75 to 600 mg/day BID or TID, in addition to current AED therapy | Analysis of 6 ES, OL<br><br>Patients with partial onset epilepsy refractory to multiple antiepileptic agents | N=2,061<br><br>3.5 to 8 years | Primary:<br>Seizure control and safety<br><br>Secondary:<br>Not reported | Primary:<br>Overall, 43% had a ≥50% reduction in the 28 day seizure frequency from baseline during their last three months of pregabalin treatment. The percentage of patients who were 50% responders in the first three and last three months of treatment, irrespective of the duration between these periods, was 24%.<br><br>Overall, 27.3% of patients became seizure-free for any three months and 6.2% for any year.<br><br>In total, 1,891 (91.7%) patients experienced at least one adverse event and 262 patients (12.7%) discontinued treatment due to an adverse event. Most were mild or moderate in intensity; only 386 (18.7%) patients experienced adverse events that were rated as severe in intensity. The most common adverse events generally affected the CNS.<br><br>Secondary:<br>Not reported |
| Pereira et al[104]<br><br>Tiagabine, in addition to current AED therapy | MA of 5 PC, RCT (3 PG, 2 XO) (literature search included Medline | N=781<br><br>Minimum treatment | Primary:<br>Proportion with ≥50% reduction in seizure | Primary:<br>The overall OR for ≥50% reduction in seizure frequency with tiagabine compared to placebo was 3.16 (95% CI, 1.97 to 5.07; *P* value not reported), indicating that tiagabine was significantly more effective than placebo in reducing seizure |


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| vs<br><br>placebo, in addition to current AED therapy | to January 2008)<br><br>Patients 12 to 71 years of age with drug-resistant localization related (partial) epilepsy | duration 8 weeks | frequency, treatment withdrawal for any reason, safety and effects on cognition<br><br>Secondary:<br>Not reported | frequency.<br><br>The overall RR for treatment withdrawal for any reason for tiagabine compared to placebo was 1.81 (95% CI, 1.25 to 2.62; *P* value not reported).<br><br>Tiagabine was associated with significantly more dizziness, fatigue, nervousness and tremor than placebo (*P* values not reported).<br><br>The limited data suggested that tiagabine had no significant effects on cognition (*P* values not reported).<br><br>Secondary:<br>Not reported |
| Jette et al[105] (abstract)<br><br>Topiramate, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | MA of 10 RCT (Cochrane Review 2008)<br><br>Patients with drug-resistant partial epilepsy | N=1,312<br><br>Treatment duration 11 to 19 weeks | Primary:<br>Proportion with ≥50% reduction in seizure frequency in the treatment period compared to baseline, proportion of participants having treatment withdrawn and adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>The overall RR for ≥50% reduction in seizure frequency for topiramate was 2.85 compared to placebo (95% CI, 2.27 to 3.59; *P* value not reported). Dose regression analysis showed increasing effect with increasing dose, but found no advantage for doses over 300 or 400 mg per day.<br><br>The RR for treatment withdrawal was 2.26 for topiramate compared to placebo (95% CI, 1.55 to 3.31; *P* value not reported).<br><br>Topiramate was associated with significantly higher risks of ataxia, dizziness, fatigue, nausea, somnolence and “thinking abnormality”; *P* values were not reported.<br><br>Secondary:<br>Not reported |
| Zhang et al[106] (abstract)<br><br>Topiramate 200 mg/day, target dose | DB, PC, RCT<br><br>Patients with refractory partial epilepsy; at least | N=86<br><br>20 weeks | Primary:<br>Seizure frequency<br><br>Secondary: | Primary:<br>Overall, 47.8 and 7.5% of patients receiving topiramate and placebo reached ≥50% reduction in complex partial seizures.<br><br>Secondary: |


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| Concomitant AEDs continued at original dosages. | four seizures per four weeks during an eight week baseline period, despite medication with up to three standard AED | | Safety | With topiramate, the most common adverse events were dizziness, somnolence, fatigue, headache, and difficulty with memory. Most events were transient and mild or moderate in severity. |
| Puri et al[107]<br><br>Topiramate, adjunctive therapy | Pooled analysis of 2 trials<br><br>Infants <2 years of age with refractory partial-onset seizures | N=284<br><br>Up to 1 year | Primary:<br>Safety<br><br>Secondary:<br>Seizure frequency | Primary:<br>The most common treatment-emergent adverse events (≥30%) were fever (52%), respiratory tract infections (51%), anorexia (35%), and acidosis (31%). Most events were mild to moderate in severity. Treatment-emergent adverse events leading to discontinuation were reported in 17 (6%) infants and the most common event was "convulsions aggravated" in six infants.<br><br>Overall, eight deaths were reported.<br><br>Changes from pretreatment baseline to endpoint Z scores for growth parameters were as follows: -1.82±1.19 (body weight), -0.45±1.60 (body length), and -0.36±1.02 (head circumference).<br><br>Secondary:<br>In both trials, the median monthly seizure rates for both partial-onset seizures and "all seizure types" decreased substantially from pretreatment baseline to OL extension endpoint, although this analysis was not powered to demonstrate significant differences. More than 50% of infants were free of partial-onset seizures from the eighth month onward until the OL extension endpoint. |
| Hemming et al[108]<br><br>Vigabatrin 1,000 to 6,000 mg/day, in addition to current AED therapy<br><br>vs | MA (11 PG or XO RCTs)<br><br>Patients 10 to 65 years of age with drug-resistant partial epilepsy (simple partial, | N=747<br><br>Duration varied | Primary:<br>Proportion with ≥50% reduction in seizure frequency in the treatment period compared to baseline, | Primary:<br>Patients treated with vigabatrin were significantly more likely to obtain a ≥50% reduction in seizure frequency compared to those treated with placebo (RR, 2.58; 95% CI, 1.87 to 3.57; *P* value not reported).<br><br>Those treated with vigabatrin were also significantly more likely to have treatment withdrawn (RR, 2.49; 95% CI, 1.05 to 5.88; *P* value not reported). |


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| placebo, in addition to current AED therapy | complex partial or secondary generalized tonic-clonic seizures) | | proportion of participants having treatment withdrawn and adverse effects<br><br>Secondary:<br>Not reported | Patients treated with vigabatrin were more likely to experience a number of adverse events, significantly so for fatigue or drowsiness (*P* values not reported).<br><br>The authors noted that there was some evidence of small study effect bias, with smaller studies tending to report greater estimates of RR than larger studies.<br><br>Secondary:<br>Not reported |
| Lu et al[109] (abstract)<br><br>Zonisamide 300 or 400 mg/day<br><br>vs<br><br>placebo<br><br>Treatments were added on to existing AED therapies. | DB, PC, RCT<br><br>Adults with refractory partial-onset epilepsy | N=104<br><br>16 weeks | Primary:<br>Seizure frequency<br><br>Secondary:<br>Safety | Primary:<br>Zonisamide resulted in significantly greater efficacy compared to placebo (responder rate, 55.8 vs 36.0%; *P*<0.05), including 55.2% (16/29) with zonisamide 300 mg/day and 56.5% (13/23) with zonisamide 400 mg/day. There was no difference between zonisamide 300 and 400 mg/day (*P*>0.05).<br><br>Similar efficacy of zonisamide was found in the control of complex partial seizures, simple partial seizures, and secondary generalized seizures.<br><br>Secondary:<br>There was no difference in the incidence of adverse effects between the two treatments. Reported adverse effects with zonisamide were related to the digestive system (32.5%), weight changes (30.2%), the hematological system (15.1%), neurological/psychiatric effects (10.3%), the urinary system (7.9%), and the cardiovascular system (4.0%). Only digestive system adverse effects constituted a significantly higher proportion of adverse effects with zonisamide compared to placebo (32.5 vs 30.2%; *P*<0.05). |
| Chadwick et al[110]<br><br>Zonisamide 100 to 500 mg/day plus conventional AED treatment<br><br>vs | MA (4 RCTs)<br><br>Patients 12 to 77 years of age with drug-resistant partial epilepsy (simple partial, complex partial or secondary | N=850<br><br>12 or 24 weeks | Primary:<br>Proportion with ≥50% reduction in seizure frequency in the treatment period compared to baseline, proportion of | Primary:<br>The overall RR for ≥50% reduction in seizure frequency for zonisamide 300 to 500 mg/day was 2.44 compared to placebo (95% CI, 1.81 to 3.30). The RR for zonisamide 100 to 500 mg/day was 2.35 (95% CI, 1.74 to 3.17). Two trials provided evidence of a dose-response relationship for this outcome; *P* values were not reported.<br><br>The RR for treatment withdrawal was 1.64 for zonisamide 300 to 500 mg/day compared to placebo (95% CI, 1.20 to 2.26), and 1.47 for zonisamide 100 to 500 |


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| placebo plus conventional AED treatment | generalized tonic-clonic seizures) | | participants having treatment withdrawn and adverse effects<br><br>Secondary:<br>Not reported | mg/day compared to placebo (95% CI, 1.07 to 2.02; *P* values were not reported).<br><br>Zonisamide was associated with significantly higher risks of agitation, anorexia, ataxia, dizziness and somnolence than placebo. *P* values were not reported.<br><br>Secondary:<br>Not reported |
| Baulac et al[111]<br><br>Zonisamide 200 to 500 mg/day<br><br>vs<br><br>carbamazepine ER 400 to 1,200 mg/day | DB, MC, RCT<br><br>Patients 18 to 75 years of age, who were newly diagnosed with epilepsy (≥2 partial seizures with or without secondary generalization or generalized tonic-clonic seizures without clear focal origin) in the previous 12 months and were treatment naïve or received 1 AED for <2 weeks | N=583<br><br>Up to 110 weeks (4-week titration, 26-, 52- or 78-week flexible dosing and 26-week mainten-ance period) | Primary:<br>Proportion of patients remaining seizure-free during the 26-week maintenance period<br><br>Secondary:<br>Proportion of patients remaining seizure-free for ≥52 weeks, time to start of a 26-week and 52-week seizure-free period, and time to withdrawal because of absence of efficacy or adverse event | Primary:<br>In the PP population, 79.4% of patients treated with zonisamide were seizure-free for 26 weeks during the maintenance period compared to 83.7% of patients treated with carbamazepine. The absolute treatment difference, adjusted for country group, was -4.5% (95% CI, -12.2 to 3.1). The lower limit of the CI for the absolute difference (-12.2%) narrowly exceeded the -12% prespecified noninferiority margin. The relative treatment difference was -5.4% (95% CI, -14.7 to 3.7). The lower limit of the 95% CI was above the relative -20% margin for demonstrating noninferiority.<br><br>Secondary:<br>The proportion of patients in the PP population remaining seizure-free for 52 weeks was 67.6% of zonisamide-treated patients compared to 74.7% of carbamazepine-treated patients. The absolute treatment difference, adjusted for country, was -7.9% (95% CI, -17.2 to 1.5). In the ITT population, 55.9% of patients did not have a seizure for 52 weeks in the zonisamide group compared to 62.3% in the carbamazepine group. The absolute treatment difference between groups was -7.7% (95% CI, 16.1 to 0.7).<br><br>For the PP population, the median time to become seizure-free for 26 weeks was 204 days in both treatment groups (HR, 0.92; 95% CI, 0.75 to 1.14). The median time to become seizure-free for 52 weeks was 381 days for both treatment groups (HR, 0.88; 95% CI, 0.70 to 1.11). Similar results were reported in the ITT population.<br><br>Withdrawal rates due to lack of efficacy or adverse events were low in both groups and did not differ significantly between treatments. |


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| **Treatment of Generalized or Partial Seizures** | | | | |
| Gamble et al[112]<br><br>Carbamazepine monotherapy<br><br>vs<br><br>lamotrigine monotherapy | MA (5 RCTs)<br><br>Children or adults with generalized-onset tonic-clonic or partial-onset seizures | N=1,384<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment, seizure freedom at six months and time to first seizure<br><br>Secondary:<br>Not reported | Primary:<br>Time to treatment withdrawal was significantly improved with lamotrigine compared to carbamazepine (HR, 0.55; 95% CI, 0.35 to 0.84). Seizure freedom at six months (HR, 0.92; 95% CI, 0.81 to 1.04) and time to first seizure (HR, 1.14; 95% CI, 0.92 to 1.43) favored carbamazepine although the results were not statistically significant. (HR >1 indicated an event was more likely on lamotrigine than carbamazepine; *P* values were not reported).<br><br>Secondary:<br>Not reported |
| Tudur Smith et al[113] (abstract)<br><br>Carbamazepine monotherapy<br><br>vs<br><br>phenobarbital monotherapy | MA (4 RCTs)<br><br>Children or adults with generalized-onset tonic-clonic or partial-onset seizures | N=684<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment, time to 12-month remission, time to first seizure<br><br>Secondary:<br>Not reported | Primary:<br>Time to withdrawal was significantly improved with carbamazepine over phenobarbital (HR, 1.63; 95% CI, 1.23 to 2.15), which indicates that carbamazepine was better tolerated than phenobarbital. There was no significant difference between treatment groups for the time to 12-month remission and time to first seizure (HR, 0.87; 95% CI, 0.65 to 1.17 and HR, 0.85; 95% CI, 0.68 to 1.05, respectively). HR >1 indicated an event was more likely on phenobarbital than carbamazepine; *P* values were not reported.<br><br>Further analysis of each type of seizure indicated that phenobarbital provided statistical benefit over carbamazepine for time to first partial-onset seizure, whereas carbamazepine demonstrated benefit over phenobarbital in patients for time to first generalized-onset tonic-clonic seizures.<br><br>Secondary:<br>Not reported |
| Tudur Smith et al[114] (abstract)<br><br>Carbamazepine monotherapy<br><br>vs | MA (3 RCTs)<br><br>Children or adults with partial-onset seizures or generalized-onset tonic-clonic | N=551<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment, time to 12-month and six-month remission, time | Primary:<br>There was no overall difference between carbamazepine and phenytoin with regards to time to withdrawal of allocated treatment (HR, 0.97; 95% CI, 0.74 to 1.28), time to 12-month remission (HR, 1.00; 95% CI, 0.78 to 1.29), time to six-month remission (HR, 1.10; 95% CI, 0.87 to 1.39) and time to first seizure (HR, 0.91; 95% CI, 0.74 to 1.12). HR >1 indicated an event was more likely on phenytoin than carbamazepine. *P* values were not reported. |


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| phenytoin monotherapy | seizures | | to first seizure<br><br>Secondary:<br>Not reported | Secondary:<br>Not reported |
| Marson et al[115] (abstract)<br><br>Carbamazepine monotherapy<br><br>vs<br><br>valproate monotherapy | MA of 5 RCT (included literature search of Medline through 2000)<br><br>Patients with partial-onset seizures or generalized-onset tonic-clonic seizures | N=1,265<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment, time to 12-month remission, time to first seizure<br><br>Secondary:<br>Not reported | Primary:<br>There was no overall difference between carbamazepine and valproate with regards to time to withdrawal of allocated treatment (HR, 0.97; 95% CI, 0.79 to 1.18), time to 12-month remission (HR, 0.87; 95% CI, 0.74 to 1.02), and time to first seizure (HR, 1.09; 95% CI, 0.96 to 1.25). HR >1 indicated an event was more likely on valproate. *P* values were not reported. A test for an interaction between treatment and seizure type was significant for time to first seizure, but not the other outcomes.<br><br>There was some evidence to support the preference of carbamazepine for partial-onset seizures, but no evidence to support the preference of valproate for generalized-onset seizures. CIs were too wide to infer equivalence. The age distribution of adults classified as having generalized seizures indicated that significant numbers of patients may have had their seizures misclassified.<br><br>Secondary:<br>Not reported |
| Marson et al[116] (abstract)<br><br>Carbamazepine vs gabapentin vs lamotrigine vs oxcarbazepine vs topiramate (Arm A, n=1,721)<br><br>Valproate vs lamotrigine vs topiramate (Arm B, n=716) | MC, PG, RCT<br><br>Patients >5 years of age with partial or generalized seizures | N=2,437<br><br>24 months | Primary:<br>Time to treatment failure (withdrawal of the study drug for reasons of unacceptable adverse events or inadequate seizure control or both) and time to 12-month remission of seizures | Primary:<br>Arm A recruited 88% of patients with symptomatic or cryptogenic partial epilepsy and 10% with unclassified epilepsy. Arm B recruited 63% of patients with idiopathic generalized epilepsy and 25% with unclassified epilepsy.<br><br>For Arm A, lamotrigine had the lowest incidence of treatment failure and was statistically better than carbamazepine, gabapentin, and topiramate (but not oxcarbazepine). At one and two years after randomization, 12 and 8% fewer patients experienced treatment failure on lamotrigine than carbamazepine. The "superiority" of lamotrigine over carbamazepine was due to its better tolerability but there was satisfactory evidence indicating that lamotrigine was not clinically "inferior" to carbamazepine for measures of its efficacy (treatment failure due to inadequate seizure control and time to achieving a 12-month remission; *P* values were not reported.) |


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| When clinicians felt carbamazepine was the optimal standard drug, patients were allocated to Arm A, and when valproate was the optimal drug, patients were allocated to Arm B. | | | Secondary:<br>Not reported | For time to treatment failure, valproate was preferred to both lamotrigine and topiramate. Valproate was the drug least likely to be associated with treatment failure for inadequate seizure control and was the preferred drug for time to achieving a 12-month remission; *P* values were not reported.)<br><br>Secondary:<br>Not reported |
| Cereghino et al[117]<br><br>Diazepam 5 to 20 mg rectally<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Outpatients or institutionalized patients<br>≥2 years of age with a history of acute repetitive seizures (primary generalized, complex partial with or without becoming secondarily generalized, or simple partial with a motor component) with at least two seizure episodes within the previous year and at least one seizure in | N=158<br><br>Duration not reported | Primary:<br>Seizure count following drug administration<br><br>Secondary:<br>Time to next seizure, time elapsed between administration plus 15 minutes to the occurrence of the next seizure within the 12-hour observation period, caregiver and investigator global assessments and safety | Primary:<br>Patients receiving treatment with diazepam experienced fewer post-treatment seizures compared to patients receiving placebo (0 vs 2; *P*=0.029).<br><br>Secondary:<br>The time to next seizure was significantly prolonged with diazepam administration compared to placebo (*P*=0.007). More patients who received diazepam were seizure-free in the 12-hour post-treatment observation period compared to placebo (55 vs 34%; *P*=0.031).<br><br>The mean caregiver global assessment score was higher in the diazepam treatment group compared to the placebo group (6.73 vs 5.60; *P*=0.018). Similarly, the mean investigator global assessment score was higher with diazepam compared to the placebo-treated group (7.55 vs 5.57*;* *P*=0.001).<br><br>There was a trend toward a higher incidence of adverse events in the diazepam group compared to the placebo group (46 vs 28%); however, the difference was not statistically significant. The most frequently reported adverse events were somnolence, headache and diarrhea. There were no episodes of respiratory depression reported. No changes in laboratory parameters were observed. |


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| Lippa et al[118]<br><br>Levetiracetam 250 to 1,500 mg BID | OL, PRO<br><br>Patients ≥50 years of age with Alzheimer's disease, mixed dementia or mild cognitive impairment; seizures of partial onset with or without secondary generalization, stable general medical condition and seizure frequency of ≤4 per month | N=24<br><br>12 weeks | Primary:<br>Efficacy for seizure control and impact on cognition<br><br>Secondary:<br>Safety and impact on behavioral measures | Primary:<br>Eleven of the 16 (68.8%) patients who completed the trial were seizure-free for the duration of the study. Five patients reported ≥1 seizures during the three month trial period (mean number of seizures, 0.5; median, 0.0; maximum, 3). Four of these patients were on a dose of 750 mg BID; the fifth was on 1,000 mg BID.<br><br>MMSE scores improved an average of 2.2 points (SD, 3.0; *P*=0.1) from baseline at 12 weeks, representing a substantial improvement. Improvements were noted specifically for the delayed recall portion of the MMSE, with an average improvement of 0.6 (SD, 0.7; *P*=0.01) on the three word recall. The ADAS-Cog scores improved by an average of 4.3 points (SD, 6.4; *P*=0.02) from baseline at 12 weeks.<br><br>Secondary:<br>The most commonly reported adverse event was fatigue (20.8%). A total of 4/5 patients experiencing fatigue discontinued treatment within the first week due to this adverse event.<br><br>Little change was seen in caregiver reported behavior and function. No substantial changes were seen for the activities of daily living scale (mean change, 1.5 out of possible 100 points; *P*=0.8), Tariot's Behavior Ratings scale (mean change, -2.7 out of 52; *P*=0.8) or the CMAI (mean change, -1.2 out of 203; *P*=0.9). There was also no trend for incident behavioral disturbances, such as irritability or aggression, as reported on these scales. |
| Sake et al[119] (abstract)<br><br>Lacosamide | Post hoc exploratory analyses were performed on pooled data in which patients were grouped based upon inclusion or non- | N=1,308<br><br>16 to 18 weeks | Primary:<br>Change in seizure frequency per 28 days, proportion of patients experiencing ≥50% reduction | Primary:<br>The majority of patients (82%) were utilizing at least one 'traditional' sodium channel-blocking concomitant AED. In this subgroup of patients, adjunctive lacosamide showed significant reductions in seizure frequency (*P*< 0.01 for all dosages) and significantly greater 50% and 75% responder rates (*P*< 0.01 for 400 mg/day; *P*< 0.01 [50% responder rate] and *P*< 0.05 [75% responder rate] for 600 mg/day) compared to placebo.<br><br>Secondary: |


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| | inclusion of at least one 'traditional' sodium channel-blocking AED (carbamazepine, lamotrigine, oxcarbazepine, and phenytoin derivatives) as part of their concomitant AED regimen; adults with partial-onset seizures with or without secondary generalization | | in seizure frequency, proportion of patients experiencing ≥75% reduction in seizure frequency<br><br>Secondary: Safety | Treatment-emergent adverse events and discontinuations due to such events in this subgroup were dose related and similar to the general population. In the remaining subgroup of patients, i.e. those not taking 'traditional' sodium channel-blocking AEDs as part of their concomitant AED regimen (n= 231; 18%), a pronounced, dose-related seizure reduction was observed with lacosamide (*P*< 0.01, 400 and 600 mg/day for median percent seizure reduction and 50% or 75% responder rates). Also in this group of patients, incidences of treatment-emergent adverse events were low, and discontinuations due to such events did not appear to increase with dose. Analyses of ECG, laboratory and vital sign assessments did not identify abnormalities in either subgroup that were outside of the known safety profile of lacosamide observed in the pooled phase II/III population. |
| Dasheiff et al[120]<br><br>Clorazepate 15 to 120 mg daily (frequency not specified)<br><br>vs<br><br>methsuximide 600 to 2,700 mg daily (frequency not specified)<br><br>vs<br><br>valproate 500 to 4,000 mg daily (frequency not | OL, PRO<br><br>Patients with complex partial epilepsy with or without secondary generalization, with or without simple partial seizures (“auras”), and who had failed phenytoin, carbamazepine and phenobarbital | N=66<br><br>3 years | Primary: Change in seizure frequency, number of patients who were seizure-free and safety<br><br>Secondary: Not reported | Primary:<br>The seizure frequency was determined to be decreased in six eight and fifteen patients treated with clorazepate, methsuximide and valproate, respectively. None of the anticonvulsant treatments were shown to reduce seizure frequency during treatment compared to baseline values (*P*>0.05 for all).<br><br>Seven patients tolerated the medications and became seizure-free for up to six months with treatment (three patients each in the clorazepate and valproate groups and one patient receiving methsuximide). Only the patient receiving clorazepate was seizure-free at one year.<br><br>The most frequently reported adverse events were gastrointestinal in nature, followed by mental status changes and problems with coordination. Valproate produced various adverse events including nausea, dysphagia, weight gain, or weight loss but significant elevation of liver function tests occurred only once and was reversible. |


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| specified)<br><br>Patients usually remained on at least one of the first-line AEDs. | | | | Secondary:<br>Not reported |
| Muller et al[121]<br><br>Oxcarbazepine monotherapy<br><br>vs<br><br>phenytoin monotherapy | MA (2 RCTs)<br><br>Adults and children with partial-onset seizures or generalized-onset tonic-clonic seizures | N=480<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment; time to achieve six-, 12- and 24-month remission and time to first seizure<br><br>Secondary:<br>Not reported | Primary:<br>The overall results indicate that oxcarbazepine is significantly better than phenytoin for time to treatment withdrawal (HR, 1.64; 95% CI, 1.09 to 2.47). There was no overall difference between oxcarbazepine and phenytoin in time to six-month remission (HR, 0.89; 95% CI, 0.66 to 1.22), time to 12-month remission (HR, 0.92; 95% CI, 0.62 to 1.37), and time to first seizure (HR, 1.07; 95% CI, 0.83 to 1.39). HR >1 indicated an event was more likely on phenytoin than oxcarbazepine. *P* values were not reported.<br><br>Results stratified by seizure type indicate no significant advantage for either drug for patients with generalized-onset seizures, but a potentially important advantage in time to withdrawal for oxcarbazepine for patients with partial-onset seizures (HR, 1.92; 95% CI, 1.17 to 3.16; *P* value not reported).<br><br>The authors noted that the age distribution of adults classified as having generalized epilepsy suggested a significant number of patients may have had their epilepsy misclassified.<br><br>Secondary:<br>Not reported |
| Taylor et al[122]<br><br>Phenobarbital monotherapy<br><br>vs<br><br>phenytoin monotherapy | MA (4 RCTs)<br><br>Adults and children with partial-onset seizures or generalized-onset tonic-clonic seizures | N=599 (represents 65% of potential data)<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment, time to 12-month remission and time to first seizure | Primary:<br>The results indicated a statistically significant clinical advantage for phenytoin compared to phenobarbital with regards to time to treatment withdrawal (HR, 1.62; 95% CI, 1.22 to 2.14) and a nonsignificant advantage in terms of 12-month remission (HR, 93; 95% CI, 0.70 to 1.23). Results for time to first seizure suggest a nonsignificant clinical advantage for phenobarbital compared to phenytoin (HR, 0.84; 95% CI, 0.68 to 1.05). HR >1 indicated an event was more likely on phenobarbital than phenytoin; *P* values were not reported. |


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| | | | Secondary:<br>Not reported | The authors noted that since there were no significant differences for seizure outcomes, the higher withdrawal rate with phenobarbital may be due to adverse effects.<br><br>Secondary:<br>Not reported |
| Tudur Smith et al[123]<br><br>Phenytoin monotherapy<br><br>vs<br><br>valproate monotherapy | MA (5 RCTs)<br><br>Adults and children with partial-onset seizures or generalized-onset tonic-clonic seizures | N=669 (represents 60% of potential data)<br><br>Duration not reported | Primary:<br>Time to withdrawal of treatment, time to achieve 12-month remission and time to first seizure<br><br>Secondary:<br>Not reported | Primary:<br>The overall results suggest no overall difference between phenytoin and valproate with regards to time to treatment withdrawal (HR, 1.10; 95% CI, 0.79 to 1.54), time to 12-month remission (HR, 1.04; 95% CI, 0.78 to 1.38), time to six-month remission (HR, 0.89; 95% CI, 0.71 to 1.11) and time to first seizure (HR, 0.92; 95% CI, 0.74 to 1.14). (HR >1 indicated an event was more likely on phenytoin than valproate; *P* values were not reported.)<br><br>No statistical interaction between treatment and seizure type was found.<br><br>Secondary:<br>Not reported |
| Novotny et al[124]<br><br>Topiramate 5, 15 or 25 mg/kg/day BID, in addition to current AED therapy<br><br>vs<br><br>placebo, in addition to current AED therapy | DB, PC, PG, RCT<br><br>Infants 1 to 24 months with a diagnosis of partial onset seizures with or without secondary generalization, ≥41 weeks gestational age, weighing ≥3.2 kg and <15.5 kg, length ≥49 cm are receiving | N=149<br><br>20 days | Primary:<br>Median percentage reductions in daily partial onset seizures<br><br>Secondary:<br>Percentage of treatment responders (defined as ≥50% reduction in seizure rate for partial onset seizure and all seizure types as | Primary:<br>There was no difference (*P*=0.97) in median percentage reduction from baseline in daily partial onset seizure rate between topiramate 25 mg/kg/day and placebo (20.4 vs 13.1%). Lower doses of topiramate were not significantly different from placebo.<br><br>Secondary:<br>The percentages of treatment responders in the topiramate groups (5 mg/kg/day, 27%; 15 mg/kg/day, 38%; 25 mg/kg/day, 44%) were not different from placebo (36%; *P*>0.4 for all).<br><br>The median percentage reduction in seizure rate for all seizure types based on vEEG data, or for partial onset seizure or all seizure types based on infant take-home records, was also not different between any of the topiramate groups and placebo (*P*>0.2 for all).<br><br>The incidence of treatment emergent adverse events was higher in the combined |


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| | regular enteral feeding | | recorded on a 48 hour vEEG), percentage reduction in seizure rates for all seizure types as recorded on 48 hour vEEG and for partial onset seizure and all seizure types as recorded on infant take home records and safety | topiramate groups (81%) compared to placebo (51%). |
| Ramsay et al[125]<br><br>Topiramate 100 mg/day, target dose<br><br>vs<br><br>phenytoin 300 mg/day, target dose | DB, NI, RCT<br><br>Patients 12 to 65 years of age, ≥50 kg, and 1 to 20 unprovoked, complex partial or primary/ secondarily generalized tonic-clonic seizures within the past three months | N=261<br><br>28 days | Primary:<br>Time to first complex partial or generalized tonic-clonic seizure<br><br>Secondary:<br>Time to first complex partial and time to first generalized tonic-clonic seizure, safety | Primary:<br>At trial end, the estimated seizure-free rate was 81.1 vs 90.3% with topiramate and phenytoin. NI of topiramate to phenytoin could not be established (HR, 2.0; 95% CI, 0.98 to 4.12; *P*=0.366), the phenytoin could not be shown to be superior to topiramate.<br><br>Secondary:<br>Results on covariates were obtained when generalized tonic-clonic seizures and complex partial seizures were analyzed separately (data not reported).<br><br>A higher proportion discontinued treatment with phenytoin compared to topiramate for all reasons (21.1 vs 12.8%), and due to adverse events (13.4 vs 6.8%). The most common treatment-related adverse events with both treatments were dizziness, paresthesia and somnolence. |
| Ben-Menachem et al[126]<br><br>Topiramate 25 or 50 mg/day vs 200 or 500 mg/day as | MA of 3 DB, RCT (literature search included Medline to January 2008) | N=1,335<br><br>Median duration 181days to | Primary:<br>Six- or 12-month seizure freedom, time to first seizure, | Primary:<br>In a comparison of topiramate 50 and 500 mg/day, the higher dose was associated with significantly greater freedom from partial seizures at six months compared to the lower dose (54 vs 39%, respectively; *P*=0.02). In a comparison of topiramate 50 and 400 mg/day, the time to first seizure was significantly longer with the higher |


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| monotherapy<br><br>Topiramate 50 mg/day vs 400 mg/day as monotherapy<br><br>Topiramate 100 mg/day or 200 mg/day vs carbamazepine 600 mg/day (patients with partial seizures) or valproate 1,250 mg/day (patients with generalized epilepsy). | Adults and children with new or recently diagnoses partial or generalized epilepsy | 9 months | time to study exit and safety<br><br>Secondary:<br>Not reported | dose compared to the lower dose (*P*<0.001), and the probability of 12-month seizure freedom was significantly higher (76 vs 59%, respectively; *P*=0.001).<br><br>In a comparative study of three AEDs, there was no significant difference in rates of six month seizure freedom with topiramate (44 to 49%), carbamazepine (44%) and valproate (44%). Time to first seizure and time to study exit were also not significantly different between treatment arms (*P* values not reported).<br><br>Adverse events in the three studies were similar between topiramate dose groups, although the incidence generally increased with increasing doses, occurred earlier in treatment, and decreased with prolonged therapy. In a pooled analysis of the three trials, the most commonly occurring adverse events during dose titration were paresthesia (25%), fatigue (16%), dizziness (13%), somnolence (13%) and nausea (10%); the most frequent adverse events during maintenance therapy were headache (20%), decreased appetite (11%) and weight loss (11%).<br><br>Secondary:<br>Not reported |
| Dupont et al[127]<br><br>Zonisamide 200 to 500 mg/day BID, in addition to current AED therapy<br><br>Patients entered 2 fixed-dose periods where doses could not be up or down titrated (Period 1: weeks 10 to 13 and Period 2: weeks 16 to 19). | OL<br><br>Patients 18 to 75 years of age with partial onset seizures (simple or complex) with or without secondary generalization | N=274<br><br>19 weeks | Primary:<br>Change in monthly seizure frequency from baseline to fixed-dose period 2<br><br>Secondary:<br>Change in monthly seizure frequency from baseline to fixed-dose period 1; responder rate (patients | Primary:<br>Patients had a median reduction in seizure frequency from baseline to fixed-dose period 2 of 33.3% (95% CI, 23.1 to 42.9).<br><br>Secondary:<br>There was a similar reduction in seizure frequency from baseline to fixed-dose period 1 of 32.1% (95% CI, 20.0 to 46.2).<br><br>From baseline to fixed-dose period 2, over 40% of patients achieved a ≥50% reduction in seizure frequency and ≥15.0% of patients achieved seizure freedom. Data regarding fixed-dose period 1 is not reported.<br><br>A total of 124 patients (74.3%) demonstrated an improvement in their illness from baseline to the end of week 19. There was a trend towards an improvement in quality of life scores on the QOLIE-31 scale between baseline and the end of week 19 (mean improvement, 1.95 points; 95% CI, -0.09 to 3.99). Statistically significant improvements in seizure severity scores, as measured by the LSSS, were |


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| | | | achieving ≥50%, ≥75% or 100% reduction in seizure frequency from baseline to both fixed-dose periods); change in CGI, QOLIE-31 and LSSS and safety | observed between baseline and the end of week 19, with a mean change of -2.40 (95% CI, -3.24 to -1.57).<br><br>In 209 patients, 74.4% reported adverse events, most commonly fatigue (16.7%), somnolence (15.3%) and headache (8.9%). |
| **Treatment of Other Seizures** | | | | |
| Ng et al[128]<br><br>Clobazam low-dosage (target 0.25 mg/kg/day)<br><br>vs<br><br>clobazam medium-dosage (target 0.5 mg/kg/day)<br><br>vs<br><br>clobazam high-dosage (target 1 mg/kg/day)<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 2 to 60 years of age weighing ≥12.5 kg with an onset of LGS before age 11 | N=238<br><br>15 weeks | Primary:<br>Percentage decrease in mean weekly drop seizure rates<br><br>Secondary:<br>Percentage decreases in average weekly rate of nondrop seizures and total (drop and nondrop) seizures; responder rates; and physicians' and caregivers' global evaluations of the patients' | Primary:<br>The mean percentage decrease in average weekly rate of drop seizures was 12.1% for placebo compared to 41.2% for the 0.25 mg/kg/day (*P*=0.0120), 49.4% for clobazam 0.5 mg/kg/day (*P*=0.0015), and 68.3% for clobazam 1.0 mg/kg/day (*P*<0.0001).<br><br>Secondary:<br>The mean percentage decrease in average weekly rate of total seizures was 9.3% for placebo compared to 34.8% for clobazam 0.25 mg/kg/day (*P*=0.0414), 45.3% for clobazam 0.5 mg/kg/day (*P*=0.0044), and 65.3% for clobazam 1.0 mg/kg/day (*P*=0.0001). There was no significant difference in the average weekly rates of nondrop seizures.<br><br>The percentage of patients with ≥50% decreases in average weekly rate of drop seizures was 31.6% for placebo compared to 43.4% for clobazam 0.25 mg/kg/day, 58.6% for clobazam 0.5 mg/kg/day, and 77.6% for clobazam 1.0 mg/kg/day. The likelihood of achieving ≥50% response was greater for the medium-dosage (OR, 2.8; 95% CI, 1.2 to 6.5; *P*=0.0159) and high-dosage (OR, 7.5; 95% CI, 3.0 to 18.5; *P*=0.0001) clobazam groups compared to the placebo group.<br><br>The percentages of patients who were at least minimally improved ranged from 71.2 to 80.7% (physicians' assessments) and 79.2 to 81.6% (caregivers' |


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| | | | overall changes in symptoms over time | assessments) for clobazam vs 47.3% (physicians' assessments) and 45.5% (caregivers' assessments) for placebo.<br><br>The percentages of patients who were much improved or very much improved ranged from 46.2 to 64.9% (physicians' assessments) and 41.5 to 59.2% (caregivers' assessments) for clobazam vs 23.6% (physicians' assessments) and 25.5% (caregivers' assessments) for placebo.<br><br>The percentages of patients with at least one adverse event were 67.8% for placebo, 72.4% for the low-dosage group, 88.7% for the medium-dosage group, and 76.3% for the high-dosage group. Adverse events with ≥10% difference between placebo and any clobazam group were somnolence, pyrexia, lethargy, drooling, and constipation. |
| Conry et al[129]<br><br>Clobazam low-dosage (target 0.25 mg/kg/day)<br><br>vs<br><br>clobazam high-dosage (target 1.0 mg/kg/day) | RCT, DB, MC<br><br>Patients 2 to 26 years of age with LGS | N=68<br><br>7 weeks | Primary:<br>Percent reduction in drop seizure rates (average per week)<br><br>Secondary:<br>Responder rates, percent reduction in weekly nondrop seizures, physicians' and caregivers' global evaluations | Primary:<br>The mean drop seizure rate was reduced in the low-dose from 141 to 91 drop seizures per week and in the high-dose group from 207 to 32 drop seizures per week. The percent change from baseline was significant in the low-dose group (12%; *P*=0.0162) and the high-dose group (85%; *P*<0.0001). The reduction in drop seizure rates was significantly greater in the high-dose group compared to the low-dose group (*P*=0.0001).<br><br>Secondary:<br>Significantly more patients in the high-dose group compared to the low-dose group had a reduction in weekly drop seizure rates of ≥25% (89 vs 56%; *P*=0.0025), ≥50% (83 vs 38%; *P*=0.0001), and ≥75% (67 vs 25%; *P*=0.0006).<br><br>In the low-dose group, the percent change from baseline in nondrop seizures was not significant (9%; *P*=0.1466). In the high-dose group, the percent change from baseline in nondrop seizures was significant (59%; *P*<0.0001). The reduction in nondrop seizure rates was significantly greater in the high-dose group compared to the low-dose group (*P*=0.0222).<br><br>In the parent/caregiver global evaluations, patients in the high-dose group were more likely to show significant improvements in overall symptoms compared to the low-dose group. A total of 94% of patients in the high-dose group compared to |


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| | | | | 55% of patients in the low-dose group were much improved or very much improved at week three compared to baseline. At week seven, the percentage of patients considered to be much improved or very much improved increased in the high-dose group (93%), but decreased in the low-dose group (43%). The high-dose group showed significantly lower scores than the low-dose group at three weeks (1.7 vs 2.4; *P*=0.0024) and at seven weeks (1.6 vs 2.6; *P*=0.0002).<br><br>In the investigator global evaluations, patients in the high-dose group were more likely to show significant improvements in overall symptoms compared to the low-dose group. At week three, 94% of patients in the high-dose group compared to 45% of patients in the low-dose group were much improved or very much improved. At week seven, 90% of patients in the high dose group and 41% of patients in the low-dose group were much improved or very much improved. The high-dose group showed significantly lower scores than the low-dose group at three weeks (1.8 vs 2.7; *P*=0.0001) and at seven weeks (1.8 vs 2.8; *P*<0.0001).<br><br>The most common adverse events with clobazam were somnolence, lethargy, sedation, salivary hypersecretion, constipation, aggression, hypomania, and insomnia. The incidence of treatment-emergent adverse events, regardless of relation to therapy, was similar between the low-dose group (84%) and the high-dose group (86%). The low dose group and high dose group were also similar in incidence of mild (47 vs 44%), moderate (34 vs 36%), and severe (3 vs 6%) adverse events. |
| Ng et al[130]<br><br>Clobazam 0.5 mg/kg/day and adjusted per clinical need (maximum 40 mg/day) | MC, OL, ES<br><br>Patients 2 to 60 years of age with LGS who were previously enrolled in either Ng et al or Conry et al | N=267<br><br>Up to 60 months | Primary:<br>Percent reduction in drop seizure rates (average per week) and percent reduction in weekly rate of total seizures<br><br>Secondary: | Primary:<br>The median percentage decreases from baseline in average weekly rate of drop seizures for total patients, regardless of duration of clobazam treatment, were 71.1% at three months and 91.6% at 24 months.<br><br>The median percentage decreases in total seizures in these patients were 64.8% at three months and 81.5% at 24 months.<br><br>The proportion of patients with a ≥25%, ≥50%, ≥75% or 100% decrease in average weekly seizure rate from baseline increased from over 24 months for both drop and total seizures. The proportion of patients with a ≥50% reduction drop seizures was 61.5% at three months (n=252) and 79.5% at 24 months (n=88). The |


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| | | | Time to discontinuation of treatment, proportion of treatment responders, physicians' and caregivers' global evaluations of the patients' overall changes in symptoms and safety | proportion of patients with a ≥50% reduction in total seizures was 61.5% at three months and 70.3% at 24 months (n=91).<br><br>Secondary:<br>The time to discontinuation of clobazam ranged from 17 to 1317 days, with 75% of patients discontinuing treatment by around 38 months.<br><br>Most patients were considered by the physician to be "very much improved" or "much improved" at all time points (range, 66.3 to 82.3%). Similarly, the majority of patients were "very much improved" or "much improved" at all time points as evaluated by parent/caregiver (range, 61.5 to 80.5%).<br><br>Overall, 219 (82.0%) patients reported at least one treatment-emergent adverse event during the study, with 140 (52.4%) patients reporting more than one treatment-related adverse event. The most common treatment-emergent adverse events (≥10% of patients) were upper respiratory tract infection (18.4%), fall (14.2%), pneumonia (13.9%), somnolence (12.7%), otitis media (12.0%), pyrexia (10.5%) and constipation (10.1%). Upper respiratory tract infections and pneumonia events occurred mostly in pediatric patients.<br><br>One hundred and sixty patients (59.9%) reported mild or moderate adverse events, while severe adverse events occurred in 59 patients (22.1%). Severe treatment-emergent adverse events reported for ≥1.0% of patients were pneumonia and convulsion (4.1% each), status epilepticus and pneumonia aspiration (1.5% each), and lobar pneumonia, sepsis, septic shock, urinary tract infection, dehydration, sedation, somnolence and aggression (1.1% each). |
| Lee et al[131]<br><br>Clobazam 5 to 10 mg/day titrated to clinical response (ranged from 0.16 to 1.60 mg/kg/day)<br><br>The selection of | RETRO<br><br>Patients with LGS (mean age, 91 months) | N=46<br><br>35 months (mean) | Primary:<br>Proportion of patients who remained seizure-free, proportion of treatment responders (≥50% reduction | Primary:<br>The proportions of patients who became seizure-free following treatment with clobazam were 32.6, 16.6, 14.1 and 16.1% after one, three, six and 12 months, respectively (P values not reported). Five patients (10.8%) remained seizure-free for more than 12 months following initiation of clobazam.<br><br>The proportions of responders to clobazam treatment were 21.7% at one month, 11.9% at three months, 11.4% at six months and 3.2% at 12 months (P values not reported). |


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| concomitant AEDs was dependent on the expertise of a physician. | | | from baseline in seizure frequency), proportion of patients who were non-responders (≤50% reduction from baseline in seizure frequency) and proportion of patients who developed tolerance (increase in seizure frequency to a level of ≥50% pre-clobazam after an initial response for a minimum of one month) and safety<br><br>Secondary:<br>Not reported | The non-responder rate remained fairly consistent, ranging from 12.9 to 17.9% over 12 months of treatment (P values not reported).<br><br>Of the 25 patients who achieved a ≥50% reduction in seizures after one month of clobazam treatment and 12 developed tolerance (48%). The mean time to tolerance development was 4.6 months.<br><br>Seven patients reported adverse events (15.2%), including six patients with excessive sleeping or drowsiness and one who developed behavioral changes. Most adverse events were transient and mild. One patient who had behavioral changes had discontinued the medication and recovered following discontinuation of clobazam. During the study period 10 patients discontinued the drug (loss of efficacy in five patients, epilepsy surgery in one patient and death in one patient).<br><br>Secondary:<br>Not reported |
| Bensch et al[132]<br><br>Clonazepam up to 0.25 mg/kg divided BID or TID<br><br>vs | DB, MC, PRO, XO<br><br>Children of all ages with all types of seizures who had tried all | N=20<br><br>2 months | Primary:<br>Improvements in seizure frequency, patient preference, percentage | Primary:<br>Clonazepam was determined to be significantly more effective than placebo in reducing seizure frequency in 14 patients compared to four patients who experienced greater seizure improvements with placebo ($P<0.05$). In the remaining two cases there was no difference in seizure frequency between clonazepam and placebo. |


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| placebo<br><br>The maximum dose was 10 mg daily.<br><br>Clonazepam was administered in addition to the patient's background anticonvulsant therapy that remained unchanged through the evaluation period. | available AEDs and continued to experience at least one fit per week | | reduction in seizure frequency and adverse events<br><br>Secondary:<br>Not reported | There was no difference in patient/caregiver treatment preference between clonazepam and placebo with 12 cases preferring clonazepam over placebo, while eight patients preferred placebo over clonazepam (*P* value not significant).<br><br>Compared to baseline, significantly more patients experienced a decrease in seizure frequency when treated with clonazepam compared to placebo (9 vs 3 and 7 vs 4 in both XO periods, respectively; $P<0.05$ for both).<br><br>Five patients were seizure-free following clonazepam treatment, while five others experienced at least a 75% reduction in seizure frequency and three had reductions of more than 50%. Two patients were seizure-free when receiving placebo, while one patient had a reduction of more than 75% and two had a reduction of more than 50%.<br><br>Adverse events were reported during the clonazepam period by 18 of 20 parents of patients completing the trial. Only sleep disorder was reported during the placebo period. The most common adverse events were tiredness, vertigo and psychiatric disturbances, mainly aggressiveness. Five patients withdrew from the study due to adverse events.<br><br>Secondary:<br>Not reported |
| Mikkelsen et al[133]<br><br>Clonazepam up to 6 mg daily based on age (frequency not reported)<br><br>vs<br><br>placebo<br><br>Patients less than six years of age received a | SB, XO<br><br>Patients who experienced at least six seizures every four weeks in spite of adequate traditional treatment with AEDs | N=20<br><br>8 weeks | Primary:<br>Change in seizure frequency, proportion of seizure-free patients and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>In patients with simple absence seizures (n=10), clonazepam was significantly more effective at reducing seizure frequency compared to placebo ($P<0.05$). Clonazepam was more effective in seven cases, while clonazepam and placebo were equally effective in three cases.<br><br>During clonazepam treatment, eight patients became seizure-free and one had more than a 75% reduction in the daily number of seizures. The maximal efficacy of treatment was obtained within the first two weeks. No patients developed grand mal seizures during the trial.<br><br>Nine of ten patients with absence seizures experienced adverse events during treatment with clonazepam, mostly varying degrees of sedation. In four patients, |


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| 0.25% clonazepam solution or placebo. | | | | the adverse events of clonazepam subsided within one week. Five patients had lasting side-effects.<br><br>Of patients with myoclonic atonic epilepsy (n=10), clonazepam was more effective than placebo in seven cases, and treatments were equal in three cases (*P*<0.05).<br><br>Seven patients became free or nearly free from seizures while receiving clonazepam. The maximum efficacy of clonazepam was obtained within the first three weeks. One patient with concomitant grand mal epilepsy had no change in seizure frequency with clonazepam.<br><br>Five patients reported no side-effects with clonazepam, while two had transient and three had lasting adverse events. Most consisted of varying degrees of sedation.<br><br>Secondary:<br>Not reported |
| Mikkelsen et al[134]<br><br>Clonazepam 6 mg divided TID<br><br>vs<br><br>carbamazepine 900 mg divided TID<br><br>In patients <18 years of age and with a body weight of less <60 kg, carbamazepine was administered at a dose corresponding to 15 mg/kg. | DB, RCT<br><br>Previously untreated patients with recently diagnosed psychomotor epilepsy | N=36<br><br>6 months | Primary:<br>Changes in seizure frequency, proportion of seizure-free patients at six months, adverse events and serum levels<br><br>Secondary:<br>Not reported | Primary:<br>Both clonazepam and carbamazepine were associated with significant reductions from baseline in seizure activity (*P*<0.01); however, no difference were reported between the two treatments (*P*>0.10). For patients receiving treatment for at least one month, the number monthly seizures was 0.2 for carbamazepine and zero for clonazepam (difference, 0.2; 95% CI, -0.3 to 0.4).<br><br>The proportion of seizure-free patients during the six months of treatment was 49% of those treated with carbamazepine and 46% on clonazepam (*P* value not reported).<br><br>Only one patient did not experience adverse events during treatment. Overall, adverse events were brief and no differences were observed between the two groups with regard to sedation, headache, dizziness, impaired memory, marital relations, irritability or complaints (*P*>0.05).<br><br>Carbamazepine plasma levels were within the range of 16 to 40 µmoles/L. The plasma clonazepam levels were higher and had greater variations between |


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| | | | | patients (20 to 685 nmoles/L).<br><br>Secondary:<br>Not reported |
| Vasella et al[135]<br><br>Clonazepam 0.1 mg/kg divided TID or QID and titrated weekly until seizures were controlled on until a dose of 0.3 mg/kg was reached | PRO<br><br>Infants and children with infantile spasms or LGS | N=37<br><br>Up to 16 months | Primary:<br>Response to treatment and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>Seizures were considerably improved or completely controlled in eight patients treated with clonazepam (five patients with infantile spasms and three with LGS). Spasms ceased within one to two weeks in three patients by the third week of treatment in one patient.<br><br>After six months of treatment, six patients remained seizure-free and two patients had significantly fewer seizures. Improvement in the EEG was observed in four of these patients, while four patients had transient or no improvements in EEG.<br><br>Temporary remission of seizures occurred in six patients (three with infantile spasms and three with LGS) treated with clonazepam. Seizures disappeared within two to four weeks in five patients but reoccurred within three weeks to seven months. In the other patient the number of seizures was reduced for one year.<br><br>Seven patients received ACTH in addition to clonazepam and achieved lasting improvements. Five patients received ACTH because seizures recurred despite a good initial response to clonazepam therapy. Two of these patients received ACTH because clonazepam did not sufficiently improve seizures. Five patients receiving ACTH in addition to clonazepam remained seizure-free for one to 17 months following therapy. Six of the seven patients who received ACTH had marked improvements in their EEGs.<br><br>Five patients received ACTH one to four weeks after clonazepam was started and achieved a temporary response to treatment. In four patients, seizures disappeared initially but recurred in less than eight months despite continued clonazepam therapy. Improvement in the EEG was less marked than in the group with lasting improvement after ACTH.<br><br>Eight patients experienced minimal or no change in seizure activity, despite clonazepam treatment. |


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| | | | | One or more adverse events were reported in 19 patients treated with clonazepam, with the most common being mucous obstruction of nasopharynx, increased salivation and difficulty swallowing (eight patients). Other adverse events included drowsiness (five patients), constipation (three patients), ataxia (three patients), muscular weakness and hypotonia (two patients) and hyperexcitability (one patient).<br><br>Secondary:<br>Not reported |
| Iivanainen et al[136]<br><br>Clonazepam 1 mg daily plus valproate sodium 300 mg daily both divided BID<br><br>Clonazepam was titrated to a maximum of 6 to 10 mg daily and valproate was titrate to a maximum dose of 1,500 to 1,800 mg daily. | OL, PRO<br><br>Patients with 18 years of age or older with progressive myoclonic epilepsy who did not benefit from treatment with combinations of phenytoin, carbamazepine, phenobarbital, primidone and diazepam | N=26<br><br>Up to 72 months | Primary:<br>Change from baseline scores for grand mal seizures, myoclonus, locomotion, general performance, speech, alertness and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>After four months of treatment with clonazepam and valproate sodium, mean clinical variable scores were significantly improved for myoclonus ($P<0.001$), general performance ($P<0.001$), locomotor ability ($P<0.01$) and speech ($P<0.05$). Scores for alertness and grand mal seizures improved; however, the difference was not statistically significant (*P=NS)*. The most dramatic improvement occurred in locomotor ability. Five patients "learned" to walk again during the new therapy after being bedridden for three to five years.<br><br>At the 72 month evaluation (n=19), median clinical scores remained significantly improved compared to baseline values for myoclonus ($P<0.01$), locomotion ($P<0.05$), and general performance ($P<0.05$). Although improved compared to baseline values, scores for grand mal seizures and speech were not significantly different after 72 months (*P* value not significant).<br><br>Fourteen patients reported mild fatigue and slight vertigo following the initiation of clonazepam. All adverse events were temporary and there were no abnormalities in the results of blood and urine tests during the study that were attributed to the medication.<br><br>Secondary:<br>Not reported |
| Nanda et al[137]<br><br>Clonazepam up to 3 | 2 OL, PRO<br><br>Patients aged 11 | N=30 and N=36 | Primary:<br>Improvements in seizure | Primary:<br>In the initial DB study, 12 of 15 patients with frequent myoclonic jerks (12 of whom also had tonic-clonic seizures), experienced a reduction in seizure frequency and |


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| mg daily divided BID | to 40 with epilepsy were included in a one year OL, ES following nine weeks of DB treatment with clonazepam or placebo<br><br>In the second OL study patients were aged 11 to 44 with a diagnosis epilepsy who were taking a combination of phenytoin, phenol-barbitone and primidone | 12 and 16 months | frequency and adverse events<br><br>Secondary: Not reported | myoclonic jerks by 100%. Three patients had reductions of 80%. Tonic-clonic seizures were ceased in eight patients and four other patients experienced a reduction of seizures of 50%. The effectiveness of clonazepam therapy in the patients who improved was maintained for the following year. In the present OL study, the clonazepam dose was increased to maintain effectiveness in four patients. Four patients were able to reduce the doses of their other anticonvulsants or stop therapy altogether while taking clonazepam.<br><br>In the DB trial four patients had atypical absences with tonic-clonic seizures, of which, clonazepam reduced seizure frequency by 100% in three of these patients. In the other patient, clonazepam had no effect on seizure frequency. Two of the three patients with absence seizures were still benefiting from clonazepam throughout the one-year OL study.<br><br>Eleven patients in the DB trial experienced focal attacks and tonic-clonic seizures. Only four patients experienced a 50% reduction in tonic-clonic seizures during DB treatment with clonazepam, and only two patients continued to experience a 50% improvement one year later.<br><br>In the second (16 month) OL study, seven patients with myoclonic epilepsy and tonic-clonic seizures experienced a 100% reduction in seizure activity and were seizure-free at one year. Of seven patients with photosensitive epilepsy, six experienced a cessation of seizures and the seventh patient experienced a reduction in seizures of 80%.<br><br>In patients with only tonic-clonic seizures, clonazepam was less effective, as only two of six patients experienced an improvement of 50%, while one patient had improvements of less than 50% and one other patient experienced worsening of seizures on clonazepam. Sixteen patients with frontotemporal epilepsy received clonazepam although only nine patients experienced a reduction in attacks of 50% and continued to remain on the drug.<br><br>Drowsiness was reported in 66% of patients within the first week of clonazepam treatment, but generally improved after the first week. After week one, only six patients (all in the OL trial) continued to experience drowsiness. These patients |


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| | | | | were also ataxic, with hypotonicity of trunk and lower limb muscles. One patient in the OL trial became depressed while on clonazepam. A change of personality, with irritability and violent behavior was reported in one patient. After one year, no patients on treatment (45 patients) complained of any adverse events.<br><br>Secondary:<br>Not reported |
| Pavlidou et al[138]<br><br>Intermittent rectal diazepam 0.33 mg/kg every eight hours (first day) followed by every 12 hours on the next day (maximum 7.5 mg/dose)<br><br>vs<br><br>no treatment | PRO, RCT<br><br>Children aged 6 months to 3 years who experienced a first febrile seizure | N=139<br><br>3 years | Primary:<br>Recurrence rates<br><br>Secondary:<br>Not reported | Primary:<br>The 36-month seizure recurrence rates were significantly higher in high-risk patients who received no treatment compared to patients who received diazepam (83 vs 38%; *P*=0.005). No significant difference in seizure recurrence rate was reported between diazepam and no treatment for children considered intermediate risk (55 vs 35%; *P*=0.341) or low risk (46 vs 33%; *P*=0.412).<br><br>Secondary:<br>Not reported |
| Dreifuss et al[139]<br>NINDS<br><br>Diazepam 0.2 to 0.5 mg/kg rectally<br><br>vs<br><br>placebo<br><br>Children received one dose at the onset of acute repetitive seizures and a second dose four hours later. | DB, MC, PC, PG, RCT<br><br>Patient 2 to 60 years of age who weighted ≤100 kg with at least four episodes of acute repetitive seizures during the preceding year and at least one in the preceding three months; despite | N=125<br><br>Duration not reported | Primary:<br>Seizure frequency and global assessment of treatment outcome by the caregiver<br><br>Secondary:<br>Time to first recurrence of seizures after the initial treatment and | Primary:<br>Diazepam was significantly more effective compared to placebo both for reducing seizure frequency and for improving the care giver's global assessment of the treatment outcome (*P*<0.001 for both).<br><br>The frequency of seizures was significantly lower in children receiving diazepam compared to placebo (*P*<0.001) and for adults receiving diazepam compared to placebo (*P*=0.02).<br><br>The caregiver's global assessment of treatment outcome was significantly improved for children receiving diazepam compared to placebo (*P*<0.001). No significant difference was reported for global assessment among adults treated with diazepam or placebo (*P*=0.09).<br><br>Secondary: |


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| Adults received three doses, one dose at onset, and two more doses four and 12 hours after onset. | a stable AED regimen | | safety | The time to the first seizure recurrence was significantly prolonged in the diazepam group compared to placebo (*P*<0.001).<br><br>There were no reports of respiratory difficulty in patients receiving diazepam. Thirty-five patients reported at least one adverse effect, but the difference between the diazepam and placebo groups was not significant (46.7 vs 30.4%, respectively; *P*=0.13). |
| Kriel et al[140]<br><br>Diazepam 2.5 to 20 mg rectally (Study 1)<br><br>or<br><br>diazepam 5 to 20 mg rectally (Study 2)<br><br>vs<br><br>placebo<br><br>In Study 1, children received a second dose four hours after the initial treatment. | 2 DB, PC, PRO, RCT<br><br>Children 2 to 17 years of age previously enrolled in either the NINDS (Study 1) or Athena Neuroscience study (Study 2) with multiple seizures (complex partial or generalized type [tonic, clonic, tonic-clonic, atypical absence, or myoclonic]) despite a stable AED regimen | N=185<br><br>Duration not reported | Primary:<br>Seizure frequency, time to next seizure, and caregiver's global evaluation of outcome and safety<br><br>Secondary:<br>Not reported | Primary:<br>There was a significant reduction in seizure frequency among children administered diazepam compared to placebo (0.00 vs 0.25; *P*=0.001). In addition, significantly more diazepam-treated children remained seizure-free during the 12-hour observation period compared to placebo (59 vs 31%; *P*=0.001).<br><br>The time to the next seizure was significantly longer in diazepam-treated children compared to children who received placebo (*P*=0.0002).<br><br>Compared to placebo, children receiving diazepam had greater improvements in the caretaker's global evaluation in Study 1 (*P*<0.001), but not in Study 2 (*P*=0.053).<br><br>Somnolence was the only adverse event that occurred significantly more frequently in the diazepam group (*P*=0.0095). The most frequently reported adverse events were somnolence, headache, diarrhea, ataxia, incoordination, skin reactions and rectal pain. There were no reports of respiratory depression in either treatment group.<br><br>Secondary:<br>Not reported |
| Cereghino et al[141]<br><br>Diazepam 2.5 to 20 mg rectally (Study 1) | 2 DB, PC, PRO, RCT<br><br>Patients 18 years of age or older | N=96<br><br>Duration not reported | Primary:<br>Seizure frequency, time to next seizure, and caregiver's | Primary:<br>The median number of seizures per hour was significantly lower with diazepam administration compared to placebo (0 vs 0.13; *P*=0.001). In addition, a higher proportion of patients in the diazepam group were seizure-free 12 hours following administration compared to the placebo group (71 vs 28%; *P*<0.001). |


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| or<br><br>diazepam 5 to 20 mg rectally (Study 2)<br><br>vs<br><br>placebo<br><br>In Study 1, adults received three doses: at onset, four hours later and 12 hours following initial treatment. | previously enrolled in either the NINDS (Study 1) or Athena Neuroscience study (Study 2) with multiple seizures (complex partial or generalized type [tonic, clonic, tonic-clonic, atypical absence, or myoclonic]) despite a stable AED regimen | | global evaluation of outcome and safety<br><br>Secondary:<br>Not reported | Following rectal administration of diazepam, the time to next seizure was significantly prolonged compared to patients receiving placebo (*P*<0.001).<br><br>Global assessment as provided by the patient's caregiver was significantly improved in Study 1 (*P*=0.02), but not in Study 2 (*P*=0.17).<br><br>The proportion of patients experience at least one adverse event was 32% of the diazepam group and 23% of the placebo group. The most frequently adverse events were somnolence (13%) and dizziness (6%). The median respiratory rates did not differ between the two treatment groups.<br><br>Secondary:<br>Not reported |
| Mitchell et al[142]<br><br>Diazepam 0.2 to 0.5 mg/kg rectally once<br><br>Patients previously enrolled in the NINDS study were allowed two doses four hours apart. The remaining patients were administered once dose no more frequent than every five days and no more than five times per month. | OL, PRO<br><br>Patients ≥2 years of age with seizure clusters or prolonged seizures who were enrolled in one of two previous double-blind, PC trials or a single-dose safety trial | N=149<br><br>24 months | Primary:<br>Seizure frequency and adverse events and respiratory rates following administration, caregiver and physician global ratings at 24 months, hospitalize-tions, emergency room visits and paramedic calls for treatment | Primary:<br>In the 12 hours following diazepam administration, the median seizure frequency was zero for all 149 patients. Seventy seven percent of diazepam administrations prevented seizures in the 12 hours after treatment.<br><br>In patients receiving at least two doses of diazepam (n=125), the median number of seizures was zero for both first and last administrations, with 63% of subjects having no subsequent seizures after the first administration, and 69% having none after the last administration. (*P* value not reported).<br><br>There was no difference in the number of seizures that occurred in the 12 hour post-administration period among high utilizers of diazepam (two to seven administrations) and the high utilizers (eight to 78 administrations).<br><br>After first administration of diazepam, three of 149 subjects received additional medical treatment, and six were treated in emergency room. After the second administration (n=125), one patient received medical treatment at home, and four |


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| | | | Secondary:<br>Not reported | were treated in the emergency room. Following a third administration (n=110) two patients received medical treatment in the home and six were treated in the emergency room.<br><br>Somnolence was the most frequently reported adverse event, occurring in 17% of subjects. Somnolence due to diazepam was difficult to differentiate from that due to postictal sleep, but was considered to be related to medication in 9% of reports. Hypoventilation was transient in two subjects, neither of which required treatment. No serious adverse events, as defined by the Food and Drug Administration, were attributed to diazepam treatment<br><br>Caregivers and investigators rated diazepam treatment positively at both 12 and 24 months.<br><br>Secondary:<br>Not reported |
| Prasad et al[143] (abstract)<br><br>Diazepam vs placebo<br><br>Lorazepam vs placebo<br><br>Lorazepam vs diazepam<br><br>Lorazepam vs phenytoin<br><br>Diazepam 30 vs 20 mg intrarectal gel | MA (11 RCTs)<br><br>Patients with status epilepticus | N=2,017<br><br>Duration not reported | Primary:<br>Risk of noncessation of seizures, requirement for ventilator support and continuation of status epilepticus<br><br>Secondary:<br>Not reported | Primary:<br>Diazepam was better than placebo in reducing the risk of noncessation of seizures (RR, 0.73; 95% CI, 0.57 to 0.92), requirement for ventilatory support (RR, 0.39; 95% CI, 0.16 to 0.94) or continuation of status epilepticus requiring use of a different drug or general anesthesia (RR, 0.73; 95% CI, 0.57 to 0.92; *P* values were not reported.)<br><br>Lorazepam was better than placebo for risk of noncessation of seizures (RR, 0.52; 95% CI, 0.38 to 0.71) and risk for continuation of status epilepticus requiring a different drug or general anesthesia (RR, 0.52; 95% CI, 0.38 to 0.71; *P* values were not reported.)<br><br>Lorazepam was better than diazepam for reducing risk of noncessation of seizures (RR, 0.64; 95% CI, 0.45 to 0.90) and had a lower risk for continuation of status epilepticus requiring a different drug or general anesthesia (RR, 0.63; 95% CI, 0.45 to 0.88; *P* values were not reported.)<br><br>Lorazepam was better than phenytoin for risk of noncessation of seizures (RR, 0.62; 95% CI, 0.45 to 0.86; *P* values were not reported.) |


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| | | | | Diazepam (30 mg intrarectal gel) was better than a lower dose (20 mg intrarectal gel) in premonitory status epilepticus for the risk of seizure continuation (RR, 0.39; 95% CI, 0.18 to 0.86; *P* values were not reported.)<br><br>Secondary:<br>Not reported |
| Treiman et a[144]<br><br>Diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg<br><br>vs<br><br>lorazepam 0.1 mg/kg<br><br>vs<br><br>phenobarbital 15 mg/kg<br><br>vs<br><br>phenytoin 18 mg/kg | DB, MC, RCT<br><br>Adults with overt or subtle generalized convulsive status epilepticus | N=518<br><br>5 years | Primary:<br>Success (when all motor and electrical seizure activity stopped within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes) and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>For treatment success in overt status epilepticus, a significant difference in success rates was reported: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (*P*<0.02). For subtle status epilepticus, there were no significant differences between the treatment groups (*P*<0.18).<br><br>Lorazepam showed significantly higher treatment success compared to phenytoin in pair wise comparison of overt status epilepticus (*P*<0.002).<br><br>There were no significant differences among any of the treatment groups with respect to adverse effects or 30 day outcomes.<br><br>Secondary:<br>Not reported |
| Glauser et al[145]<br><br>Ethosuximide 60 mg/kg (highest allowable daily dose), frequency not specified<br><br>vs<br><br>valproic acid 60 mg/kg (highest allowable daily | DB, RCT<br><br>Children 2.5 to 13 years of age who had childhood absence epilepsy of new onset; with bilateral synchronous, symmetric spike | N=453<br><br>16 or 20 weeks | Primary:<br>Freedom from treatment failure<br><br>Secondary:<br>Evidence of attentional dysfunction | Primary:<br>Forty seven percent (n=209) children were free from treatment failure. Ethosuximide- and valproic acid-treated patients had higher freedom from failure rates (53 and 58%, respectively) than those given lamotrigine (29%; OR with ethosuximide vs lamotrigine, 2.66; 95% CI, 1.65 to 4.28; OR with valproic acid vs lamotrigine, 3.34; 95% CI, 2.06 to 5.42; *P*<0.001 for both comparisons).<br><br>The two most common reasons for treatment failure were lack of seizure control (24%) and intolerable adverse events (22%). The majority of children who had ongoing seizures were in the lamotrigine cohort. There were no significant differences among the treatment groups in the frequency of treatment failures due |


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| dose), frequency not specified<br><br>vs<br><br>lamotrigine 600 to 2,000 mg/day, frequency not specified | waves on a normal background with ≥1 electrographically recorded seizure lasting ≥3 second on a 1 hour, awake video EEG; weight of ≥10 kg; BMI <99th percentile and had a normal CBC, ALT, AST and bilirubin | | | to either intolerable adverse events or withdrawal from the study. In eight patients, treatment was discontinued owing to generalized tonic-clonic seizures: three subjects in the ethosuximide group, four in the valproic acid group and one in the lamotrigine group.<br><br>Secondary:<br>Attentional dysfunction was more common with valproic acid than with ethosuximide (49 vs 33%; OR, 1.95; 95% CI, 1.12 to 3.41; *P*=0.03). |
| Biton et al[146] (abstract)<br><br>Ethotoin, in addition to current AED therapy | RETRO<br><br>Patients 17 to 51 years of age with intractable seizures (not specified) who had been treated with ethotoin as adjunctive therapy | N=46<br><br>Mean follow-up 10.6 months | Primary:<br>Proportion with ≥50% reduction in overall seizure frequency<br><br>Secondary:<br>Not reported | Primary:<br>Overall, ~51% of patients had a reduction of ≥50% in overall seizure frequency one month after initiation of ethotoin. This was reduced to ~25% for the last three months of follow-up.<br><br>Tonic seizure frequency was reduced most dramatically, by >50%, in 60% of patients at one month and in 35% of patients for the last three months of follow-up.<br><br>Secondary:<br>Not reported |
| Hancock et al[147]<br><br>Felbamate vs placebo (1 trial, n=73)<br><br>Lamotrigine vs placebo (2 trials, n=195)<br><br>Rufinamide vs placebo | MA (7 RCTs)<br><br>Patients (mean age of 10 to 13 years) with LGS | N=694<br><br>Duration varied | Primary:<br>Compare the effects of single agents, either as first- or second-line adjunctive therapy, on cessation of all and specific | Primary:<br>A MA of the seven RCTs was not performed because each trial looked at different populations, therapies and outcomes. Results from the individual studies are summarized below. Note: patients had various seizure types.<br><br>In one study, patients receiving felbamate experienced an overall decrease in all seizure types by 19% compared to an overall increase of 4% on placebo (*P*=0.002). Five of 28 patients receiving felbamate compared to 0/22 patients receiving placebo had total cessation of atonic seizures (RR, 5.7; 95% CI, 0.5 to |


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| (1 trial, n=138)<br><br>Topiramate vs placebo (1 trial, n=98)<br><br>The MA also included 1 trial each for cinromide* and thyrotropin releasing hormone The results of these trials were not included in the summary. | | | types of seizures; safety and deaths<br><br>Secondary: Not reported | 149.8; *P* value not reported), for an overall reduction of 44 and 9%, respectively (*P*=0.02). Seven of 16 patients receiving felbamate compared to 1/13 patients receiving placebo had total cessation of tonic-clonic seizures (RR, 5.7; 95% CI, 0.8 to 40.5; *P* value not reported). One patient in the felbamate arm stopped because of somnolence and ataxia, and one in the placebo arm because of pancreatitis. There were no deaths reported.<br><br>Two studies compared lamotrigine to placebo. One trial reported that 7/13 children showed improvement in the lamotrigine phase compared to the placebo phase, with one child showing a 100% reduction in seizures. Additional results from this study were not reported. Another study reported an overall decrease of 32% in seizures with lamotrigine vs an overall increase of 9% for placebo. Patients receiving lamotrigine compared to placebo also experienced reductions in the following seizure types: 34 vs 9% in drop attacks and 13 vs 38% in absence seizures. Lamotrigine also decreased tonic-clonic seizures by 36% compared to a 10% increase for placebo. Three participants on lamotrigine had treatment withdrawn (one due to deterioration in seizure control and two due to rash) compared to seven participants receiving placebo (six due to deterioration in seizure control and one due to rash). There were no deaths reported; *P* values were not reported.<br><br>One study reported a 33% reduction in all seizures types in patients receiving rufinamide compared to a 12% increase for placebo. Patients receiving rufinamide compared to placebo also experienced reductions in the following seizure types: 28 vs 2% in tonic seizures, 46 vs 18% in tonic-clonic seizures, 43 vs 1% in atonic-clonic seizures, 30 vs 14% in myoclonic seizures, 51 vs 30% in absence seizures and 70 vs 11% in partial-onset seizures. Rufinamide also decreased atonic seizures by 45% compared to a 21% increase for placebo; *P* values were not reported.<br><br>In one study, patients receiving topiramate experienced a decrease in total seizures by 21% compared to 9% for placebo (*P*=0.037). One of 46 patients receiving topiramate compared to 0/50 patients receiving placebo had complete cessation of drop attacks (RR, 3.3; 95% CI, 0.1 to 7.8; *P* value not reported), for an overall decrease of 15% for topiramate compared to an increase of five percent for |


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| | | | | placebo (*P*=0.041). No participant was reported as having had treatment stopped due to adverse effects and no deaths were reported.<br><br>Secondary:<br>Not reported |
| Fattore et al[148]<br><br>Levetiracetam, up to 30 mg/kg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 4 to 16 years of age with newly diagnosed childhood or juvenile absence epilepsy | N=59<br><br>2 weeks (followed by OL follow-up) | Primary:<br>Responder rate (freedom from clinical seizures on days 13 and 14 from EEG seizures during a standard EEG recording with hyper-ventilation and intermittent photic stimulation on day 14)<br><br>Secondary:<br>Patients free from clinical and EEG seizures on days 11 to 14, four to seven, and one to 14; patients with at least a 50% reduction in total duration of EEG seizures during the 24 hour EEG on day 14; | Primary:<br>Nine of 38 and one of 21 patients receiving levetiracetam and placebo were responders (23.7 vs 4.8%; *P*=0.08). Seven of 38 patients<br><br>Secondary:<br>Differences between the two treatments were not observed for any of the secondary outcomes evaluated.<br><br>Of the 38 patients receiving levetiracetam, 12 continued on therapy and were seizure free for at least 267 days at the last follow-up.<br><br>No serious adverse events were reported, and treatment was generally well tolerated. Seven patients receiving levetiracetam and three receiving placebo reported adverse events. Treatment-emergent adverse events were somnolence, irritability, dysphoria, dizziness, and drowsiness. |


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| | | | percentage change in number of EEG discharges during 24 hour EEG on day 14 vs baseline; percentage change in duration of EEG discharges during 24 hour EEG on day 14 vs baseline, safety | |
| Lo et al[149]<br><br>Levetiracetam<br><br>vs<br><br>placebo<br><br>Levetiracetam was evaluated as monotherapy and as adjunctive therapy. Eight trials investigated adjunctive levetiracetam for refractory seizures, one as monotherapy for newly diagnosed seizures, and one as monotherapy for | MA (10 RCTs)<br><br>Adult patients with epilepsy | N=Not reported<br><br>Duration varied | Primary:<br>Greater than 50% reduction in seizure frequency<br><br>Secondary:<br>Safety | Primary:<br>Adjunctive levetiracetam was more effective compared to placebo in achieving ≥50% reduction of seizure frequency, when added to baseline antiepileptic regimen (pooled RR, 2.15; 95% CI, 1.65 to 2.82; *P*<0.01).<br><br>Secondary:<br>Treatment-emergent adverse events include somnolence, irritability, headaches, dizziness, respiratory tract infections, and nausea. Incidences of these events are not significantly more frequent compared to those seen in patients with baseline regimen of several AEDs. Likelihood of serious adverse events necessitating withdrawal from trial was not significantly different between levetiracetam and control (pooled RR, 1.37; 95% CI, 0.88 to 2.13; *P*=0.17). Subgroup analyses suggested similar effects across different dosages. |


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| Tennison et al[150]<br><br>Methsuximide, in addition to current AED therapy | RETRO<br><br>Children 0.8 to 21 years of age with intractable epilepsy despite maximally tolerated doses of multiple AEDs; seizure types included absence, myoclonic, tonic, complex partial and secondarily generalized | N=25<br><br>Duration not reported | Primary:<br>Reduction in seizure frequency, safety<br><br>Secondary:<br>Not reported | Primary:<br>In 15/25 children, the addition of methsuximide resulted in a ≥50 reduction in seizure frequency. Only 1/15 responders experienced an eventual increase in seizures leading to the discontinuation of methsuximide. Neither increased seizures nor complete control was observed in any patient; *P* values were not reported.<br><br>Methsuximide was well tolerated with no serious or irreversible adverse effects reported.<br><br>Secondary:<br>Not reported |
| Painter et al[151]<br><br>Phenobarbital 25 µg/mL, frequency not specified<br><br>vs<br><br>phenytoin 3 µg/mL, frequency not specified<br><br>The alternate drug was added if initial treatment failed. | RCT, SB<br><br>Neonates with seizures | N=59<br><br>5 years | Primary:<br>Complete seizure control determined by EEG<br><br>Secondary:<br>Not reported | Primary:<br>Phenobarbital controlled seizures completely in 43% of patients, while phenytoin controlled seizures in 45% of patients (*P*=1.00).<br><br>Secondary:<br>Not reported |
| Bondarenko et al[152]<br><br>Pregabalin 300 or 600 mg/day, in addition to | RETRO<br><br>Patients with symptomatic | N=100<br><br>6 months | Primary:<br>Frequency of seizures | Primary:<br>At the end of the first month, among patients receiving combination therapy with pregabalin 300 mg/day, the total number of seizures decreased by 39% as compared to the period of carbamazepine monotherapy (*P*<0.001). At three |


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| current AED therapy (carbamazepine)<br><br>vs<br><br>pregabalin 300 or 600 mg/day, in addition to current AED therapy (valproate) | focal epilepsy with frequent polymorphous seizures | | Secondary: Safety | months, the total number of seizures in this group decreased by 45% (*P*<0.001), with a 48% reduction after six months of combination therapy, as compared to baseline (*P*<0.001). Among the patients receiving combination therapy with pregabalin 600 mg/day, reductions in seizures were somewhat greater than in the preceding group: by 56, 59 and 61%, respectively (*P*<0.001).<br><br>Smaller reductions in seizures were seen in the group of patients receiving valproic acid derivatives with pregabalin 300 mg/day: by 32, 34 and 37%, respectively (*P*<0.01). The combination of valproates with pregabalin 600 mg/day was more effective, with reduction by 51, 53 and 56%, respectively (*P*<0.005).<br><br>Secondary:<br>Overall, patients showed good tolerance to pregabalin. Adverse events included transient drowsiness and vertigo, which was seen during the pregabalin titration period in eight patients. |
| Glauser et al[153]<br><br>Rufinamide titrated (over 14 days) up to a maximum of 45 mg/kg/day (3,200 mg in adults ≥70 kg) BID<br><br>vs<br><br>placebo | DB, MC, PG, PC, RCT<br><br>Patients 4 to 30 years of age with LGS, weighing ≥18 kg, with a history of multiple seizure types, a minimum of 90 seizures in the month before enrollment, an EEG within 6 months of study entry showing a pattern of slow spike-and-wave complexes, on a fixed dose of 1 to | N=138<br><br>84 days (14-day titration phase plus 70-day mainten-ance period) | Primary: Percent change in total seizure frequency, tonic-atonic seizure frequency and seizure severity (based on the global evaluation of the patient's condition)<br><br>Secondary: Treatment response (percentage of patients with ≥50% reduction in seizure | Primary:<br>The rufinamide group experienced a significantly greater median percentage reduction in total seizure frequency compared to patients receiving placebo (32.7 vs 11.7%; *P*=0.0015).<br><br>While patients in the rufinamide group experienced a 42.5% median decrease in the frequency of tonic-atonic seizures, patients receiving placebo experienced an increase of 1.4% (*P*<0.0001).<br><br>The percentage of rufinamide patients that experienced ≥50% reduction in tonic-atonic seizure frequency was greater than that in the placebo group (42.5 vs 16.7%; *P*=0.002).<br><br>A significantly greater percentage of rufinamide -treated patients reported an improvement in seizure severity compared to placebo-treated patients (53.4 vs 30.6%; *P*=0.0041).<br><br>Secondary:<br>The percentage of rufinamide patients that experienced ≥50% reduction in total seizure frequency was greater than that in the placebo group (31.1 vs 10.9%; |


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| | 3 concomitant AEDs | | frequency), percent change in seizure frequency (for each seizure type other than tonic-atonic seizures), parental global evaluation and adverse events | *P*=0.0045).<br><br>Rufinamide adjunctive treatment reduced the frequency of absence and atypical absence seizures (50.6 vs 29.8%; *P*=0.022), myoclonic seizures (30 vs 13%; *P*=0.57) and tonic-clonic seizures (45.6 vs 18%; *P*=0.33) compared to placebo.<br><br>There was no significant difference between the two treatment groups in the mean composite score of the parent/guardian global evaluation of the patient's condition at the end of the DB phase (*P* value not reported). All individual items were similar between treatment groups (*P*>0.2) except for seizure severity, which improved more with rufinamide (*P*=0.0041).<br><br>There were no significant differences between the treatment groups in the incidence of adverse events, except for somnolence and vomiting which were more common in the rufinamide group (*P* value not reported). |
| Kluger et al[154]<br><br>Rufinamide 25 to 60 mg/kg/day<br><br>Patients were receiving a fixed-dose regimen of 1 to 3 concomitant AEDs. | ES, OL<br><br>Patients 4 to 37 years of age with inadequately controlled LGS who had previously completed a 12 week, DB trial | N=124<br><br>Duration not specified (trial was open ended; trial was terminated at 44 months) | Primary:<br>Seizure frequency, tonic-atonic seizure frequency<br><br>Secondary:<br>Safety | Primary:<br>A reduction in median total seizure frequency compared to baseline was observed at every time point in all patients. During the first nine months, a progressive decrease in seizure frequency was observed, which continued at similar levels for the rest of the treatment period. A continued reduction in total seizure frequency was observed in the 63 patients who received rufinamide during the DB study. Patients treated with placebo during the DB study (n=59), achieved a 1.5% decrease in total seizure frequency during the DB study, but after two weeks of rufinamide treatment, the same patients achieved a 22% median reduction in total seizures compared to baseline.<br><br>Similar to total seizure frequency, the frequency of tonic-atonic seizures also decreased at every time point for each cohort during the ES. There was a progressive decrease in the frequency of tonic-atonic seizures over the first nine months, with reductions continuing for all cohorts during the rest of the study. Within the final six months of treatment, 56 patients reached ≥50% reduction in tonic-atonic seizures, 42 patients reached ≥75% reduction in tonic-atonic seizures, and 11 patients became seizure free.<br><br>Secondary: |


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| | | | | Overall, 91.1% of patients reported an adverse vent during the study, with 70.2% being considered to be drug-related. Events reported in the ES were similar to those observed in the DB study. Rash was reported in four patients. No clinically significant changes in laboratory values, vital signs, or ECG were observed. There were more serious adverse events reported in the ES compared to the DB study. |
| Kim et al[155]<br><br>Rufinamide 20 to 40 mg/kg/day<br><br>The target dose was modified according to the patient's tolerability and the treatment efficacy. | OL<br><br>Patients <20 years of age with LGS experienced ≥4 convulsive seizures and several other types of seizures in the previous month | N=128<br><br>16 weeks<br><br>(4-week titration, 12 week mainten-ance) | Primary:<br>Reduction in seizure-frequency following 12 weeks of treatment, safety and tolerability<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with rufinamide reduced the overall seizure frequency by 31.7%. Overall, 7.8% of patients treated with adjunctive rufinamide remained seizure-free (n=10) while 18.0% of patients (n=23) experienced a reduction in seizures by >75%. Adjunctive rufinamide treatment reduced seizures by 50 to 75% in 10.2% of patients (n=13), and by <50% in 8.6% of patients (n=11). Of note, 39.1% (n=50) of patients experienced no change in seizure frequency and 16.4% (n=21) reported >25% increase in seizure frequency. Patients with a ≥50% reduction in seizure frequency were defined as responders.<br><br>A treatment response to adjunctive rufinamide occurred in 39.4% of patients with convulsive seizures, 36.4% of patients with drop attacks, 33.3% of patients with myoclonic seizures and 20.0% of patients with spasms. Among ten patients who became seizure-free after adjunctive rufinamide treatment, six (60.0%) had convulsive seizures, three had drop attacks, and only one had epileptic spasms as the primary seizure type.<br><br>The causes of premature discontinuation of rufinamide included inadequate seizure control in 11 patients (8.6%), adverse effects in 4 patients (3.1%), and loss to follow-up of 1 patient (0.8%).<br><br>Adverse events were reported in 32.8% patients (n=42). The most commonly reported adverse events were fatigue (n=15), poor appetite (n=9), as well as somnolence, rash, hyperactivity, poor quality of sleep, and vomiting. Adverse events that lead to premature discontinuation of rufinamide were fatigue, vomiting, menorrhagia, and eye blinking, (one patient each). All of these symptoms resolved spontaneously after discontinuing treatment.<br><br>Secondary:<br>Not reported |


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| Pulman et al[156]<br><br>Tiagabine plus conventional AED treatment<br><br>vs<br><br>placebo or a different add-on AED plus conventional AED treatment | SR (5 RCTs)<br><br>Patients with drug resistant localization related seizures | N=not reported<br><br>Duration varied | Primary:<br>50% or greater reduction in seizure frequency, treatment withdrawal, cognitive effects, quality of life<br><br>Secondary:<br>Safety | Primary:<br>*Tiagabine vs placebo*<br>50% or greater reduction in seizure frequency (PG trials):<br>The overall RR for a response to tiagabine is 3.16 (95% CI, 1.97 to 5.07), indicating that patients are significantly more likely to respond to tiagabine compared to placebo. The RR for the worst case and best case scenario are 2.70 (95% CI, 1.75 to 4.19) and 3.32 (95% CI, 2.08 to 5.32), respectively.<br><br>50% or greater reduction in seizure frequency (XO trials):<br>From two trials, of the 46 people randomized in one trial, eleven (24%) had a 50% reduction in seizure frequency in the tiagabine compared to the placebo phase. Of the 44 patients randomized in the other trial, twelve (27%) had a 50% reduction in seizure frequency in the tiagabine compared to the placebo phase. Pooling these data, weighted according to the inverse variance gives an estimate of the proportion of responders of 0.25 (95% CI, 0.16 to 0.34).<br><br>Treatment withdrawal:<br>Treatment withdrawal data were only available for the PG trials. The overall RR for discontinuation for any reason is 1.81 (95% CI, 1.25 to 2.62) indicating that people are significantly more likely to withdraw from tiagabine compared to placebo.<br><br>Cognitive effects:<br>There is insufficient evidence to conclude that tiagabine has an effect on cognition.<br><br>Quality of life:<br>From two trials, neither found a significant difference between tiagabine and placebo; therefore, there is insufficient evidence to conclude that tiagabine has an effect on quality of life.<br><br>*Tiagabine vs topiramate*<br>50% or greater reduction in frequency:<br>Within this trial, there was no significant differences between the two add-on therapies (RR, 0.54; 95% CI, 0.19 to 1.58).<br><br>Treatment withdrawal: |


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| | | | | No significant differences were found between the two treatments from withdrawal from the trial (RR, 1.43; 95% CI, 0.74 to 2.74).<br><br>Cognitive effects:<br>Authors did not compare the two add-on treatments for this outcome.<br><br>Quality of life:<br>Authors did not compare the two add-on treatments for this outcome.<br><br>Secondary:<br>*Tiagabine vs placebo*<br>Analysis of PG trials demonstrated the following adverse events are significantly associated with tiagabine (RR): dizziness, 1.69% (99% CI, 1.31 to 2.51); fatigue, 1.38 (99% CI, 0.89 to 2.14); nervousness, 10.65 (99% CI, 0.78 to 146.08); tremor, 4.56 (99% CI, 1.00 to 20.94). For the XO trials, one trial reported that eight and 10 patients reported adverse events when receiving tiagabine (dizziness and incoordination) and placebo (accidental injury).<br><br>*Tiagabine vs topiramate*<br>Not reported |
| Elterman et al[157]<br><br>Vigabatrin 100 to 148 mg/kg/day (high dose)<br><br>vs<br><br>vigabatrin 18 to 36 mg/kg/day (low dose)<br><br>Patients could be on stable doses of non-infantile spasm AEDs such as phenobarbital or clonazepam. | MC, RCT, SB<br><br>Patients <2 years of age with newly diagnosed (<3 months) infantile spasms, weighing ≥3.5 kg | N=221<br><br>14 to 21 days (followed by 3 years of OL treatment) | Primary:<br>Spasm cessation (seven consecutive days of spasm freedom beginning within the first 14 days)<br><br>Secondary:<br>Proportion of patients who were spasm free for seven | Primary:<br>Overall, 11.3% (25/221) of patients were spasm free, with a significant difference between treatment groups in the first 14 days of treatment. In the high dose group, 15.9% (17/107) were spasm free vs 7.0% (8/114) in the low dose group (*P*=0.0375).<br><br>Secondary:<br>A significantly greater number of patients attained spasm freedom in the high dose group (73/107; 68.2%) compared to 51.8% (59/114) in the low dose group (*P*=0.0126). Analyses show a separation between treatment groups within one week of vigabatrin therapy initiation, with a greater response occurring in the high dose group (*P*=0.0016). The median time to spasm cessation was six weeks in the high dose group and 13 weeks in the low dose group.<br><br>For the primary responders, the mean time to relapse was 162 days (range, 53 to |


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| | | | consecutive days at any time during the trial and remained spasm free for the duration of the trial, relapses, safety | 270) in the high dose group and 45 days (range, 31 to 58 days) in the low dose group. Of the 171 patients who became spasm free for seven consecutive days, 39 (22.8%) relapsed, and 28 of 39 (71.8%) became spasm free again.<br><br>Throughout the trial, 115/222 patients (51.8%) experienced at least one adverse event considered to be related to treatment. Of the 1,587 unique events reported, 219 (13.8%) were considered to be related treatment. Of these events, 219 unique events, five were severe, 64 were moderate, and 150 were mild, and two were unknown. The most common vigabatrin-related events were sedation (16.7%), somnolence (13.5%), irritability (9.9%), sleep disorder (4.5%), constipation (3.6%), lethargy (3.6%), decreased appetite (3.2%), and hypotonia (2.3%). |
| Lee et al[158]<br><br>Zonisamide 3 to 5 mg/kg/day BID, in addition to current AED therapy | RETRO<br><br>Children with epilepsy intractable to treatment with existing AEDs, experiencing >4 seizures/month before initiation of zonisamide, their seizures not controlled by ≥2 conventional AEDs before initiation of zonisamide and followed for ≥6 months | N=163<br><br>6 months | Primary:<br>Efficacy (seizure reduction rate)<br><br>Secondary:<br>Not reported | Primary:<br>Seventy nine (48.5%) patients experienced a reduction in seizure frequency of >50%, and 25 (15.3%) became seizure-free. The rate of seizure reduction <50% in children with partial seizures was 40.5% (17/42) and in children with generalized seizures was 51.2% (62/121). Of the 36 patients who manifested mainly myoclonic seizures, 20 (55.6%) showed a seizure reduction of >50% and nine (25.0%) were seizure-free.<br><br>Secondary:<br>Not reported |
| **Bipolar Disorder** | | | | |
| Joshi et al[159]<br><br>Carbamazepine ER, titrated to an effective | OL, PRO<br><br>Outpatients 6 to 12 years of age | N=27<br><br>8 weeks | Primary:<br>Severity of symptoms of mania | Primary:<br>A statistically significant improvement from baseline after two weeks of treatment with further treatment for completers at week eight was observed (*P* value not reported). At eight weeks, 52% (n=14) of patients had a 30% reduction in baseline |


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| dose (maximum 1,200 mg/day), frequency not specified | with a diagnosis of bipolar disease I or II or bipolar disease not otherwise specified, with significant severity of current manic, hypomanic or mixed symptoms on the YMRS | | Secondary: Severity of symptoms of depression and ADHD | YMRS and 44% (n=12) had a 50% reduction. A total of 34% (n=9) of patients achieved remission of mania symptoms (YMRS score <12).<br><br>Secondary:<br>A statistically significant improvement in the symptoms of both depression and psychosis as reflected by the change from baseline to end point in the mean scores of CDRS (34.8±10.9 vs 26.9±11.6; *P*=0.001) and BPRS (40.1±9.9 vs 30.0±6.8; *P*<0.001), respectively.<br><br>Forty three percent of patients demonstrated improvement in symptoms of depression and 62% demonstrated improvement in ADHD symptoms. |
| McElroy et al[160]<br><br>Divalproex ER titrated to an effective dose (not to exceed 30 mg/kg/day), frequency not specified<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Patients ≥18 years of age diagnosed with bipolar I or II disorder or bipolar disorder not otherwise specified and who were currently experiencing a hypomanic, manic or mixed episode; moderate to severe hypomania or mild mania within the past 2 weeks; operationally | N=62<br><br>8 weeks | Primary: Change in hypomanic/ mild manic symptoms as assessed by the YMRS<br><br>Secondary: IDS, CGI-BP, HARS and GAF scales | Primary:<br>Patients receiving divalproex ER had a significantly greater rate of reduction in mean total YMRS score than placebo (*P*=0.024).<br><br>Secondary:<br>Patients receiving divalproex ER had significantly greater rates of reduction in CGI-BP mania (*P*=0.044) and CGI-BP overall scores (*P*=0.047). The associated standardized effect sizes were moderate. There were no differences in the rates of change in the IDS (*P*=0.271), CGI-BP depression (*P*=0.187), HARS (*P*=0.494) or GAF (*P*=0.200) scores. |


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| | defined as having a YMRS score ≥10 and <21 at baseline and ≥1 prior to study screening visit ≥3 days, but not <2 weeks, before baseline; an overall CGI-BP score ≥2 and <5; were outpatients and receiving no psychotropics for the one week before baseline assessment | | | |
| Hirschfeld et al[161]<br><br>Divalproex ER titrated to an effective dose, frequency not specified<br><br>vs<br><br>placebo | RCT<br><br>Patients 18 to 65 years of age diagnosed with bipolar I disorder (manic or mixed type) with a MRS score >25 with ≥4 items having a score ≥3 on the final day of the screening/washo ut period | N=225<br><br>21 days | Primary:<br>Change from baseline to final evaluation in MRS score<br><br>Secondary:<br>Change from baseline to final evaluation in Manic Syndrome Score, Behavior and Ideation Score, Brief Agitation Rating Scale, Overt Aggression | Primary:<br>There was no statistically significant difference in MRS change from baseline to any time-point for patients treated with divalproex ER compared to those treated with placebo (mean change from baseline, -10.1 vs -8.7; *P* value not reported).<br><br>Secondary:<br>There were no statistically significant differences in any of the secondary efficacy measures. |


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| | | | Scale and BPRS total scores and subscale scores | |
| Macritchie et al[162] (abstract)<br><br>Valproate<br><br>vs<br><br>placebo<br><br>vs<br><br>lithium | MA (1 RCT)<br><br>Patients with bipolar disorder; literature was searched for trials comparing valproate with placebo, alternative mood stabilizers or neuroleptics where the stated intent of intervention was maintenance treatment of bipolar disorder | N=372<br><br>12 months | Primary:<br>Determine the efficacy of valproate maintenance treatment in preventing or attenuating further episodes of bipolar disorder, acceptability of treatment, safety and mortality<br><br>Secondary:<br>Not reported | Primary:<br>One trial of 12 months duration was identified comparing divalproex, lithium, and placebo. It had several methodological limitations. The primary analysis of time to occurrence of mood episode described in the main trial report found no reliable difference between the treatments, although there was a trend for divalproex to be more effective than lithium. In the analysis in this review, patients taking divalproex who left the study because of the occurrence of a mood episode were significantly less in number than those on placebo (RRR, 37%; RR, 0.63; 95% CI, 0.44 to 0.90). There was no significant difference in the numbers of patients receiving divalproex compared to those receiving lithium who left the study because they suffered any mood episode (RRR, 22%; RR, 0.78; 95% CI, 0.52 to 1.17). There was insufficient information to allow subgroup analyses of rapid-cycling disorder; *P* values were not reported.<br><br>The divalproex group had significantly more patients experiencing tremor (RRI, 223%; RR, 3.23; 95% CI, 1.85 to 5.62), weight gain (RRI, 187%; RR, 2.87; 95% CI, 1.34 to 6.17) and alopecia (RRI, 143%; RR, 2.43; 95% CI, 1.05 to 5.65) than the placebo group. In comparison to lithium, divalproex was associated with more frequent sedation (RRI, 58%; RR, 1.58; 95% CI, 1.08 to 2.32) and infection (RRI, 107%; RR, 2.07; 95% CI, 1.16 to 3.68), but less suffered thirst (RRR, 62%; RR, 0.38; 95% CI, 0.18 to 0.81) and polyuria (RRR, 57%; RR, 0.43; 95% CI, 0.22 to 0.82). *P* values were not reported.<br><br>Secondary:<br>Not reported |
| Macritchie et al[163] (abstract)<br><br>Valproate<br><br>vs | MA (10 RCTs)<br><br>Patients with bipolar disorder; literature was searched for | N=932<br><br>Duration not reported | Primary:<br>Determine the efficacy (failure to respond by end of study assessed by | Primary:<br>Valproate was more efficacious than placebo (RRR, 38%; RR, 0.62; 95% CI, 0.51 to 0.77) in the treatment of mania. There was no significant difference between valproate and lithium (RRI, 5%; RR, 1.05; 95% CI, 0.74 to 1.50) or between valproate and carbamazepine (RRR, 34%; RR, 0.66; 95% CI, 0.38 to 1.16). Valproate was less effective than olanzapine (failure to achieve clinical response; |


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| carbamazepine (n=59)<br><br>vs<br><br>haloperidol (n=36)<br><br>vs<br><br>lithium (n=158)<br><br>vs<br><br>olanzapine (n=363)<br><br>vs<br><br>placebo (n=316)<br><br>(Note: n=the total number of patients in the comparison trial with valproate.) | trials comparing valproate with placebo, other mood stabilizers and antipsychotics in the treatment of any bipolar affective episode; only studies comparing valproate with other interventions in mania were found (no studies were found examining its use in depression or mixed affective episodes) | | <50% reduction in the YMRS) and acceptability of treatment of acute episodes of bipolar disorder<br><br>Secondary:<br>Not reported | RRI, 25%; RR, 1.25; 95% CI, 1.01 to 1.54; average of 2.8 point less change on the MRS; 95% CI, 0.83 to 4.79). *P* values were not reported.<br><br>There were no significant differences in acceptability as measured by total number of subjects withdrawing from the study. There were significant differences in the adverse event profiles of valproate and olanzapine, with more sedation and weight gain on olanzapine; *P* values were not reported.<br><br>Secondary:<br>Not reported |
| Liu et al[164]<br><br>Traditional mood stabilizers (lithium, divalproex sodium, carbamazepine), other anticonvulsants (lamotrigine, oxcarbazepine, topiramate), SGAs (aripiprazole, olanzapine, quetiapine, | MA (46 OL trials and RCTs)<br><br>Pediatric patients with bipolar mania | N=2,666<br><br>Duration varied | Primary:<br>Treatment response<br><br>Secondary:<br>Not reported | Primary:<br>*OL studies*<br>All drug classes had a response rate significantly greater than zero (*P*≤0.001 for all comparisons). The pooled estimate of the rate of response ranged from 48.9 to 52.1%. Using meta-regression, there was no significant difference in the rate of response between drug classes (*P*=0.47) or between specific drug compounds (*P*=0.56).<br><br>*RCTs*<br>The pooled estimate for the OR was significantly greater than 1.0 (OR, 2.23; *P*<0.001), indicating a significantly increased likelihood of response when on the drug compared to placebo. This overall significant separation from placebo was |


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| risperidone, ziprasidone), and naturopathic compounds | | | | mainly accounted for by the highly significant effect of SGAs (*P*<0.001). Findings were not significant for divalproex (*P*=0.92) and modestly significant for the other anticonvulsants (*P*=0.04). Within each drug class, effect sizes were no significantly different from one another.<br><br>Secondary:<br>Not reported |
| **Diabetic Peripheral Neuropathy** | | | | |
| Rosenstock et al[165]<br><br>Pregabalin 100 mg TID<br><br>vs<br><br>placebo TID | DB, MC, PC, PG, RCT<br><br>Patients with 1- to 5-year history of DPN and average daily pain score ≥4 on an 11-point numeric pain-rating scale | N=146<br><br>8 weeks | Primary:<br>Pain score<br><br>Secondary:<br>SF-MPQ scores, sleep interference scores, PGIC and CGIC scores, SF-36 Health Survey scores, POMS scores, adverse events | Primary:<br>Mean pain score was significantly improved with pregabalin compared to placebo (3.99 vs 5.46; *P*=0.0001).<br><br>Secondary:<br>Compared to placebo, pregabalin treatment resulted in significant improvements in mean sleep interference score, SF-MPQ total score, VAS score, present pain intensity score, PGIC, CGIC, bodily pain scores of the SF-36 health survey, and tension/anxiety and total mood disturbance of the POMS evaluation (*P*≤0.05 for all).<br><br>No significant differences were observed between treatment groups in mental health and vitality scores of the SF-36 health survey and anger/hostility, vigor/activity, and fatigue/inertia scores of the POMS evaluation (*P*>0.05).<br><br>The most commonly reported adverse events were dizziness (35.5 vs 11.4%), somnolence (19.7 vs 2.9%), infection (14.5 vs 5.7%), and peripheral edema (10.5 vs 1.4%). |
| Richter et al[166] (abstract)<br><br>Pregabalin 150 or 600 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients with painful DPN | N=246<br><br>6 weeks | Primary:<br>Pain score<br><br>Secondary:<br>Sleep interference, pain intensity, sensory and affective pain | Primary:<br>Pregabalin significantly reduced pain score from baseline compared to placebo (4.3 vs 5.6; *P*=0.0002) and increased the percentage of patients with ≥50% decrease from baseline pain (39 vs 15% for placebo; *P*=0.002).<br><br>Secondary:<br>Pregabalin significantly improved sleep interference score, pain intensity, sensory and affective pain scores, and CGIC and PGIC scores compared to placebo. |


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| | | | scores, CGIC, PGIC, adverse events | Dizziness was the most common adverse reaction. |
| Lesser et al[167]<br><br>Pregabalin 75, 300, and 600 mg/day administered in divided doses (TID)<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients with 1- to 5-year history of DPN and average weekly pain score ≥4 on an 11-point numeric pain-rating scale | N=338<br><br>5 weeks | Primary:<br>Pain score<br><br>Secondary:<br>Sleep interference score, global impression of change, SF-MPQ, SF-36 Health Survey, PGIC, CGIC, adverse events | Primary:<br>Compared to placebo, mean pain score was significantly improved with pregabalin 300 (*P*=0.0001) and 600 mg/day (*P*=0.001), but not with pregabalin 75 mg/day (*P*=0.6267).<br><br>Secondary:<br>Compared to placebo, percentages of reduction in pain, mean sleep interference scores, SF-MPQ total scores, PGIC and CGIC, VAS scores, and present pain intensity scores were significantly improved with pregabalin 300 mg/day and 600 mg/day, but not with pregabalin 75 mg/day (*P*≤0.05 for all).<br><br>Most common reported adverse events were dizziness (7.8 to 39.0 vs 5.2%), somnolence (3.9 to 26.8 vs 4.1%), and peripheral edema (3.9 to 13.4 vs 2.1%). |
| Quilici et al[168]<br><br>Duloxetine<br><br>vs<br><br>pregabalin and gabapentin<br><br>Placebo was used a common comparator. | MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials)<br><br>Patients with diabetic peripheral neuropathic pain | N=not specified<br><br>≥5 to 13 weeks | Primary:<br>Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall health improvement (PGI of Improvement and PGIC)<br><br>Secondary:<br>Safety | Primary:<br>*Direct comparisons*<br>All three agents were superior to placebo for all efficacy parameters. For 24-hour pain severity effect values were -1.13 (95% CI, -1.36 to -0.89), -0.90 (95% CI, -1.23 to -0.57), and -1.44 (95% CI, -2.21 to -0.66) with duloxetine, pregabalin, and gabapentin. Corresponding effect values for response rates were 0.86 (95% CI, 0.63 to 1.09; NNT, 5; 95% CI, 3 to 7) and 0.84 (95% CI, 0.52 to 1.16; NNT, 5; 95% CI, 4 to 8) with duloxetine and pregabalin, and for PGI of Improvement/PGIC were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin.<br><br>*Indirect comparisons*<br>For the primary efficacy outcome of 24-hour reduction in pain severity, a difference of -0.248 (95% CI, -0.677 to 0.162) was observed in favor of duloxetine over pregabalin. Duloxetine was not inferior to pregabalin on this outcome. For response rates, the difference between duloxetine and pregabalin was close to zero and not significant. For PGI of Improvement/PGIC outcomes, pregabalin showed an improvement of 0.542 points over duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060). |


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| | | | | Secondary:<br>Duloxetine produced a significantly lower incidence of dizziness compared to pregabalin. No differences between these two treatments were observed in the rates of premature discontinuation, diarrhea, headache, and somnolence. |
| Tanenberg et al[169]<br><br>Duloxetine<br><br>vs<br><br>pregabalin<br><br>vs<br><br>duloxetine plus pregabalin | MC, NI, OL, RCT<br><br>Adult patients with type 1 or 2 with $HbA_{1c}$ ≤12.0%, and diabetic peripheral neuropathic pain who had been treated with gabapentin (900 mg/day) and had an inadequate response | N=407<br><br>12 weeks | Primary:<br>Reduction from baseline in the weekly mean of the daily 24-hour pain diary ratings at week 12<br><br>Secondary:<br>Worst pain and night pain ratings, Clinician Global Impression of Severity, Brief Pain Inventory severity and interference, Beck Depression Inventory II, Patient Global Impression of Improvement, Sheehan Disability Scale, response rate, safety | Primary:<br>The estimated mean change in the daily pain severity score at 12 weeks was -2.6 for duloxetine and -2.1 for pregabalin, representing an observed 0.49 advantage of duloxetine; therefore, NI was established.<br><br>Significant superiority vs pregabalin in the mean daily pain diary ratings was observed at weeks, two, three, and five through 11 with duloxetine and with duloxetine plus gabapentin at weeks two and eight, but between-treatment differences at the 12 week end point met NI criteria, not statistical superiority.<br><br>The NI comparison between duloxetine and combination therapy on the differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met.<br><br>Secondary:<br>Reduction from baseline in Brief Pain Inventory average pain and Brief Pain Inventory worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other Brief Pain Inventory pain measures, CGI of Severity, depressive symptoms, or the Sheehan Disability Scale global measure. Also, no significant between-treatment differences were found among the various response outcomes.<br><br>Significantly more discontinuations occurred as a result of adverse events with duloxetine (19.6%; *P*=0.04) compared to pregabalin (10.4%), but no vs combination therapy (13.3%; *P*=0.19). Peripheral edema associated with pregabalin (3.7%) was the only adverse event reported as a reason for discontinuation with significantly greater frequency compared to other treatments (duloxetine, 0%; *P*=0.3; combination therapy, 0%; *P*=0.03). Rates of discontinuation for other reasons did not differ among the treatments. The treatment-related adverse events of nausea, insomnia, hyperhidrosis, and |


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| | | | | decreased appetite occurred significantly more frequently with duloxetine compared to pregabalin. The frequency of insomnia was also significantly greater with duloxetine compared to combination therapy. The occurrence of peripheral edema was significantly greater with pregabalin compared to the other two treatments. Combination treatment was associated with significantly greater occurrences of nausea, hyperhidrosis, decreased appetite, and vomiting compared to pregabalin monotherapy. |
| Wernicke et al[170]<br><br>Duloxetine 60 mg BID<br><br>vs<br><br>routine care (gabapentin, amitriptyline, and venlafaxine) | ES, OL, RCT<br><br>Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes | N=293<br><br>52 weeks | Primary:<br>Not reported<br><br>Secondary:<br>Health outcomes, safety | Primary:<br>Not reported<br><br>Secondary:<br>There were significant treatment-group differences observed in favor of duloxetine in the SF-36 physical component summary score, and subscale scores of physical functioning, bodily pain, mental health, and vitality. A significant treatment-by-investigator interaction was seen for general health perceptions (*P*=0.073), mental health (*P*=0.092), and social functions (*P*=0.003) subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire.<br><br>During the trial, four deaths occurred. Deaths were considered to be unrelated to the study drug or protocol procedures. During the trial, 22 (11.2%) duloxetine vs 16 (16.7%) routine care-treated patients experienced at least one serious adverse event. The most frequently reported serious adverse events for both treatments together were cerebrovascular accident and diabetes, and these events were not considered to be drug-related. Fourteen (4.8%) patients discontinued due to any adverse event; which included 11 and three duloxetine- and routine care-treated patients (*P*=0.560). A total of 157 (53.6%) patients reported at least one treatment-emergent adverse event, and there were no treatment-group differences in the overall incidence of these events.<br><br>There was a significant increase in mean uric acid levels in routine care-treated patients compared to duloxetine-treated patients with regard to chemistry/urinalysis.<br><br>Both treatments experienced a slight increase in $HbA_{1c}$, with duloxetine-treated patients experiencing a larger increase in the mean change from baseline to |


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| | | | | endpoint (*P*<0.001). No significant treatment-group differences were observed in low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride levels.<br><br>There were no significant treatment-group differences observed in the mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint.<br><br>There were no significant treatment-group differences observed in either subset of patients in the ulnar F-wave, ulnar distal sensory latency, and peroneal compound muscle action potential from baseline to endpoint for all patients. There was a significant increase observed in the peroneal F-wave measure for routine care-treated patients (*P*=0.05).<br><br>There were no significant treatment-group differences observed for any of the ophthalmologic exam measures.<br><br>There was a significant treatment-group difference observed in the mean change in microalbumin/creatinine ratio from baseline to endpoint (*P*=0.031), with duloxetine-treated patients experiencing a bigger mean decrease compared to routine care-treated patients.<br><br>There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight.<br><br>One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in systolic blood pressure, and there were no significant differences between treatments.<br><br>There were no ECG parameters that were significantly different between treatments. Significantly more routine-care patients had potentially clinically significant Fridericia-corrected QT interval increases (*P*=0.034). |
| Raskin et al[171]<br><br>Duloxetine 60 mg BID | ES, OL, RCT<br><br>Adult patients | N=237<br><br>52 weeks | Primary:<br>Not reported | Primary:<br>Not reported |


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| vs<br><br>routine care (gabapentin, amitriptyline, and venlafaxine) | who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes | | Secondary:<br>SF-36, EQ-5D, safety | Secondary:<br>No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.<br><br>A higher proportion of routine care-treated patients experienced one or more serious adverse events. No significant treatment-group difference was observed in the overall incidence of treatment-emergent adverse events. The treatment-emergent adverse events reported by at least 10% of patients receiving duloxetine 60 mg BID were nausea, and by the patients receiving routine care were peripheral edema, pain in the extremity, somnolence, and dizziness. Duloxetine did not appear to adversely affect glycemic control, lipid profiles, nerve function, or the course of diabetic peripheral neuropathic pain. |
| **Fibromyalgia** | | | | |
| Hauser et al[172]<br><br>Gabapentin 1,200 or 2,400 mg/day (1 trial) or pregabalin 150 to 600 mg/day (4 trials)<br><br>vs<br><br>placebo | MA (5 RCTs)<br><br>Adult patients with fibromyalgia | N=2,117 who completed treatment (n=1,507 gabapentin/ pregabalin, n=610 placebo)<br><br>Median treatment duration 11 weeks (range 8 to 26 weeks) | Primary:<br>Improvement of pain, sleep, depressed mood, fatigue, and anxiety; and safety<br><br>Secondary:<br>Not reported | Primary:<br>There was strong evidence for a reduction of pain (SMD, -0.28, 95% CI, -0.36 to -0.20; *P*<0.001), and improved sleep (SMD, -0.39, 95% CI, -0.48 to -0.39; *P*<0.001), but not for depressed mood (SMD, -0.12; 95% CI, -0.30 to 0.06; *P*=0.18).<br><br>The pooled NNT (all dosages) to achieve at least a 30% pain reduction was 8.5 (95% CI, 6.4 to 12.6; *P* value not reported).<br><br>There was strong evidence for a nonsubstantial reduction of fatigue (SMD, -0.16; 95% CI, -0.23 to -0.09; *P*<0.001) and of anxiety (SMD, -0.18; 95% CI, -0.27 to -0.10; *P*<0.001).<br><br>There was a significant overall difference between placebo and pregabalin 300, 450 and 600 mg/day regarding the dropout rates (*P*=0.007), treatment-related adverse events (*P*=0.005), dizziness (*P*=0.001), somnolence (*P*=0.04), weight gain (*P*=0.02), peripheral edema (*P*=0.03) and negative neurocognitive effects (*P*=0.003). Gabapentin compared to placebo had more dropouts due to adverse events (*P*=0.005), dizziness (*P*=0.01) and weight gain (*P*=0.01).<br><br>Secondary:<br>Not reported |


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| **Generalized Anxiety Disorder and Panic Disorders** | | | | |
| van Balkom et al[173]<br><br>Benzodiazepines<br><br>vs<br><br>antidepressants<br><br>vs<br><br>psychological panic management<br><br>vs<br><br>exposure in vivo<br><br>vs<br><br>placebo<br><br>Combinations of the above treatment arms were also investigated. | MA of 106 trials<br><br>Patients being treated for panic disorder with or without agoraphobia | N=5,011<br><br>Duration varied | Primary:<br>Panic, agoraphobia, depression and general anxiety<br><br>Secondary:<br>Not reported | Primary:<br>Antidepressants, psychological panic management and antidepressants/ exposure in vivo combination demonstrated significant improvement compared to a control condition in reduction of panic, agoraphobia, depression and anxiety.<br><br>High-potency benzodiazepines showed significant improvement to control condition only in panic, agoraphobia and anxiety.<br><br>There were no significant differences in treatments for panic disorder.<br><br>Antidepressant/exposure in vivo test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia.<br><br>A significantly greater improvement was noted in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety.<br><br>Secondary:<br>Not reported |
| **Migraines and Trigeminal Neuralgia** | | | | |
| Chronicle et al[174]<br><br>Acetazolamide (1 trial), carbamazepine (1 trial), clonazepam (1 trial), divalproex sodium (4 trials), gabapentin (2 trials), lamotrigine (1 trial), topiramate (6 | MA of 23 RCT<br><br>Adults with migraines | N=2,927<br><br>Treatment duration 4 to 24 weeks (mean 12.3 weeks) | Primary:<br>Assess efficacy and tolerability for preventing migraine attacks<br><br>Secondary:<br>Not reported | Primary:<br>Analysis of data from 10 trials (n=902) demonstrated that anticonvulsants as a class reduced migraine frequency by about 1.3 attacks per 28 days as compared to placebo (WMD, -1.31; 95% CI, -1.99 to -0.63; *P* value not reported).<br><br>Data from 13 trials (n=1,773) showed that anticonvulsants as a class more than doubled the number of patients for whom migraine frequency is reduced by 50% or more relative to placebo (RR, 2.25; 95% CI, 1.79 to 2.84; NNT, 3.9; 95% CI, 3.4 to 4.7; *P* value not reported). |


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| trials), sodium valproate (2 trials) and vigabatrin (1 trial) vs placebo<br><br>Divalproex sodium vs propranolol (1 trial)<br><br>Sodium valproate vs flunarizine* (1 trial)<br><br>Topiramate vs propranolol (1 trial)<br><br>Topiramate vs sodium valproate (1 trial) | | | | There was no significant difference in the number of patients treated with divalproex sodium vs propranolol, sodium valproate vs flunarizine, or topiramate 100 mg daily vs propranolol 160 mg daily for whom migraine frequency was reduced by 50% or more (*P* values not reported). The authors reported a slight but significant advantage for topiramate 50 mg daily over sodium valproate 400 mg daily with regards to posttreatment mean headache frequencies (*P* value not reported). It should be noted that the doses used in this study were not those used in routine clinical practice for the management of migraine.<br><br>Relatively few robust trials were available for agents other than sodium valproate/divalproex sodium and topiramate; gabapentin in particular needs further evaluation. Acetazolamide, clonazepam, lamotrigine and vigabatrin were not "superior" to placebo (one trial each).<br><br>For six trials of sodium valproate and divalproex sodium, NNH were the following: 15.0, asthenia; 16.3, dizziness; 7.0, nausea; 12.5, tremor and 18.8, weight gain. For three trials of topiramate (100 mg dose), NNH were the following: 11.7, anorexia; 31.2, fatigue; 16.6, memory problems; 23.1, nausea; 2.4, paresthesia; 15.3, taste disturbance and 11.1, weight loss.<br><br>Secondary:<br>Not reported |
| Wang et al[175] (abstract)<br><br>Topiramate<br><br>vs<br><br>carbamazepine | MA (6 RCTs)<br><br>Adults with trigeminal neuralgia | N=354<br><br>Duration not reported | Primary:<br>Not reported<br><br>Secondary:<br>Not reported | Primary:<br>Not reported<br><br>Secondary:<br>Not reported<br><br>Topiramate was more effective compared to carbamazepine after a treatment duration of twp months (RR, 1.20; 95% CI, 1.04 to 1.39; *P*= 0.01). No difference was found in the effectiveness rate after one month of treatment (RR, 1.00; 95% CI, 0.87 to 1.14; *P*= 0.94), in the remission rate after one month (RR, 1.06; 95% CI, 0.83 to 1.36; *P*= 0.63), and in the remission rate after two months (RR, 1.31; 95% CI, 0.96 to 1.80; *P*= 0.09). |


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| | | | | There was no difference in adverse events between the two treatments. |
| Afshari et al[176]<br><br>Topiramate 25 mg/day for 1 week, increasing to 50 mg/day for remainder of the study<br><br>vs<br><br>valproate 200 mg/day for 1 week, increasing to 400 mg/day for the remainder of the study<br><br>Patients were allowed to take acetaminophen, NSAIDS, ergotamine, triptans and opioids for acute attacks. | DB, PG, RCT<br><br>Patients 18 to 65 years of age with a diagnosis of migraine with or without aura according to IHS criteria, history of migraines for at least 6 months and having experienced at least 4 to 10 migraine attacks per month separated by a pain-free period of at least 48 hours; age at onset had to be less than 50 years | N=76 (random-ized)<br><br>N=56 (ITT population)<br><br>12 weeks | Primary: Migraine frequency, responder rate (≥50% reduction in 4-week migraine frequency), headache severity, duration of headache episode, associating symptoms, MIDAS score, HIT-6 score<br><br>Secondary: Safety | Primary:<br>A significant decrease in migraine frequency from baseline was reported at the end of the study in the topiramate group (6.8±2.0 compared to 3.0±1.9) and in the valproate group (7.5±1.9 compared to 3.6±1.8, *P*=0.0 for both groups compared to baseline). No significant difference was observed between treatment groups in migraine frequency (*P*=0.25).<br><br>No significant difference in responder rate was observed between the topiramate and valproate groups (71.6 and 64.3% respectively, *P* value not reported).<br><br>A significant decrease in headache severity from baseline was observed from baseline in both the topiramate (8.6±1.7 at baseline, decreasing to 6.7±2.0, 6.2±1.9 and 5.2±1.5 over three visits) and valproate groups (8.6±1.7 at baseline, decreasing to 6.7±1.5, 6.4±1.6 and 6.3±1.9 over three visits; *P*=0.0 for both groups compared to baseline). The reduction in the topiramate group was significantly greater than the reduction in the valproate group (*P*=0.027).<br><br>The duration of each headache episode decreased from 13±10.9 hours at baseline to 6±2.9 hours at the end of the study for topiramate patients and from 13.5±13.7 hours to 7.5±4.7 hours in the valproate group. This was significant for each group compared to baseline (*P*=0.0), though the difference between groups was not significant (*P*=0.15).<br><br>Associating symptoms including photophobia, phonophobia, nausea and vomiting were similar compared at baseline and at the end of the study. The symptoms were generally similar in each group at baseline, but at the end of the study, vomiting was reported in five and 13 patients in the topiramate and valproate groups respectively (*P*=0.04). No significant difference in other associating symptoms was observed.<br><br>MIDAS score decreased from 18.7±13.3 at baseline to 7.6±7.8 at the end of the study in the topiramate group and from 18.6±15.0 to 11.5±10.4 in the valproate group. This reduction from baseline in both groups was statistically significant (*P* |


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| | | | | value not reported), though the difference between groups was not significant (*P*=0.12).<br><br>HIT-6 score decreased from 64.5±4.7 at baseline to 49.7±8.1 at the end of the study in the topiramate group and from 65.8±5.0 to 57.2±6.9 in the valproate group. The differences were significant from baseline and the difference between treatment groups was statistically significant favoring topiramate (*P*=0.00).<br><br>Secondary:<br>One or more adverse events were reported in 64.3% of patients in the topiramate group and in 78.6% of patients in the valproate group. Adverse events were generally mild or moderate.<br><br>The most common adverse events reported with topiramate include decreased appetite, paresthesia, vertigo, fatigue, somnolence and nausea. The most common adverse events reported with valproate include increased appetite, hair loss, somnolence, tremor, vertigo and nausea.<br><br>All patients who experienced eye pain and decrease visual acuity were referred to an ophthalmologist and no specific problems were detected.<br><br>Patients in the topiramate group experience significant weight loss compared to baseline while patients in the valproate group experienced significant weight gain compared to baseline. |
| **Multiple Conditions** | | | | |
| Wiffen et al[177]<br><br>Carbamazepine<br><br>vs<br><br>placebo | MA (12 RCTs)<br><br>Patients with acute and chronic pain including patients with acute herpes zoster (1 trial), DPN (2 trials), PHN (1 trial), | N=404<br><br>Duration not reported | Primary:<br>Evaluate analgesic effectiveness and adverse effects of carbamazepine for acute and chronic pain | Primary:<br>There was no evidence that carbamazepine was effective for acute pain.<br><br>The NNT for any pain relief for carbamazepine in trigeminal neuralgia was 1.9 (95% CI, 1.4 to 2.8). For DPN there was insufficient data for an NNT to be calculated. The NNH for carbamazepine for minor harm was 3.7 (95% CI, 2.4 to 7.8). The NNH for major harm was not statistically significant for carbamazepine compared to placebo. *P* values were not reported.<br><br>Secondary: |


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| | post stroke pain (1 trial) and trigeminal neuralgia (7 trials) | | Secondary:<br>Not reported | Not reported |
| Moore et al[178]<br><br>Gabapentin 1,200 mg/day<br><br>vs<br><br>placebo, no treatment, or any other active comparator<br><br>Only results for PHN are reported (5 trials), when possible. | SR (29 RCTs)<br><br>Adult patients with 1 of 12 chronic pain conditions; 78% of patients had PHN, painful DPN, or mixed neuropathic pain | N=3,571<br><br>≥2 weeks | Primary:<br>Patient reported pain intensity reduction of ≥30 and ≥50%, PGIC<br><br>Secondary:<br>Any pain-related outcome indicating some improvement, withdrawals due to lack of efficacy, withdrawals due to adverse events, safety | Primary:<br>Pooled data from three trials (n=892) demonstrate that 33 and 20% of patients receiving gabapentin and placebo achieved ≥50% reduction in pain (risk ratio, 1.7; 95% CI, 1.3 to 2.2; NNT, 7.5; 95% CI, 5.2 to 14.0). In an AC comparing gabapentin to nortriptyline for nine weeks, 34 and 37% of patients achieved ≥50% reduction in pain.<br><br>Pooled data from two trials (n=563) demonstrate that 15 and 6% of patients receiving gabapentin and placebo reported a PGIC of very much improved (risk ratio, 2.7; 95% CI, 1.5 to 4.8; NNT, 11; 95% CI, 7.0 to 22.0).<br><br>Pooled data from four trials (n=1,121) demonstrate that 38 and 20% of patients receiving gabapentin and placebo reported a PGIC of much or very much improved (risk ratio, 1.9; 95% CI, 1.5 to 2.3; NNT, 5.5; 95% CI, 4.3 to 7.7).<br><br>Secondary:<br>Data on any pain-related outcome indicating some improvement and withdrawals due to lack of efficacy were not reported.<br><br>Seventeen trials of 3,022 patients reported an adverse event withdrawal, which occurred in 12% of patients receiving gabapentin ≥1,200 mg/day, and eight percent of patients receiving placebo (risk ratio, 1.4; 95% CI, 1.1 to 1.7; NNH, 32; 95% CI, 19 to 100). Seventeen trials of 3,063 patients reported on withdrawals of any cause, which occurred in 20% of patients receiving gabapentin ≥1,200 mg/day compared to 19% of patients receiving placebo (risk ratio, 1.1; 95% CI, 0.9 to 1.2).<br><br>Eleven trials of 2,356 patients reported on patients experiencing at least one adverse event, which occurred in 66 and 51% of patients receiving gabapentin ≥1,200 mg/day and placebo (risk ratio, 1.3; 95% CI, 1.2 to 1.4; NNH, 6.6; 95% CI, 5.3 to 9.0). Fourteen trials of 2,702 patients reported on patients experiencing |


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| | | | | serious adverse events, which occurred in 4.0 and 3.2% of patients receiving gabapentin ≥1,200 mg/day and placebo (risk ratio, 1.3; 95% CI, 0.9 to 2.0).<br><br>Somnolence, drowsiness, or sedation was reported as an adverse event in 16 trials of 2,800 patients, and it occurred in 16 and 5% of patients receiving gabapentin ≥1,200 mg/day and placebo (risk ratio, 3.2; 95% CI, 2.5 to 4.2; NNH, 9.2; 95% CI, 7.7 to 12.0). Peripheral oedema was reported as an adverse event in nine trials of 2,042 patients, and it occurred in 8.2 and 2.9% of patients (risk ratio, 3.4; 95% CI, 2.1 to 5.3; NNH, 19; 95% CI, 14 to 29). Ataxia or gait disturbances were reported as an adverse event in five trials of 544 patients, and occurred in 8.8 and 1.1% of patients (risk ratio, 4.5; 95% CI, 1.9 to 11.0; NNH, 13; 95% CI, 9 to 24). Deaths were rare in included trials. Four deaths occurred in PHN trials; two and one with placebo and gabapentin. |
| Gilron et al[179]<br><br>Placebo (lorazepam 0.3 mg, with a target daily dose of 1.6 mg) for 5 weeks<br><br>vs<br><br>morphine sustained-release 30 mg, with a target daily dose of 120 mg for 5 weeks<br><br>vs<br><br>gabapentin 400 mg, with a target daily dose of 3,200 mg for 5 weeks<br><br>vs | DB, PC (active), RCT, 4-way XO<br><br>Patient 18 to 89 years of age with painful diabetic neuropathy or PHN; patients with diabetic neuropathy had distal, symmetric, sensory diabetic polyneuropathy as determined on the basis of their medical history and either an unequivocal decrease in response to pinprick, temperature, or | N=57 (n=35 with diabetic neuropathy, n=22 with PHN)<br><br>20 weeks | Primary:<br>Mean daily pain intensity in patients receiving a maximum tolerated dose<br><br>Secondary:<br>Pain (SF-MPQ), maximal tolerated doses, mood, quality of life, safety | Primary:<br>Daily pain at maximal tolerated doses of trial drugs were as follows: 5.72±0.23 at baseline, 4.49±0.34 with placebo, 4.15±0.33 with gabapentin, 3.70±0.34 with morphine, and 3.06±0.33 with combination therapy ($P$<0.05 for combination vs placebo, gabapentin, and morphine). The analysis of the percent change in pain intensity indicated greater reduction of pain with the use of combination therapy compared to placebo (20.4% greater reduction; $P$=0.03), and other comparisons were not significant. The primary analysis showed no significant main effect of either sequence or treatment period, but the effects of drug treatment ($P$<0.001) and carryover ($P$=0.04) were significant.<br><br>Secondary:<br>Patients' total scores in response to SF-MPQ with combination therapy were lower compared to placebo ($P$<0.05), gabapentin ($P$<0.05), or morphine ($P$<0.05).<br><br>The maximal tolerated dose of morphine was 45.3±3.9 mg as a single agent, as compared to 34.4±2.6 mg with combination therapy ($P$<0.05). The maximal tolerated dose of gabapentin was 2,207±89 mg as a single agent, compared to 1,705±83 mg with combination therapy ($P$<0.05). The maximal tolerated dose of lorazepam was 1.38±0.05 mg.<br><br>Patients' scores for pain-related interference with mood with combination therapy |


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| gabapentin 300 mg plus morphine sustained-release 15 mg, with target daily doses of 2,400 and 60 mg for 5 weeks | vibration in both feet or bilaterally decreased or absent ankle-jerk reflexes; patients with PHN had had an eruption of herpes zoster rash not more recently than 6 months prior to enrollment | | | were lower compared to placebo (*P*<0.001) and morphine (*P*=0.03), and scores for pain-related interference with general activity, normal work, sleep, and enjoyment of life were significant when patients were receiving any active treatment compared to placebo (*P*<0.05 for all).<br><br>Based on SF-36 responses, combination therapy was associated with higher scores for vitality (*P*=0.007) and social functioning (*P*=0.004) compared to placebo, and higher scores compared to morphine for vitality (*P*=0.03) and social functioning (*P*=0.04). All active treatments were associated with significantly lower scores on the Beck Depression Inventory compared to placebo.<br><br>At maximal tolerated doses, combination therapy was associated with a higher frequency of constipation compared to gabapentin (*P*=0.006) but not morphine, and with a higher frequency of dry mouth compared to morphine (*P*=0.03) but not gabapentin. |
| Wiffen PJ et al[180]<br><br>Gabapentin<br><br>vs<br><br>placebo | MA (15 RCTs)<br><br>Patients with acute and chronic pain; trials included patients with acute post-operative pain (1 trial), DPN (7 trials), PHN (2 trials), cancer-related neuropathic pain (1 trial), phantom limb pain (1 trial), Guillain Barre syndrome (1 trial), spinal cord injury pain (1 | N=1,468<br><br>Duration not reported | Primary:<br>Evaluate analgesic effectiveness and adverse effects of gabapentin for acute and chronic pain<br><br>Secondary:<br>Not reported | Primary:<br>The study in acute post-operative pain (n=70) showed no benefit for gabapentin compared to placebo for pain at rest.<br><br>In chronic pain, the NNT with gabapentin for improvement in all trials with evaluable data was 4.3 (95% CI, 3.5 to 5.7), with 42% of participants improving on gabapentin compared to 19% on placebo. The NNH for adverse events leading to withdrawal from a trial was not significant with 14% of patients withdrawing from active arms compared to 10% in the placebo arms. The NNH for minor harm was 3.7 (95% CI, 2.4 to 5.4; *P* values were not reported.)<br><br>The NNT with gabapentin for effective pain relief in DPN was 2.9 (95% CI, 2.2 to 4.3) and for PHN 3.9 (95% CI, 3.0 to 5.7; *P* values were not reported).<br><br>Secondary:<br>Not reported |


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| | trial) and various neuropathic pains (1 trial) | | | |
| Chou et al[181]<br><br>Gabapentin vs placebo (6 trials)<br><br>Gabapentin vs tricyclic antidepressants (3 trials)<br><br>Tricyclic antidepressants vs placebo (9 trials). | MA (18 RCTs)<br><br>Patients with DPN or PHN | Total N=not reported (sample sizes n=12 to 334)<br><br>2 to 12 weeks | Primary:<br>Proportion of patients reporting significant pain relief (defined as ≥50% improvement in pain score compared to baseline or proportion reporting at least moderate or good improvement in pain or global efficacy on a categorical scale) and safety<br><br>Secondary:<br>Not reported | Primary:<br>In three head-to-head trials (n=120), there was no difference between gabapentin and tricyclic antidepressants (amitriptyline or nortriptyline) for achieving pain relief for DPN and PHN (RR, 0.99; 95% CI, 0.76 to 1.29; *P* value not reported). There was no difference between gabapentin vs tricyclic antidepressants in rates of withdrawal due to adverse events (RR, 0.27; 95% CI, 0.03 to 2.34; *P* value not reported), but only three cases were reported in two trials. None of the trials reported serious adverse events. There was no significant difference between gabapentin and tricyclic antidepressants in risk of dizziness, dry mouth or somnolence.<br><br>In indirect analyses, gabapentin was worse than tricyclic antidepressants for achieving pain relief (RR, 0.41; 95% CI, 0.23 to 0.74; *P* value not reported).<br><br>The discrepancy between direct and indirect analyses was statistically significant (*P*=0.008). PC tricyclic trials were conducted earlier than the gabapentin trials, reported lower placebo response rates, had more methodological shortcomings, and were associated with funnel plot asymmetry.<br><br>Secondary:<br>Not reported<br><br>The authors concluded that though direct evidence is limited, we found no difference in likelihood of achieving pain relief between gabapentin and tricyclic antidepressants for DPN and PHN. |
| Guan et al[182]<br><br>Pregabalin 150 to 600 mg/day<br><br>vs | DB, MC, PG, RCT<br><br>Chinese patients 18 to 75 years of age with a primary diagnosis | N=347<br><br>8 weeks | Primary:<br>Mean pain score (daily pain rating scale)<br><br>Secondary:<br>Daily Sleep | Primary:<br>Treatment with pregabalin resulted in significant improvement from 6.30±1.58 to 3.70±0.14 compared to treatment with placebo (6.40±1.53 to 4.30±0.19), with a least squares mean score difference of -0.6 (*P*=0.005). The duration-adjusted average change score was significantly better with pregabalin (*P*=0.001). A repeated measures analysis of daily pain rating scale scores during the eight weeks found significant efficacy for pregabalin beginning at two weeks (*P*<0.02) |


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| placebo | of painful DPN or PHN; patients with DPN had type 1 or 2 diabetes with $HbA_{1c}$ ≤11.0% and painful, distal, symmetrical, sensorimotor polyneuropathy between 1 to 5 years; patients with PHN had pain ≥3 months after recovery from herpes zoster skin rash, moderate to severe neuropathic pain over 4 consecutive days | | Interference Scale, SF-MPQ scale, PGIC or CGIC, safety | and continuing through week eight (with the exception of week four).<br><br>A response rate, defined as the proportion of patients with ≥30% reduction in daily pain rating scale, was significantly larger with pregabalin compared to placebo (64.0 vs 52.0%; *P*=0.041).<br><br>Secondary:<br>Treatment with pregabalin resulted in significant improvements in all secondary outcomes compared to treatment with placebo (Sleep interference score: least squares mean difference, -0.5; 95% CI, -0.93 to -0.07; *P*=0.023, SF-MPQ VAS score [0 to 100], -6.56; 95% CI, -11.65 to -1.47; *P*=0.012; SF-MPQ present pain intensity score, -0.35; 95% CI, -0.58 to -0.12; *P*=0.003; PGIC score (0 to 7), -0.33; 95% CI, -0.55 to -0.11; *P*=0.004; and CGIC score (0 to 7), -0.39; 95% CI, -0.63 to -0.16; *P*=0.001).<br><br>A total of 103 patients reported at least one adverse events with pregabalin compared to 41 patients receiving placebo (*P*=0.105), with the most common event being dizziness, occurring with an incidence of 11.2% among pregabalin-treated patients. Other adverse events were lethargy, somnolence, peripheral edema, and increased weight, which were common with both treatments and there were no differences between them. Most adverse events were mild in severity. No deaths occurred during the trial. Five serious adverse events occurred; two of which (chest pain and ischemic stroke) resulted in discontinuations. |
| Moon et al[183]<br><br>Pregabalin 150 to 600 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Outpatients ≥18 year of age with a diagnosis of peripheral neuropathic pain syndrome from DPN, PHN, or post-traumatic neuropathic pain | N=241<br><br>10 weeks | Primary:<br>End point (eight weeks) mean daily pain rating scale score (average of the last seven available scores)<br><br>Secondary:<br>Weekly mean | Primary:<br>Daily pain rating scale scores at end point was significantly lower with pregabalin compared to placebo (least squares mean difference, -0.50; 95% CI, -1.00 to 0.00; *P*=0.049). A numeric reduction in mean daily pain rating scale scores at end point was also reported for the evaluable pregabalin population compared to placebo; however, the comparison did not reach significant (least squares mean difference, -0.48; 95% CI, -1.00 to 0.05; *P* value not significant).<br><br>Secondary:<br>Using repeated-measures analysis of the weekly mean daily pain rating scale scores, the least squares mean daily pain rating scale scores for pregabalin were lower compared to placebo during weeks one to eight, with difference ranging from |


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| | (including postsurgical); patients diagnosed with DPN had painful distal, symmetrical, or sensorimotor polyneuropathy due to diabetes (type 1 or 2); $HbA_{1c}$ ≤11.0%; and documented symptoms of DPN for 1 to 5 years; patients with PHN had a diagnosis ≥3 months after healing from an acute herpes zoster skin rash; and patients with post-traumatic neuropathic pain had a diagnosis of chronic pain for ≥3 months | | daily pain rating scale score, the Duration Adjusted Average Change of adjust mean daily pain rating scale, the proportion of responders whose daily pain rating scale scores at end point were reduced ≥30 or ≥50% compared to baseline scores, Daily Sleep Interference Scale, EQ-5D, Medical Outcome Study, HADS, PGIC, CGIC, safety | -0.45 to -0.29. Significance was reached only for comparisons at week four (-0.43; 95% CI, -0.85 to -0.01; *P*=0.044) and week eight (-0.45; 95% CI, -0.88 to -0.02; *P*=0.039). The difference in least squares mean daily pain rating scale scores over the eight week DB period with pregabalin compared to placebo was -0.38 (95% CI, -0.75 to -0.01; *P*=0.042).<br><br>Mean change in Duration Adjusted Average Change scores from baseline to end point was -1.24±1.32 and -0.87±1.49 with pregabalin and placebo, a significant difference in favor of pregabalin (least squares mean difference, -0.37; 95% CI, -0.74 to -0.01; *P*=0.044).<br><br>A ≥50% reduction in daily pain rating scale score from baseline was reported by more patient receiving pregabalin compared to patients receiving placebo (26.1 vs 14.3%; *P*=0.041). In total, 42.2 and 35.1% of patients receiving pregabalin and placebo reported ≥30% reduction in daily pain rating scale scores from baseline to end point, a difference that did not reach significance (*P* value not reported).<br><br>Analyses resulting in a significant treatment difference between baseline and end point that favored pregabalin were the end point mean Medical Outcome Study sleep interference score (least squares mean difference, -0.65; *P*=0.018), Medical Outcome Study sleep disturbance (-5.62; *P*=0.034), Medical Outcome Study sleep quantity (-0.44; *P*=0.018), and the HADS-A score (-0.85; *P*=0.038). Medical Outcome Study somnolence favored placebo (4.71; *P*=0.046). No significant differences were found between treatments for Medical Outcome Study snoring score (favored placebo), Medical Outcome Study awakening short of breath or with a headache, Medical Outcome Study optimal sleep, Medical Outcome Study sleep adequacy, Medical Outcome Study overall sleep problems index, EQ-5D utility score or VAS, or HADS-D.<br><br>On the PGIC scale at week eight, 74.7% of patients receiving pregabalin and 72.0% of patients receiving placebo reported their condition improved (*P* value not significant). On the CGIC scale at week eight, 73.1 and 66.2% considered themselves improved (*P*=0.046).<br><br>The proportions of early discontinuations due to adverse events were 4.9% with |


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| | | | | pregabalin and 7.7% with placebo. Half of the patients receiving pregabalin (50.0%) and 35.9% of patients receiving placebo reported adverse events. Treatment-related adverse events were reported by 43.8 and 29.5% of patients receiving pregabalin and placebo. In patients receiving pregabalin, dizziness, somnolence, face edema, peripheral edema, and weight gain were the most frequently reported adverse events. |
| Vranken et al[184]<br><br>Pregabalin 150 mg, 1 to 4 capsules per day (flexible-dose regimen)<br><br>vs<br><br>placebo<br><br>Patients taking concomitant analgesic mediation were allowed to enter the trial if neuropathic pain treatment was on a stable regimen ≥90 days before screening.<br><br>Previous gabapentin had to be discontinued ≥3 days prior to trial entry. | DB, PC, RCT<br><br>Patients ≥18 years of age suffering from severe neuropathic pain (described as burning pain, paroxysmal episodes of shooting pain, or pain on light touch), VAS score >6 caused by lesion or dysfunction of in the CNS (brain or spinal cord injury), pain for ≥6 months that started after sustaining the lesion of dysfunction of the CNS, and LANSS questionnaire score >12 | N=40<br><br>4 weeks | Primary:<br>Pain score (VAS)<br><br>Secondary:<br>Pain Disability Index, EQ-5D, SF-36, safety | Primary:<br>Pain intensity scores before and after four weeks of treatment changed from 7.4±1.0 to 7.1±2.0 with placebo and from 7.6±0.8 to 5.1±2.9 with pregabalin. Pregabalin significantly decreased pain scores compared to placebo (difference, 2.18; 95% CI, 0.57 to 3.80; *P*=0.01). There was no difference in pain relief with pregabalin between patients with neuropathic pain due to brain injury and spinal cord injury.<br><br>Secondary:<br>There was no difference between treatments in Pain Disability Index scores.<br><br>Pregabalin significantly improved EQ-5D utility VAS scores compared to placebo (*P*<0.001).<br><br>Pregabalin significantly improved the bodily pain domain of the SF-36 compared to placebo (*P*=0.009). Pregabalin improved the remaining seven domains of the SF-36 compared to placebo, but differences did not reach significance.<br><br>Pregabalin was generally well tolerated and few adverse events were reported. The most frequently reported adverse events were CNS-related (dizziness, decreased intellectual performance, and somnolence). There was no difference in the incidence of adverse events between the two treatments. |


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| Siddall et al[185]<br><br>Pregabalin 150 to 600 mg/day, administered BID<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients ≥18 years of age with a spinal cord injury (paraplegia or tetraplegia) that had been incurred ≥1 year previously, in whom it had been nonprogressive for ≥6 months, and chronic (≥3 months or with relapses and remission ≥6 months that started after sustaining the spinal cord injury) central neuropathic pain | N=137<br><br>12 weeks | Primary:<br>Pain score (daily pain diaries)<br><br>Secondary:<br>Responder rates, SF-MPQ, sleep interference, mood, patient global measure of change, safety | Primary:<br>Pregabalin was superior to placebo on the primary efficacy variable, the between treatment group comparison of the endpoint pain score (difference, 1.53; 95% CI, 0.92 to 2.15; *P*<0.001). The change from baseline was negligible with placebo and was approximately two points with pregabalin. In the analysis of pain scores by week, scores were significantly lower with pregabalin as early as week one and remained so for the duration of the study. Results were similar when analyzed in patients with complete spinal lesions (difference, 1.79; 95% CI, 0.9 to 2.7; *P*<0.001), incomplete spinal lesions (difference, 1.25; 95% CI, 0.1 to 2.2; *P*<0.05), and in patients (n=9) with lesions at or below L2 (difference, 1.57; 95% CI, 0.9 to 2.2; *P*<0.001).<br><br>Secondary:<br>The proportion of patients with ≥30% reduction (42 vs 16; *P*=0.001) and ≥50% reduction (22 vs 8%; *P*<0.05) in pain score from baseline at endpoint were significantly higher with pregabalin compared to placebo. Based on the 30 and 50% responder rate the NNT was 3.9 and 7.1. At trial end, 15.9 and 43.3% of patients receiving pregabalin and placebo had severe pain.<br><br>Reduction from baseline to trial end on each of the five SF-MPQ scales was greater with pregabalin compared to placebo (*P*≤0.002 for all).<br><br>Reduction from baseline to trial end on sleep interference score was greater with pregabalin compared to placebo (*P*<0.001) and a significantly difference between the two treatments was observed at week one and maintained for the duration of the trial. Pregabalin was associated with a greater reduction in the overall sleep problems index compared to placebo at trial end (*P*=0.021). The improvement in sleep quantity (*P*<0.05) and reduction in sleep disturbance (*P*<0.001) on the Medical Outcomes Study-sleep scale were significantly greater with pregabalin compared to placebo. There were no differences between the two treatments on the other five subscales (snoring, awaken short of breath, adequacy, somnolence, proportions of patients with optimal sleep).<br><br>Reduction from baseline to trial end in the HADS anxiety score was greater with pregabalin compared to placebo (*P*=0.043), but there were no differences in the |


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| | | | | HADS depression score.<br><br>A higher proportion of patients receiving pregabalin rated themselves as improved compared to placebo (56.5 vs 21.5%) and the distribution of changes across the two treatments was in favor of pregabalin (*P*<0.001).<br><br>Treatment-emergent adverse events were reported in most patients with both treatments (96 vs 75%). Adverse events were generally mild or moderate in severity, with severe events being reported in 19 and 12% of patients. Overall, adverse events resulted in the discontinuation of 21 and 13% of patients. Somnolence and dizziness were the two most common adverse events. Somnolence resulted in the discontinuation of four patients receiving pregabalin compared to none of the patients receiving placebo. No patient discontinued treatment due to dizziness. The other most frequently reported adverse events were also generally mild or moderate, most were CNS-related, and they infrequently resulted in discontinuation. |
| Sharma et al[186]<br><br>Pregabalin 150, 300, or 600 mg/day<br><br>vs<br><br>placebo | RETRO (9 MC, PC, RCTs)<br><br>Adult patients with PHN or DPN; patients with PHN were adults with neuropathic pain for ≥6 months after healing of the herpes zoster rash, average daily pain score ≥4; patients with DPN were adults with type 1 or 2 diabetes, $HbA_{1c}$ ≤11.0%, painful | N=1,982<br><br>Duration not specified | Primary:<br>Time to onset for individual treatment arms that statistically separated from placebo<br><br>Secondary:<br>Not reported | Primary:<br>For DPN, five of the seven treatment arms successfully maintained efficacy at trial end point. In the PHN trials, six of seven treatment arms demonstrated efficacy at end point. Depending on the pregabalin treatment arm, the time to onset for significant pain relief vs placebo ranged from treatment day one to treatment day seven in DPN trials. The time to onset was treatment day one for four treatment arms and treatment day two for the remaining successful treatment arms in the PHN trials. Of the total 1,205 DPN or PHN patients treated with pregabalin, 760 (63%) experienced significant pain relief on day one or two. In the 11 treatment arms for which efficacy was maintained at trial end point, the daily dosage at time to onset was 300 mg for four of the five successful arms in DPN patients and 75 mg in the other successful arm. For two DPN trials in which the time to onset was on treatment days seven and four, the dose-escalation schedules were the most gradual, reaching 300 mg/day level on treatment day six or later. For the PHN treatment arms in which efficacy was seen on treatment days one or two, the dosage at time to onset was 75 mg in five arms and 150 mg in the remaining arm.<br><br>In the individual effect analysis, only patients who were responders (those with a 30% or greater reduction from baseline in mean pain score at end point) were |


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| | distal symmetric sensorimotor poly-neuoropathy, average daily pain score ≥4, and ≥40 mm score | | | considered. A one point or greater improvement in mean pain score was seen significantly earlier for pregabalin responders compared to patients receiving placebo (*P*<0.0001). Across all DPN trials, at least 25% of patients achieved a one point or greater improvement in mean pain score by day one (pregabalin at 300 mg/day) or two (pregabalin at 600 mg/day) compared to day four for placebo (150 mg/day; *P*=0.0232, 300 an 600 mg/day; *P*<0.0001). Across all PHN trials, at least 25% of patients receiving pregabalin achieved a one point or greater improvement in mean pain score by treatment day two, whereas this criterion for placebo patients was not met until day 18 (*P*<0.001). Half of the pregabalin treated patients showed a one point or greater improvement with only three to five days of treatment depending on the dose and type of neuropathic pain experienced.<br><br>Secondary:<br>Not reported |
| Semel et al[187]<br><br>Pregabalin 150, 300, or 600 mg/day<br><br>vs<br><br>placebo | Pooled analysis of 11 PC, RCTs<br><br>Adult patients with DPN or PHN; patients with DPN had a diagnosis of type 1 or 2 diabetes and a diagnosis of painful DPN for ≥3 months to ≥1 years; patients with PHN had pain present for ≥3 or >6 months after healing of herpes zoster rash | N=2,516<br><br>Duration not specified | Primary:<br>Endpoint average pain score on daily pain rating scale, daily pain rating scale score responders (≥30 and ≥50% reduction), daily pain rating scale score ≤3<br><br>Secondary:<br>Safety | Primary:<br>Comparable dose-related improvements in endpoint mean pain score were observed for pregabalin across age groups. Similar results were observed for improvements in endpoint mean sleep interference scores. Placebo-corrected least squares mean differences in pain with pregabalin between age groups were -0.155 (95% CI, -0.412 to 0.109; *P*=0.2497) for patients 18 to 64 years of age vs patients ≥75 years of age; -0.157 (95% CI, -0.419 to 0.105; *P*=0.2402) for patients 65 to 74 years of age vs patients ≥75 years of age; and 0.002 (95% CI, -0.215 to 0.218; *P*=0.9882) for patients 18 to 64 years of age vs patients 65 to 74 years.<br><br>Overall, there were significant differences among age groups in placebo patients with respect to pain relief (*P*=0.005), indicating a trend for decreasing placebo response with older age. Patients treated with placebo 18 to 64 years of age showed the largest improvement in average pain score (-1.47) compared to patients receiving placebo 65 to 74 years of age (-1.05; *P*=0.0112) or patients receiving placebo ≥75 years of age (-0.86; *P*=0.0031). No significant differences in placebo pain response were observed between those 65 to 74 years of age and those ≥75 years (*P*=0.3318).<br><br>Significant dose-dependent reductions in endpoint mean pain score on daily pain rating scale scores were observed for pregabalin vs placebo for pooled age groups |


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| | | | | (*P*<0.0001). For patients ≥75 years of age, significant improvements in endpoint mean pain score were observed for pregabalin vs placebo at al dosages (pregabalin 150 mg/day-placebo difference, -0.90 [*P*=0.0005]; 300 mg/day-placebo difference, -1.37 [*P*<0.0001]; and 600 mg/day-placebo difference, -1.81 [*P*<0.0001]). Significant differences in placebo-corrected endpoint mean pain were also observed for all pregabalin dosages in patients 65 to 74 years (-0.77 [*P*=0.0009], -1.28 [*P*<0.0001], and -1.71 [*P*<0.0001]). In patients 18 to 65 years, pregabalin provided significant improvements with 300 (-0.67; *P*=0.0003) and 600 mg/day (-1.08; *P*<0.0001), but not with 150 mg/day.<br><br>Generally, higher response rates were observed for ≥30% pain relief, ≥50% pain relief, and pain score at endpoint ≤3 with increasing pregabalin dose in all age groups. Moderately important improvements in pain (≥30% reduction) were observed in one-third to more than one-half of patients and substantial improvements in pain (≥50% reduction) in one-fifth to nearly one-half of patients who received 150 to 600 mg/day pregabalin across age groups regardless of the method of imputation. One-quarter to nearly one-half of patients had pain scores ≤3 at endpoint reflecting mild pain following treatment with 150 to 600 mg/day pregabalin.<br><br>Secondary:<br>The most common adverse events were dizziness, somnolence, peripheral edema, asthenia, dry mouth, weight gain, and infections. The RRs for these adverse events increased with pregabalin dose, but did not appear related to older age (≥65 years of age) or type of neuropathic pain. |
| Roth et al[188]<br><br>Pregabalin<br><br>vs<br><br>placebo | Review (9 trials)<br><br>Patients with DPN or PHN | N=not reported<br><br>Duration not specified | Primary:<br>Pain, sleep<br><br>Secondary:<br>Safety | Primary:<br>In patients with painful DPN, five RCTs assessed efficacy of pregabalin administered TID or BID. Treatment with pregabalin 300 or 600 mg/day significantly decreased endpoint mean pain scores compared to placebo. Doses of 75 and 150 mg/day (and 300 mg/day BID) did not produce significant pain relief vs placebo. Patients with PHN experienced significant reductions in mean pain scores with both TID and BID regimens across all pregabalin dosages (150 to 600 mg/day). One trial included patients with either DPN or PHN, and both flexible- (150 to 600 mg/day) and fixed-dose (600 mg/day) pregabalin significantly improved the mean pain score compared to placebo. |


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| | | | | Pregabalin 300 and 600 mg/day significantly decreased endpoint mean sleep interferences scores compared to placebo in patients with painful DPN, while lower doses of pregabalin did not differ from placebo. Significant improvements in sleep interference scores were seen as early as week one1. In patients with PHN, compared to placebo, 150, 300, and 600 mg/day of pregabalin significantly improved endpoint mean sleep interference scores and these effects were seen as early as week one.<br><br>Secondary:<br>The occurrence of adverse events appeared to be dose-related, with more frequent adverse events at higher doses. In patients with painful DPN, pregabalin was generally well tolerated, with a low rate of discontinuation due to adverse events (five to eight percent). The most frequently reported adverse events were CNS-related and of mild to moderate severity. Dizziness, somnolence, and peripheral edema were the most common adverse events reported and were common causes of discontinuation. |
| Moore et al[189]<br><br>Pregabalin<br><br>vs<br><br>placebo | MA of (25 RCTs)<br><br>Patients with acute and chronic pain; trials included patients with perioperative pain (6 trials), DPN (7 trials), PHN (5 trials), central neuropathic pain (2 trials), and fibromyalgia (5 trials) | N=7,652<br><br>24 hours acute pain, 4 to 26 weeks chronic pain | Primary:<br>Analgesic effectiveness and adverse effects of pregabalin for acute and chronic pain<br><br>Secondary:<br>Not reported | Primary:<br>There was no clear evidence of beneficial effects of pregabalin in established acute postoperative pain.<br><br>No studies evaluated pregabalin in chronic nociceptive pain, like arthritis.<br><br>Pregabalin at daily doses of 300, 450, and 600 mg was effective in patients with DPN, PHN, central neuropathic pain, and fibromyalgia. Pregabalin 150 mg daily was generally ineffective (*P* values not reported).<br><br>Efficacy was demonstrated for dichotomous outcomes equating to moderate or substantial pain relief, alongside lower rates for lack of efficacy discontinuations with increasing dose. The best (lowest) NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for pregabalin 600 mg daily compared to placebo were 5.0 (95% CI, 4.0 to 6.6) for DPN, 3.9 (95% CI, 3.1 to 5.1) for PHN, 5.6 (95% CI, 3.5 to 14) for central neuropathic pain, and 11.0 (95% CI, 7.1 to 21.0) for fibromyalgia (*P* values not reported). |


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| | | | | Higher rates of substantial benefit were found in DPN and PHN than in central neuropathic pain and fibromyalgia. For moderate and substantial benefit on any outcome, NNTs for the former were generally six and below for 300 and 600 mg daily; for fibromyalgia NNTs were much higher, and generally seven and above (*P* values not reported).<br><br>With pregabalin 600 mg/day, somnolence typically occurred in 15 to 25% of patients, and dizziness occurred in 27 to 46% of patients. Treatment was discontinued due to adverse events in 18 to 28% of patients. The proportion of patients reporting at least one adverse event was not affected by dose, nor was the number with a serious adverse event, which was not more than with placebo (*P* values not reported.)<br><br>Secondary:<br>Not reported |
| Freynhagen et al[190]<br><br>Pregabalin flexible-dose regimen of 150, 300, 450, and 600 mg/day with weekly dose escalation based on responses and tolerability<br><br>vs<br><br>pregabalin fixed-dose regimen of 300 mg/day for 1 week, followed by 600 mg/day for 11 weeks<br><br>vs | DB, MC, PC, PG, RCT<br><br>Patients with chronic PHN or painful DPN | N=338<br><br>12 weeks | Primary:<br>Pain score<br><br>Secondary:<br>Pain-related sleep interference, PGIC, adverse events | Primary:<br>Compared to placebo, both regimens of pregabalin improved pain symptoms ($P<0.002$ for both).<br><br>Secondary:<br>Both regimens of pregabalin significantly improved sleep interference ($P<0.001$ for both) and PGIC ($P<0.01$) compared to placebo.<br><br>Treatment-related adverse events occurred in 66.3% of the patients. The most common treatment-related adverse events were dizziness (4.8 vs 1.5%), peripheral edema (1.5 vs 0%), weight gain (0.7 vs 0%), and somnolence (1.8 vs 0%).<br><br>Rate of adverse events was higher in the fixed-dose group than the flexible-dose group (74.2 vs 68.8%; *P* value not reported) and more patients withdrew from treatment due to adverse events in the fixed-dose group (25 vs 17 vs 7.7% of placebo group; *P* values not reported). |


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| Xochilcal-Morales et al[191]<br><br>Pregabalin 150 to 600 mg/day | MC, OL, PRO<br><br>Patients ≥18 years of age diagnosed with neuropathic pain associated with DPN, PHN, chemotherapy-induced peripheral neuropathic pain, or HIV-related peripheral neuropathic pain; with a score ≥40 mm on a VAS and a daily pain rating score ≥4 throughout screening | N=121<br><br>12 weeks | Primary:<br>Change from baseline to end of treatment/ LOCF in weekly main pain score on daily pain rating scale<br><br>Secondary:<br>Pain, anxiety, sleep interference, treatment satisfaction, PGIC, CGIC, safety | Primary:<br>Pregabalin significantly reduced the weekly mean pain score on daily pain rating scale scores from baseline to end of treatment/LOCF (-3.8; 95% CI, -4.2 to -3.3; *P*<0.0001).<br><br>Secondary:<br>Reductions from baseline to end of treatment/least observation carried forward were observed for all secondary efficacy outcomes (*P*<0.0001). Pain and sleep interference were significantly improved compared to baseline across all weeks of the trial, as early as one week after initiation of pregabalin (*P*<0.0001).<br><br>The most commonly reported adverse events were somnolence, dizziness, weight gain, and peripheral oedema. Nine patients (7.4%) discontinued the trial because of the adverse events and 25 patients (20.7%) temporarily stopped or reduced their pregabalin dose because of adverse events. |
| **Postherpetic Neuralgia** | | | | |
| Rowbotham et al[192]<br><br>Gabapentin 3,600 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥18 years of age with pain present for >3 months after healing of a herpes zoster skin rash; pain intensity score ≥40 mm (on the | N=229<br><br>8 weeks | Primary:<br>Change in the average daily pain score<br><br>Secondary:<br>Average daily sleep scores, SF-MPQ, PGIC, CGIC, SF-36, POMS, safety | Primary:<br>The average daily pain score was significantly reduced at trial end with gabapentin (33.3% reduction) compared to placebo (7.7% reduction). At the end of eight weeks, gabapentin showed an average daily pain score of 4.2 (decrease of 2.1) compared to 6.0 with placebo (decrease of 0.5; *P*<0.001). This reduction was established at week two, with a further reduction at week four. At week eight, pain reduction was maintained at the week four level.<br><br>Secondary:<br>Gabapentin significantly improved average sleep rating scores compared to placebo (*P*<0.001). |


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| | 100 mm VAS of the SF-MPQ) at screening and randomization; average daily diary pain score ≥4 (0 to 10 scale) during baseline; and discontinuance of muscle relaxants, anticonvulsants, mexiletine, topical analgesics, and antiviral agents ≥2 weeks prior to screening | | | SF-MPQ scores were significantly improved for total pain (*P*<0.001), as well as sensory pain (*P*<0.001) and affective pain (*P*<0.001) with gabapentin compared to placebo. SF-MPQ ratings were significantly improved with gabapentin compared to placebo (*P*<0.01). This included a rating of 'no pain' at the final week in 16.0 and 8.8% of patients receiving gabapentin and placebo.<br><br>The PGIC questionnaire indicated that gabapentin provided valuable pain reduction for many patients. At trial end, 43.2 and 12.1% of patients receiving gabapentin and placebo reported their pain as 'much' or 'moderately' improved. The majority of patients receiving placebo reported no change in pain level (59.5%) compared to gabapentin (22.9%). The CGIC showed similar results.<br><br>On the SF-36, measures relating to physical functioning, role-physical, bodily pain, vitality, and mental health all showed gabapentin to be superior compared to placebo (*P*≤0.01 for all). Patients receiving gabapentin showed significantly greater improvement compared to patients receiving placebo in the POMS assessments of depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment, and total mood disturbance (*P*≤0.01 for all).<br><br>Minor adverse events deemed to be treatment-related were reported in 54.9 and 27.6% of patients receiving gabapentin and placebo. No serious adverse events were reported. One death occurred with placebo and was considered to be nontreatment-related. Overall, the most frequently reported adverse events with gabapentin were somnolence (27.4 vs 5.2%), dizziness (23.9 vs 5.2%), ataxia (7.1 vs 0%), peripheral edema (9.7 vs 3.4%), and infection (8.0 vs 2.6%). A total of 13.3 and 9.5% of patients receiving gabapentin and placebo withdrew from the trial due to an adverse event. |
| Rice et al[193]<br><br>Gabapentin 1,800 or 2,400 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥18 years of age with pain present for >3 months after healing of an | N=334<br><br>7 weeks | Primary:<br>Change in average daily pain diary score<br><br>Secondary:<br>Mean weekly sleep | Primary:<br>Change in average daily pain diary score showed significant improvements with gabapentin compared to placebo. The average score with placebo was 6.4 vs 5.3 (reduction of 15.7%), for gabapentin 1,800 mg/day was 6.5 vs 4.3 (reduction of 34.5%), and for gabapentin 2,400 mg/day was 6.5 vs 4.2 (reduction of 34.4%). The difference between placebo and gabapentin 1,800 mg/day was 18.8% (95% CI, 10.9 to 26.8; *P*<0.01). The difference between placebo and gabapentin 2,400 mg/day was 18.7% (95% CI, 10.7 to 26.7; *P*<0.01). Differences between |


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| | acute herpes zoster skin rash, and an average pain score ≥4 (11-point scale) | | interference score, SF-MPQ, CGIC, PGIC, SF-36, safety | gabapentin and placebo were significant from week one (1,200 mg/day) onward.<br><br>The proportion of patients showing a ≥50% reduction in mean pain score from baseline was significantly higher (*P*=0.001) with gabapentin 1,800 (32%) and 2,400 mg/day (34%) compared to placebo (14%).<br><br>Secondary:<br>Sleep interference diaries showed a similar pattern of improvement to the pain diary, with gabapentin showing greater improvement compared to placebo from week one onward. For the last week of treatment, the difference between placebo and gabapentin 1,800 mg/day was 0.9 (95% CI, 0.4 to 1.4; *P*<0.01). The difference between placebo and gabapentin 2,400 mg/day was 1.1 (95% CI, 0.7 to 1.6; *P*<0.01).<br><br>SF-MPQ showed improvements in all parameters during treatment, with greater improvements with gabapentin. The difference between gabapentin and placebo was significant (*P*<0.05) for the sensory score, total score, and VAS of pain during the previous week (2,400 mg/day only).<br><br>At trial end, 44 (*P*=0.002 vs placebo), 44 (*P*=0.001 vs placebo), and 19% of clinicians rated patients' conditions as 'very much improved' or 'much improved.<br><br>At trial end, 41 (*P*=0.003 vs placebo), 43 (*P*=0.005 vs placebo), and 23% of patients reported their condition as 'very much improved' or 'much improved.'<br><br>Patients receiving gabapentin experienced significantly greater improvements in mean score for the vitality scale of the SF-36 (P<0.05) compared to patients receiving placebo. Patients receiving gabapentin 1,800 mg/day showed significantly greater improvements in mean score for scales of bodily pain (*P*<0.01) and mental health (*P*<0.05) compared to patients receiving placebo.<br><br>Withdrawals due to adverse events were more common with both doses of gabapentin compared to placebo, and 38% of gabapentin withdrawals occurred within the first week, and 76% within the first three weeks. Dizziness (seven percent) and drowsiness (five to six percent) were the most common adverse |


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| | | | | events necessitating withdrawal among patients receiving gabapentin. There were five serious adverse events; one, three, and one with placebo, gabapentin 1,800 mg/day, and gabapentin 2,400 mg/day. All were considered nontreatment-related. |
| Skvarc et al[194]<br><br>Pregabalin 75 to 150 mg BID<br><br>vs<br><br>placebo | DB, PC, PRO, RCT<br><br>Outpatients 30 to 80 years of age who, despite naproxen use, had herpes zoster pain assessed ≥4 on a 0 to 10 point scale during the period between day 7 and 14 of acute disease | N=29<br><br>3 weeks | Primary:<br>Assessment of pain severity using the 11-point Likert scale<br><br>Secondary:<br>Patients' ratings of the severity of allodynia, hyperalgesia, and burning, prickling and tingling sensations, and their rating of quality of sleep and physical activity, safety | Primary:<br>The main pain score decreased from seven at the initial visit to two at the concluding visit with pregabalin; the decrease was similar (from seven to two) with placebo.<br><br>Secondary:<br>Allodynia scoring decreased from eight to 0.5 with pregabalin, and from five to zero with placebo. Pressure hyperalgesia scoring decreased from eight at the initial visit to zero at the concluding visit with pregabalin, and from six to zero with placebo. There were no significant differences between the two treatments with regard to allodynia or pressure hyperalgesia, nor with respect to other observations of pain quality: burning sensation, prickling sensation, electric shock sensation, heat hyperalgesia, and cold hyperalgesia.<br><br>There were no significant differences between the two treatments with regard to sleep and physical activity assessments.<br><br>The most common adverse events were dry mouth with an incidence of 65.5%; this was followed by tiredness (55.2%), dizziness (44.8%), somnolence (44.8%), vertigo (41.4%), constipation (20.7%), diplopia (17.2%), and flatulence (13.8%). Patients receiving pregabalin suffered more adverse events compared to patients receiving placebo (52 vs 36), but the only significant difference between the treatments was in relation to dizziness and somnolence. |
| Sabatowski et al[195]<br><br>Pregabalin 150 or 300 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients with PHN who did not respond to treatment with gabapentin ≥1,200 mg/day | N=238<br><br>8 weeks | Primary:<br>Pain score<br><br>Secondary:<br>Sleep interference, HRQoL as assessed by SF-36 Health | Primary:<br>Pregabalin 150 ($P$=0.0002) and 300 mg/day ($P$=0.0001) significantly improved mean pain scores compared to placebo.<br><br>Percentage of patients who had ≥50% decrease in mean pain scores was significantly higher in the pregabalin 150 and 300 mg/day groups compared to the placebo group (26 vs 28 vs 10%, respectively; $P$<0.05 for all).<br><br>Secondary: |


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| | | | Survey, adverse events | Pregabalin, at both doses, also significantly improved mean sleep interference scores, PGIC scores, and HRQoL compared to placebo (*P*<0.05 for all).<br><br>Adverse events that occurred in ≥10% of pregabalin-treated patients include dizziness, somnolence, peripheral edema, headache, and dry mouth. The adverse events appeared to be dose-related. |
| Dworkin et al[196]<br><br>Pregabalin 600 (if CrCl >60 mL/minute) or 300 mg/day (if CrCl 30 to 60 mL/minute)<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients with PHN | N=173<br><br>8 weeks | Primary:<br>Pain scores<br><br>Secondary:<br>Sleep interference, SF-MPQ, SF-36 Health Survey, POMS, PGIC, CGIC, adverse events | Primary:<br>Pregabalin-treated patients had greater decreases in pain compared to placebo-treated patients (pain score, 3.60 vs 5.29; *P*=0.0001).<br><br>Greater percentage of patients in the pregabalin than placebo groups experienced ≥50% decrease in pain (50 vs 20%, respectively; *P*<0.05).<br><br>Secondary:<br>Sleep, SF-MPQ scores, bodily pain and general health perception of the SF-36 Health Survey, POMS depression/dejection scale, PGIC, and CGIC were significantly improved with pregabalin when compared to placebo (*P*<0.05 for all).<br><br>No significant differences were observed between treatment arms in physical functioning, physical role limitations, social functioning, mental health, emotional role limitations, and vitality of the SF-36 Health Survey or other POMS scales.<br><br>Dizziness (28.1 vs 11.9%), somnolence (24.7 vs 7.1%), peripheral edema (19.1 vs 2.4%), amblyopia (11.2 vs 1.2%), and dry mouth (11.2 vs 2.4%) were the most frequently occurring adverse events compared to placebo. |
| Edelsberg et al[197]<br><br>Pregabalin (3 trials), capsaicin (2 trials), gabapentin (2 trials), amitriptyline (1 trial), nortriptyline (1 trial), morphine (1 trial), tramadol (1 trial), and divalproex sodium (1 | MA and SR (12 RCTs)<br><br>Patients with PHN | N=not specified<br><br>6 to 13 weeks | Primary:<br>Percentage reduction in pain intensity<br><br>Secondary:<br>RR of withdrawal due to lack of efficacy, RR of | Primary:<br>The difference in the percentage reduction in pain intensity varied from 13.8 (tramadol) to 42.4% (amitriptyline). All differences were significant.<br><br>Secondary:<br>The RR of withdrawal due to lack of efficacy varied from 0.26 (gabapentin) to 1.17 (amitriptyline), among drugs for which this outcome was reported. However, none of these RRs were significant.<br><br>RR of withdrawal due to adverse events ranged from 1.6 (divalproex sodium) to |


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| trial)<br><br>vs<br><br>placebo | | | withdrawal due to adverse events, safety | 8.4 (capsaicin); those for capsaicin (8.4), pregabalin (3.1), and gabapentin (1.9) were significant. RR of withdrawals due to adverse events was not reported for nortriptyline, morphine, or tramadol.<br><br>Agents and adverse events with RRs significantly different from those of placebo were gabapentin: dizziness (RR, 3.76; 95% CI, 2.27 to 6.22) and somnolence (RR, 4.06; 95%; 2.29 to 7.31); pregabalin: dizziness (RR, 2.49; 95% CI, 1.68 to 3.60), somnolence (RR, 3.18; 95% CI, 1.87 to 5.41), dry mouth (RR, 2.73; 95% CI, 1.12 to 6.63), and ataxia (RR, 11.70; 95% CI, 1.55 to 88.54); nortriptyline: dizziness (RR, 39.17; 95% CI, 2.49 to 616.66); and morphine: nausea (RR, 5.47; 95% CI, 2.03 to 14.76). RRs of individual adverse events were not reported for amitriptyline or divalproex sodium. |
| Ifuku et al[198]<br><br>Pregabalin<br><br>Without changing the frequency of dosing, gabapentin was substituted with pregabalin at one-sixth dosage of gabapentin.<br><br>After 2 weeks, the dosage was increased in patients who requested a dosage increase and if VAS pain score was ≥25 mm after substitution. | PRO<br><br>Patients with PHN who were being administered gabapentin, and whose pain had continued for 3 months or more after being infected with herpes zoster | N=32<br><br>Duration not specified | Primary:<br>VAS pain score<br><br>Secondary:<br>Safety | Primary:<br>During evaluation after two weeks, the VAS pain score was 46.9±22.5 mm; thus, no significant difference was observed in the score before and after the substitution (*P*>0.05). However, the score varied greatly among patients. Regarding changes in individual VAS pain scores, the score in the patients with most pain relief was -18 mm and in the patients with maximum pain exacerbation was 30 mm.<br><br>Twenty-two patients had increased dosage to improve the analgesic effect after the substitution. Although no significant difference was observed in VAS pain scores after substitution of gabapentin with pregabalin in the titration group (scores increased from 51.5±23.0 to 52.1±20.3 mm; *P*>0.05), regarding the judgment of the effect of action after the dosage increase, VAS pain scores significantly decreased from 52.1±20.3 to 35.5±21.2 mm (*P*<0.05).<br><br>Secondary:<br>Although no significant difference was observed in the number of patients with somnolence and dizziness before and after the substitution, the number of patients with peripheral edema increased significantly in the group where gabapentin was substituted with pregabalin (*P*<0.05). Serious adverse events interfering with daily life were not observed before and after the substitution. |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Ogawa et al[199] (abstract)<br><br>Pregabalin 150 to 600 mg/day | OL<br><br>Patients with PHN | N=126<br><br>52 weeks | Primary:<br>SF-MPQ<br><br>Secondary:<br>Safety | Primary:<br>SF-MPQ showed a decrease over time with treatment. The changes of VAS and present pain intensity at trial end were -28.3 mm and -1.1 score, respectively.<br><br>Secondary:<br>The commonly reported adverse events were dizziness, somnolence, peripheral edema, and weight gain, and most of them were mild to moderate in intensity. No new adverse events were observed during long-term administration compared to short-term administration (13 weeks). |

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, TID=three times daily, XR=extended-release
Study design abbreviations: AC=active-controlled, ANCOVA=analysis of covariance, CI=confidence interval, DB=double-blind, ES=extension study, HR=hazard ratio, ITT=intention to treat, LOCF=last observation carried forward, MA=meta-analysis, MC=multicenter, NI=noninferiority, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RETRO=retrospective, RCT=randomized-controlled trial, RR=relative risk, RRI=relative risk increase, RRR=relative risk reduction, SB=single-blind, SD=standard deviation, SMD=standardized mean differences, SR=systematic review, WMD=weighted mean difference, XO=cross-over
Miscellaneous abbreviations: ACTH=adrenocorticotropic hormone, ADAS-Cog=Alzheimer Disease Assessment Scale-Cognitive, AED=antiepileptic drug, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BPRS=Brief Psychiatric Rating Scale, CBC=complete blood count, CDRS=Children's Depression Rating Scale, CGI=Clinical Global Impression, CGI-BP=Clinical Global of Impression-Bipolar Version, CGIC=Clinical Global Impression of Change, CMAI=Cohen-Mansfield Agitation Inventory, CNS=central nervous system, CrCl=creatinine clearance, DPN=diabetic peripheral neuropathy, ECG=electrocardiogram, EEG=electroencephalogram, EQ-5D=Euro Quality of Life Assessment, GAF=Global Assessment of Functioning, HADS=Hospital Anxiety And Depression Scale, HARS=Hamilton Anxiety Rating Scale, $HbA_{1c}$=glycosylated hemoglobin, HIT-6=Headache Impact Test, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, IDS=Inventory of Depressive Symptoms, IHS=International Headache Society, ILAE=International League Against Epilepsy, LANSS=Leeds Assessment of Neuropathic Symptoms and Signs, LGS=Lennox-Gastaut Syndrome, LSSS=Liverpool Seizure Severity Scale, MDD=major depressive disorder, MIDAS=Migraine Disability Assessment score, MMSE=Mini Mental State Examination, MRS=Mania Rating Scale, NSAIDs=nonsteroidal anti-inflammatory drug, PGIC=Patient Global Impression of Change, PHN=postherpetic neuralgia, POMS=Profile of Mood States, QOLIE-31=Quality of Life in Epilepsy Scale-31, SF-36=Short Form 36, SF-HPQ=Short Form-McGill Pain Questionnaire, US=United States, VAS=visual analog scale, vEEG=video electroencephalogram, VNS=vagal nerve stimulator, YMRS=Young Mania Rating Scale


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## Special Populations

**Table 5a. Special Populations-Barbiturates**[1,48-50,56]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Phenobarbital | Dosage adjustment recommended in the elderly.<br><br>Dosage adjustment recommended in children. | Renal dosage adjustment recommended. | Hepatic dosage adjustment recommended; initial doses should be reduced.<br><br>Use caution. | D | Yes (% not reported); use with caution. |
| Primidone | No dosage adjustment required in the elderly.<br><br>Dose adjustment is required in pediatrics; dose depends on the patient's age and weight. | No dosage adjustment required. | No dosage adjustment required. | D | Yes (% not reported); use with caution. |

**Table 5b. Special Populations-Benzodiazepines**[1,25,28,45]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Clobazam | Dosage adjustment in elderly patients is required; an initial dose of 5 mg/day is recommended.<br><br>Safety and efficacy in children <2 years of age have not been established. | No dosage adjustment required in mild and moderate dysfunction.<br><br>Not studied in severe renal dysfunction. | Hepatic dosage adjustment required in mild to moderate dysfunction; an initial dose of 5 mg/day is recommended.<br><br>Not studied in severe hepatic dysfunction. | C | Yes; use with caution. |
| Clonazepam | Dosage adjustment required; decrease usual dose by 50%. | Use with caution. | Use with caution.<br><br>Contra-indicated with significant hepatic dysfunction. | D | Yes; do not administer to nursing women. |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | Dosage adjustment recommended in children.<br><br>Safety and efficacy for the treatment of panic disorder in patients <18 have not been established. | | | | |
| Diazepam | Dosage adjustment required; limit to the smallest effective amount to preclude the development of ataxia or over-sedation.<br><br>Safety and efficacy in children <6 months of age have not been established. | No dosage adjustment required. | Hepatic dosage adjustment required; decrease usual dose by 50%. | D | Yes; not Recomm-ended. |

**Table 5c. Special Populations-Hydantoins**[1,47,51-54]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Ethotoin | No dosage adjustment required in the elderly.<br><br>Dose adjustment is required in pediatrics; do not initiate with doses >750 mg/day. | No dosage adjustment required. | No dosage adjustment required. | D | Yes (% not reported); effects on a breast-feeding infant are unknown. |
| Phenytoin | No dosage adjustment required in the elderly.<br><br>Dose adjustment | No dosage adjustment required. | No dosage adjustment required. | D | Yes (% not reported); breast-feeding is not reco-mmended. |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | is required in pediatrics; dose depends on the patient's weight. | | | | |

**Table 5d. Special Populations-Succinimides**[1,24,33,34]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Ethosuximide | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children <3 years of age have not been established. | Use with extreme caution. | Use with extreme caution. | C | Yes (% not reported); the American Academy of Pediatrics classifies as compatible with breast-feeding. |
| Methsuximide | No dosage adjustment required.<br><br>No dosage adjustment required. | No dosage adjustment required. | No dosage adjustment required. | D | Unknown |

**Table 5e. Special Populations-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Carbamaz-epine | Use with caution in the elderly.<br><br>Dose adjustment is required in pediatrics; dose depends on the patient's age and weight. | No dosage adjustment required. | Use with caution. | D | Yes (% not reported); use with caution. |
| Divalproex | Start elderly patients at the lower end of the dosage range. | No dosage adjustment required. | Do not use in severe hepatic impairment. | D | Yes (1%-10%); the American Academy of |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | Safety and efficacy in children <10 years of age have not been established. | | | | Pediatrics classifies as usually compatible with breast-feeding. |
| Ezogabine | Dose adjustment is required; an initial dose of 50 mg TID and a maximum dose of 200 mg TID are recommended.<br><br>The safety and effectiveness in children <18 years of age have not been established. | Renal dose adjustment is required; for creatinine clearances <50 mL/minute or patients with end stage renal disease, an initial dose of 50 mg TID and a maximum dose of 250 mg TID are recommended. | Hepatic dosage adjustment is required; for moderate (Child-Pugh >7 to 9) dysfunction, an initial dose of 50 mg TID and a maximum dose of 250 mg TID are recommended; for severe (Child-Pugh >9) dysfunction, an initial dose of 50 mg TID and a maximum dose of 200 mg TID are recommended.<br><br>No dosage adjustment required in mild hepatic dysfunction. | C | Excretion through breast milk: unknown; use with caution. |
| Felbamate | Start elderly patients at the lower end of the dosage range.<br><br>Approved for use in children ages two to 14. | Dose adjustment is required. | No dosage adjustment required. | C | Yes (% not reported); effects on a breast-feeding infant are unknown. |
| Gabapentin | Dose adjustment may be required in the elderly; dose depends on renal function.<br><br>Safety and efficacy in children <3 years of age | Dose adjustment is required. | No dosage adjustment required. | C | Yes (% not reported); use with caution. |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | have not been established. | | | | |
| Lacosamide | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children <17 years of age have not been established. | Dose adjustment is required. | Not re-commended in severe hepatic impairment. | C | Unknown |
| Lamotrigine | Start elderly patients at the lower end of the dosage range.<br><br>Safety and efficacy of lamotrigine extended-release tablets in patients <13 years of age have not been established.<br><br>Efficacy in patients one to 24 months of age for the treatment of partial seizures was not demon-strated. | Dose adjustment may be required. | Dose adjustment may be required. | C | Yes (% not reported); breast-feeding is not reco-mmended. |
| Levetiracetam | No dosage adjustment required in the elderly.<br><br>Safety and efficacy of levetiracetam tablets and solution in children <4 years of age have not been established. | Dose adjustment is required. | No dosage adjustment required. | C | Yes (% not reported); effects on a breast-feeding infant are unknown. |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | Safety and efficacy of levetiracetam extended-release tablets in children <16 years of age have not been established. | | | | |
| Oxcarbaz-epine | Consider starting with 300 mg or 450 mg per day (ER only).<br><br>Approved for use in children >2 years of age (IR) and >6 years of age (ER). | Dose adjustment is required.<br><br>Renal dose adjustment is required; for creatinine clearances <30 mL/minute, an initial dose of 300 mg QD is recommended (ER). | Use caution in patients with severe hepatic impairment. | C | Yes (% not reported); effects on a breast-feeding infant are unknown. |
| Perampanel | Safety and efficacy in elderly patients have not been established.<br><br>Approved for use in children >12 years of age. | Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended. | Hepatic dose adjustment is required; a maximum dose of 6 mg in mild hepatic impairment or 4 mg in severe hepatic impairment is recommended.<br><br>Use in patients with severe hepatic impairment is not recommended. | C | Unknown |
| Pregabalin | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children have not been | Dose adjustment is required. | No dosage adjustment required. | C | Unknown |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | established. | | | | |
| Rufinamide | No dosage adjustment required in the elderly.<br><br>Safety and effectiveness in children <4 years of age have not been established. | No dosage adjustment required. | No dosage adjustment required. | C | Likely; (% not reported); potential for serious adverse reactions in exposed infants. |
| Tiagabine | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children <12 years of age have not been established. | No dosage adjustment required. | Dose adjustment may be required. | C | Unknown |
| Topiramate | Dose adjustment may be required in the elderly; dose depends on renal function.<br><br>Safety and efficacy in children <2 years of age for the capsule (sprinkle) and tablet and < 6 years of age for the extended-release capsule have not been established. | Dose adjustment is required. | Use with caution. | C | Unknown |
| Valproic acid | Start elderly patients at the lower end of the dosage range.<br><br>Approved for children age ≥10 years. | No dosage adjustment required. | Do not use in severe hepatic impairment. | D | Yes (1 to 10%); the American Academy of Pediatrics classifies as usually |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | | | | | compatible with breast-feeding. |
| Vigabatrin | Studies did not include sufficient numbers of patients aged ≥65 years to determine if they responded differently from younger patients.<br><br>Potential benefits must outweigh the potential risk of vision loss for use in children. | Dose adjustment is required. | No dosage adjustment required. | C | Yes (% not reported); breast-feeding is not reco-mmended. |
| Zonisamide | Start elderly patients at the lower end of the dosage range<br><br>Safety and efficacy in children <16 years of age have not been established. | Use with caution; do not use in patients with glomerular filtration rate <50 mL/minute. | Use caution in hepatic impairment. | C | Unknown |

ER=extended-release, IR=immediate-release, TID=three times a day

## Adverse Drug Events

**Table 6a. Adverse Drug Events (%)-Barbiturates**[1,48-50,56]

| Adverse Event(s) | Phenobarbital | Primidone |
|---|---|---|
| **Cardiovascular** | | |
| Bradycardia | √ | - |
| Hypotension | √ | - |
| Syncope | √ | - |
| **Central Nervous System** | | |
| Agitation | √ | - |
| Anxiety | - | - |
| Ataxia | √ | √ |
| Central nervous system depression | √ | - |
| Confusion | √ | - |
| Dizziness | √ | - |
| Drowsiness | - | √ |
| Emotional disturbances | - | √ |


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| Adverse Event(s) | Phenobarbital | Primidone |
|---|---|---|
| Hallucinations | √ | - |
| Hyperirritability | - | √ |
| Hyperkinesia | √ | - |
| Insomnia | √ | - |
| Nervousness | √ | - |
| Nightmares | √ | - |
| Psychiatric disturbance | √ | - |
| Somnolence | √ | - |
| Thinking abnormality | √ | - |
| **Dermatologic** | | |
| Exfoliative dermatitis | √ | - |
| Skin eruptions | - | √ |
| Stevens-Johnson syndrome | √ | - |
| Toxic epidermal necrolysis | √ | - |
| **Gastrointestinal** | | |
| Anorexia | - | √ |
| Constipation | √ | - |
| Nausea | √ | √ |
| Vomiting | √ | √ |
| **Genitourinary** | | |
| Sexual impotency | - | √ |
| **Hematologic** | | |
| Agranulocytosis | - | √ |
| Granulocytopenia | - | √ |
| Megaloblastic anemia | √ | √ |
| Red cell hypoplasia/aplasia | - | √ |
| **Respiratory** | | |
| Apnea | √ | - |
| Hypoventilation | √ | - |
| Respiratory depression | √ | - |
| **Other** | | |
| Double vision | - | √ |
| Fever | √ | - |
| Headache | √ | - |
| Hypersensitivity reactions | √ | - |
| Injection site reactions | √ | - |
| Liver damage | √ | - |
| Vertigo | - | √ |

-Event not reported.
√Percent not specified.

**Table 6b. Adverse Drug Events (%)-Benzodiazepines**[1,25,28,45]

| Adverse Events | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| **Cardiovascular** | | | |
| Bradycardia | - | - | √ |
| Cardiovascular collapse | - | - | √ |
| Hypotension | - | - | √ |
| Palpitations | - | √ | - |
| Syncope | - | - | √ |
| Vasodilation | - | - | 2 |
| **Central Nervous Systems** | | | |
| Abnormal eye movements | - | √ | - |


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| Adverse Events | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| Aphonia | - | √ | - |
| Ataxia | 5 | - | 3 |
| Choreiform movements | - | √ | - |
| Coma | - | √ | - |
| Convulsion | - | - | √ |
| Diplopia | - | √ | - |
| Dizziness | - | - | 3 |
| Drooling | 9 | - | - |
| Dysarthria | 3 | √ | √ |
| Dysdiadochokinesis | - | √ | - |
| Emotional liability | - | - | √ |
| Euphoria | - | - | 3 |
| “Glassy-eyed” appearance | - | √ | - |
| Headache | - | √ | 5 |
| Hemiparesis | - | √ | - |
| Hypotonia | - | √ | - |
| Incoordination | - | - | 3 |
| Lethargy | 10 | - | - |
| Nystagmus | - | √ | √ |
| Psychomotor hyperactivity | 4 | - | - |
| Sedation | 5 | - | - |
| Slurred speech | - | √ | √ |
| Somnolence | 22 | - | 23 |
| Somnolence or sedation | 26 | - | - |
| Speech disorder | - | - | √ |
| Thinking abnormal | - | - | √ |
| Tremor | - | √ | - |
| Vertigo | - | √ | √ |
| **Dermatologic** | | | |
| Ankle and facial edema | - | √ | - |
| Hair loss | - | √ | - |
| Hirsutism | - | √ | - |
| Rash | - | - | 3 |
| Skin rash | - | √ | - |
| **Gastrointestinal** | | | |
| Anorexia | - | √ | - |
| Coated tongue | - | √ | - |
| Constipation | 5 | √ | √ |
| Diarrhea | - | √ | 4 |
| Dry mouth | - | √ | - |
| Dysphagia | 2 | - | - |
| Encopresis | - | √ | - |
| Gastritis | - | √ | - |
| Increased appetite | - | √ | - |
| Nausea | - | √ | - |
| Sore gums | - | √ | - |
| Vomiting | 7 | - | - |
| **General Disorders/Administration Site Conditions** | | | |
| Fatigue | 5 | - | - |
| Irritability | 7 | - | - |
| Pyrexia | 13 | - | - |


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| Adverse Events | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| **Genitourinary** | | | |
| Dysuria | - | √ | - |
| Enuresis | - | √ | - |
| Nocturia | - | √ | - |
| Urinary retention | - | √ | √ |
| **Hematopoietic** | | | |
| Anemia | - | √ | - |
| Eosinophilia | - | √ | - |
| Leukopenia | - | √ | - |
| Neutropenia | - | - | √ |
| Thrombocytopenia | - | √ | - |
| **Hepatic** | | | |
| Hepatomegaly | - | √ | - |
| Jaundice | - | - | √ |
| **Infections and Infestations** | | | |
| Bronchitis | 2 | - | - |
| Pneumonia | 4 | - | - |
| Upper respiratory tract infection | 12 | - | - |
| Urinary tract infection | 4 | - | - |
| **Metabolism and Nutrition Disorders** | | | |
| Decreased appetite | 3 | - | - |
| Increased appetite | 3 | - | - |
| **Musculoskeletal** | | | |
| Muscle weakness | - | √ | - |
| Pains | - | √ | - |
| **Psychiatric Disorders** | | | |
| Aggression | 8 | - | - |
| Agitation | - | - | √ |
| Amnesia | - | √ | - |
| Confusion | - | √ | √ |
| Depression | - | √ | √ |
| Hallucinations | - | √ | - |
| Hysteria | - | √ | - |
| Increased libido | - | √ | √ |
| Insomnia | 5 | √ | - |
| Psychosis | - | √ | - |
| Respiratory | - | - | - |
| Suicidal attempt | - | √ | - |
| Cough | 5 | - | - |
| **Respiratory** | | | |
| Asthma | - | - | 2 |
| Chest congestion | - | √ | - |
| Hypersecretion in upper respiratory passages | - | √ | - |
| Respiratory depression | - | √ | - |
| Rhinorrhea | - | √ | - |
| Shortness of breath | - | √ | - |
| **Other** | | | |
| Asthenia | - | - | √ |
| Paradoxical reactions | - | √ | √ |
| Urticaria | - | - | √ |

√Percent not specified.
- Event not reported.


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**Table 6c. Adverse Drug Events (%)-Hydantoins**[1,47,51-54]

| Adverse Event | Ethotoin | Phenytoin |
|---|---|---|
| **Cardiovascular** | | |
| Chest pain | √ | - |
| Ventricular conduction depression | - | √ |
| Ventricular fibrillation | - | √ |
| **Central Nervous System** | | |
| Ataxia | √ | √ |
| Decreased coordination | - | √ |
| Dizziness | √ | √ |
| Dyskinesias | - | √ |
| Headache | √ | √ |
| Insomnia | √ | √ |
| Nystagmus | √ | √ |
| Mental confusion | - | √ |
| Motor twitching | - | √ |
| Slurred speech | - | √ |
| Transient nervousness | - | √ |
| **Connective Tissue System** | | |
| Coarsening of facial features | - | √ |
| Enlargement of lips | - | √ |
| Gingival hyperplasia | - | √ |
| Hypertrichosis | - | √ |
| Peyronie's disease | - | √ |
| **Dermatologic** | | |
| Bullous dermatitis | - | √ |
| Exfoliative dermatitis | - | √ |
| Lupus erythematosus | - | √ |
| Morbilliform rashes | - | √ |
| Purpuric dermatitis | - | √ |
| Rash | √ | - |
| Scarlatiniform rashes | - | √ |
| Stevens-Johnson syndrome | √ | √ |
| Toxic epidermal necrolysis | - | √ |
| **Gastrointestinal** | | |
| Constipation | - | √ |
| Diarrhea | √ | - |
| Nausea | √ | √ |
| Vomiting | √ | √ |
| **Hemopoietic** | | |
| Agranulocytosis | - | √ |
| Granulocytosis | - | √ |
| Leukopenia | - | √ |
| Lymphadenopathy | √ | √ |
| Macrocytosis anemia | - | √ |
| Megaloblastic anemia | - | √ |
| Pancytopenia with or without bone marrow suppression | - | √ |
| Thrombocytopenia | - | √ |
| **Immunologic** | | |
| Hypersensitivity syndrome | - | √ |
| Immunoglobulin abnormalities | - | √ |
| Periarteritis nodosa | - | √ |


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| Adverse Event | Ethotoin | Phenytoin |
|---|---|---|
| Systemic lupus erythematosus | √ | √ |
| **Other** | | |
| Double vision | √ | - |
| Fatigue | √ | - |
| Fever | √ | √ |
| Gum hypertrophy | √ | - |
| Liver damage | - | √ |
| Sensory peripheral polyneuropathy | - | √ |
| Taste perversion | - | 3.3 |
| Toxic hepatitis | - | √ |

√Percent not specified.
- Event not reported.

**Table 6d. Adverse Drug Events (%)-Succinimides**[1,24,33,34]

| Adverse Event(s) | Ethosuximide | Methsuximide |
|---|---|---|
| **Cardiovascular** | | |
| Hyperemia | - | √ |
| **Central Nervous System** | | |
| Aggressiveness | √ | √ |
| Ataxia | √ | √ |
| Auditory hallucinations | - | √ |
| Blurred vision | - | √ |
| Confusion | - | √ |
| Depression | - | √ |
| Dizziness | √ | √ |
| Drowsiness | √ | √ |
| Euphoria | √ | - |
| Fatigue | √ | - |
| Headache | √ | √ |
| Hiccups | √ | √ |
| Hyperactivity | √ | - |
| Hypochondriacal behavior | - | √ |
| Inability to concentrate | √ | - |
| Insomnia | - | √ |
| Instability | √ | √ |
| Irritability | - | √ |
| Lethargy | √ | - |
| Mental slowness | - | √ |
| Nervousness | - | √ |
| Night terrors | √ | - |
| Photophobia | - | √ |
| Psychosis | - | √ |
| Sleep disturbances | √ | - |
| Suicidal behavior/intentions | √ | √ |
| **Dermatologic** | | |
| Hirsutism | √ | - |
| Pruritic erythematosus rashes | √ | √ |
| Stevens-Johnson syndrome | √ | √ |
| Systemic lupus erythematosus | √ | - |
| Urticaria | √ | √ |
| **Gastrointestinal** | | |
| Abdominal pain | √ | √ |


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| Adverse Event(s) | Ethosuximide | Methsuximide |
|---|---|---|
| Anorexia | √ | √ |
| Constipation | - | √ |
| Cramps | √ | - |
| Diarrhea | √ | √ |
| Epigastric pain | √ | √ |
| Nausea | √ | √ |
| Vague gastric upset | √ | - |
| Vomiting | √ | √ |
| Weight loss | √ | √ |
| **Genitourinary** | | |
| Increased libido | √ | - |
| Microscopic hematuria | √ | √ |
| Proteinuria | - | √ |
| Vaginal bleeding | √ | - |
| **Hemopoietic** | | |
| Agranulocytosis | √ | - |
| Eosinophilia | √ | √ |
| Leukopenia | √ | √ |
| Monocytosis | - | √ |
| Pancytopenia with or without bone marrow suppression | √ | √ |
| **Other** | | |
| Gum hypertrophy | √ | - |
| Myopia | √ | - |
| Periorbital edema | - | √ |
| Swelling of the tongue | √ | - |

√Percent not specified.
- Event not reported.


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**Table 6e. Adverse Drug Events (%)-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cardiovascular** | | | | | | | | | | | | | | | | | |
| Angina pectoris | - | - | - | - | √ | - | - | - | - | - | - | √ | √ | √ | - | - | - |
| Atrial arrhythmia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Atrial fibrillation | - | - | - | √ | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Atrioventricular, block first degree | - | - | - | - | - | - | - | - | - | - | - | √ | - | 1 | - | - | - |
| Bradycardia | - | √ | - | √ | √ | - | - | - | √ | - | - | - | - | - | √ | - | √ |
| Bundle block right | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cardiac arrest | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cardiac failure | - | - | - | √ | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Cerebral hemorrhage | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Cerebral ischemia | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Chest pain | - | √ | - | √ | - | - | - | - | - | - | 1 to 4 | - | ≥1 | 1 to 4 | √ | 1 to 5 | √ |
| Congestive heart failure | √ | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Electrocardiogram abnormal | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Flushing | - | - | - | √ | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Gangrene | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Heart block | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Heart failure | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | √ |
| Hemorrhage | - | - | - | - | - | - | 2 | - | - | - | - | - | √ | - | - | - | - |
| Hypertension | √ | √ | - | √ | √ | - | √ | - | √ | - | - | - | √ | 1 to 2 | √ | - | √ |
| Hypotension | √ | - | - | √ | √ | - | - | - | 1 to 2 | - | √ | - | √ | √ | - | - | √ |
| Ischemic necrosis | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Myocardial infarct | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Palpitation | - | √ | - | √ | √ | √ | √ | - | √ | - | - | - | √ | - | √ | - | √ |
| Pericardial effusion | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Pericardial rub | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pericarditis | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Peripheral ischemia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Peripheral vascular disorder | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Phlebitis | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Postural hypotension | - | - | - | - | - | - | √ | - | √ | - | √ | - | √ | √ | - | - | - |
| Premature atrial contraction | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Pulmonary embolus | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Retinal vascular disorder | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| ST depressed | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Subventricular tachycardia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Syncope | √ | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | - | - | - | √ |
| Tachycardia | - | √ | - | √ | √ | - | √ | - | √ | - | - | - | √ | - | √ | - | √ |
| Thrombophlebitis | √ | - | - | √ | √ | - | - | - | - | - | √ | - | √ | - | - | - | √ |
| Torsades de pointes | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Vascular insufficiency | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Vasculitis | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Vasodilation | - | - | - | - | 1.1 | - | √ | - | - | - | - | - | 2 | - | - | - | - |
| Ventricular extrasystoles | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Ventricular fibrillation | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| **Central Nervous System** | | | | | | | | | | | | | | | | | |
| Abnormal coordination | √ | √ | 5 to 12 | - | 1.1 to 1.5 | 1 to 6 | 6 to 7 | - | 1 to 4 | <2 | 1 to 6 | 1.6 | ≥1 | 4 | √ | 7 to 16 | √ |
| Abnormal dreams | - | √ | - | - | √ | - | √ | - | - | - | √ | - | √ | - | √ | 1 to 5 | √ |
| Aggression | - | - | - | - | - | - | - | - | - | <3 | - | - | - | - | - | - | - |
| Agitation | √ | - | - | √ | √ | - | √ | 6 | 1 to 2 | - | √ | - | 1 | 3 | - | - | 9 |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amblyopia | - | √ | - | - | - | - | - | - | - | - | - | - | ≥1 to 4 | - | √ | - | - |
| Amnesia | - | 5 to 21 | <3 | - | 1.2 to 2.2 | - | √ | 2 | 1 to 5 | - | 1 to 6 | - | - | - | 5 to 21 | 5 to 7 | - |
| Anger | - | - | - | - | - | - | - | - | - | <3 | - | - | - | - | - | - | - |
| Anxiety | - | √ | 2 to 5 | 5.2 | √ | - | 4 | 2 | 5 to 7 | 2 to 4 | 2 | 3 | ≥1 | 4 to 10 | √ | 6 | 3 |
| Apathy | - | - | - | √ | √ | - | √ | - | √ | - | √ | - | √ | 1 | - | - | - |
| Aphasia | - | - | 1 to 7 | - | √ | - | √ | - | √ | - | √ | - | - | - | - | - | - |
| Apraxia | - | - | | - | √ | - | - | - | - | - | - | - | - | √ | - | - | - |
| Asthenia | - | 10 to 27 | 4 to 6 | √ | 5.7 | 2 to 4 | 8 | 1.3 to 15.0 | 1 to 6 | <2 | 2 to 7 | - | 20 to 23 | 4 to 6 | 10 to 27 | - | √ |
| Ataxia | - | - | - | - | 3.3 to 12.5 | 4 to 15 | 10 to 28 | 3 | 1 to 31 | 1 to 8 | 1 to 20 | 4.0 to 5.4 | 5 to 9 | 3 to 16 | - | - | 6 |
| Aura | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Balance disorder | - | - | - | - | - | - | - | - | - | <5 | - | - | - | - | - | - | - |
| Blurred vision | ✔ | 12 | 2 to 10 | - | - | 2 to 16 | 4 to 16 | - | - | 1 to 4 | 1 to 12 | ≥5 | - | - | 12 | 13 to 16 | - |
| Central nervous system neoplasm | - | - | - | - | √ | - | ✔ | - | - | - | - | - | √ | - | - | - | - |
| Cerebellar syndrome | - | - | - | - | √ | √ | - | - | - | - | √ | - | - | √ | - | - | - |
| Cerebral edema | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cerebrovascular accident | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Cerebrovascular disorder | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Choreoathetosis | - | - | - | √ | √ | - | √ | - | - | - | - | - | √ | - | - | - | - |
| Circumoral paresthesia | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | √ |
| Cognitive disorder | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cogwheel rigidity | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Coma | - | - | - | √ | - | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Concentration impaired | - | - | - | √ | - | - | 2 | - | 1 to 2 | - | - | - | - | - | - | - | - |
| Confusion | √ | √ | 4 to 16 | √ | √ | √ | √ | 2 | 1 to 7 | <2 | 1 to 7 | - | 5 | 3 to 4 | √ | 5 to 6 | 6 |
| Convulsion | - | - | - | - | - | - | 2 to 3 | 3 | 1 to 5 | - | - | ≥5 | - | - | - | - | √ |
| Cranial injury | - | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | - | - | - | - |
| Delirium | - | - | - | - | - | - | √ | - | √ | - | √ | - | - | - | - | - | - |
| Delusions | - | - | - | √ | - | - | √ | - | √ | - | √ | - | √ | - | - | - | - |
| Depersonalization | - | - | - | - | √ | - | √ | - | - | - | √ | - | √ | 5 to 9 | - | - | - |
| Depression | √ | 4 to 5 | - | - | 1.8 | 2 | 4 | 3 to 5 | - | - | 2 | - | 3 to 7 | 5 to 9 | 4 to 5 | 6 to 14 | 6 |
| Difficulty with memory | - | - | - | - | - | - | - | - | - | - | - | - | 4 | - | - | - | - |
| Difficulty with verbal expressions | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 2 |
| Disorientation | - | - | <5 | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | - | - |
| Disturbance in attention | - | - | 6 to 7 | - | - | √ | - | - | - | - | 4 to 6 | 3 | 6 to 14 | 4 to 9 | - | 9 | 6 |
| Dizziness | √ | 4 to 25 | 15 to 32 | - | 2.5 to 28.0 | 16 to 53 | 7 to 54 | 1.4 to 9.0 | 6 to 49 | 9 to 43 | 5 to 45 | 2.7 to 19.0 | 27 to 28 | 13 to 25 | 4 to 25 | 24 to 26 | 13 |
| Double vision | √ | 16 | - | 3.4 | 1.2 to 5.9 | 6 to 16 | 5 to 49 | 2 | 1 to 40 | - | 2 to 12 | ≥5 | ≥1 | 10 | 16 | 7 to 16 | 6 |
| Dysarthria | - | - | 2 to 8 | √ | 2.4 | √ | √ | - | - | <4 | √ | - | √ | - | - | √ | √ |
| Dysautonomia | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Dyskinesia | - | - | - | √ | - | - | √ | - | - | - | √ | - | - | √ | - | - | √ |
| Dysmetria | - | - | - | - | - | - | - | - | 1 to 3 | - | - | - | - | - | - | - | - |
| Dysphonia | - | - | - | - | - | - | - | - | √ | - | - | - | - | √ | - | - | - |
| Dystonia | - | - | - | √ | √ | - | √ | - | √ | - | √ | - | √ | √ | - | √ | √ |
| Electroencephalogram | - | - | - | - | - | - | - | - | 2 | - | - | - | - | √ | - | - | - |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| abnormal | | | | | | | | | | | | | | | | | |
| Emotional liability | - | √ | - | - | 4.2 | - | 4 | 2 to 6 | 2 to 8 | - | - | - | 3 | 3 | √ | - | - |
| Encephalopathy | - | - | - | √ | √ | - | - | - | - | - | √ | - | √ | √ | - | √ | √ |
| Euphoria | - | - | - | √ | √ | - | √ | - | √ | <2 | 2 to 7 | - | √ | - | - | - | √ |
| Extrapyramidal symptoms | - | - | - | √ | - | - | √ | - | √ | - | √ | - | - | - | - | - | - |
| Facial paralysis | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Fatigue | √ | - | 13 to 16 | 6.9 | 3.4 to 11.0 | 7 to 15 | 8 | 10 | 5 to 21 | 5 to 12 | 1 to 8 | 9.5 to 16.0 | - | 11 to 30 | - | 23 to 40 | 8 |
| Gait disturbances | - | √ | 2 to 6 | - | 1.5 | <1 to 4 | 4 | - | 3 to 17 | <4 | 1 to 8 | 1.4 to 3.0 | 3 to 5 | 3 | √ | 6 to 12 | √ |
| Guillain-Barre syndrome | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Hallucination | √ | √ | √ | √ | √ | - | √ | - | - | - | √ | - | √ | - | √ | - | - |
| Headache | √ | 31 | - | 6.9 | 3.3 | 11 to 14 | 29 | 14 | 10 to 32 | 11 to 13 | 5 to 14 | >10 | ≥1 | - | 31 | 26 to 33 | 10 |
| Hemiplegia | - | - | - | - | √ | - | √ | - | √ | - | - | - | √ | - | - | - | - |
| Hostility | - | √ | - | - | 7.6 | - | √ | 2 to 12 | - | - | √ | - | 2 to 5 | - | √ | - | - |
| Hypalgesia | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Hyperalgesia | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Hyperesthesia | - | - | - | - | √ | - | √ | - | - | - | √ | - | √ | - | - | - | √ |
| Hyperkinesia | - | - | - | - | √ | - | √ | - | √ | - | - | - | √ | 5 | - | - | √ |
| Hypersomnia | - | - | - | - | - | - | - | - | - | <3 | - | - | - | - | - | - | - |
| Hypertonia | - | - | - | - | - | - | √ | - | - | - | √ | - | √ | 3 | - | - | √ |
| Hypoesthesia | - | - | - | - | - | √ | - | - | √ | <3 | 2 to 3 | - | - | 2 to 5 | - | - | - |
| Hypokinesia | - | - | - | - | 2.5 | - | √ | - | √ | - | √ | - | √ | - | - | - | √ |
| Hypotonia | - | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | - | - | √ | √ |
| Hysteria | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - | - | - |
| Insomnia | - | 9 to | - | 8.6 | √ | - | 6 to | - | 2 to 6 | - | - | - | 5 to 6 | 8 to 9 | 9 to | - | 6 |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 15 | | | | | 10 | | | | | | | | 15 | | |
| Intracranial hypertension | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Irritability | - | - | - | - | - | √ | 3 | 7* | - | 4 to 12 | - | - | √ | - | - | 7 to 23 | 9 |
| Lack of energy | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | 4 to 7 | - |
| Language problems | - | - | - | - | - | - | - | - | - | - | - | - | 2 | - | - | - | - |
| Lethargy | - | - | - | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | - | - |
| Light headedness | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Manic reaction | - | - | - | √ | √ | - | - | - | √ | - | √ | - | - | - | - | - | - |
| Memory impairment | - | - | 3 to 9 | - | - | 1 to 6 | √ | - | - | <2 | 1 to 4 | - | - | 5 to 13 | - | 7 to 16 | 6 |
| Mental slowing | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 4 |
| Migraine | - | - | - | √ | √ | - | √ | - | √ | - | - | - | √ | √ | - | - | - |
| Mood altered | - | - | - | - | - | √ | - | - | - | <2 | - | - | - | - | - | - | - |
| Movement disorder | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - | - | √ |
| Myoclonus | - | - | √ | - | √ | - | √ | - | - | - | 1 to 4 | - | √ | - | - | - | √ |
| Nervousness | - | 7 to 11 | - | - | 2.4 | - | 2 | 1.7 to 10.0 | 2 to 7 | - | 1 | - | 10 to 14 | 4 to 19 | 7 to 11 | 2 to 5 | 2 |
| Neuralgia | - | - | - | - | - | - | √ | - | √ | - | √ | - | - | - | - | - | - |
| Neuritis | - | - | - | √ | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Neurosis | - | - | - | - | - | - | √ | - | - | - | - | - | √ | 1 | - | - | - |
| Nystagmus | - | 1 to 8 | - | √ | 8.3 | 2 to 10 | - | - | 1 to 26 | - | √ | ≥5 | 2 | 10 | 1 to 8 | 13 to 19 | 4 |
| Oculogyric crisis | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | √ |
| Paralysis | - | - | - | √ | - | - | √ | - | √ | - | - | - | √ | - | - | - | - |
| Paranoid reaction | - | - | - | √ | √ | - | √ | - | √ | - | √ | - | √ | - | - | - | - |
| Paresthesia | √ | √ | 2 to 5 | - | √ | √ | - | 2 | - | <2 | √ | - | 4 | 1 to 40 | √ | 2 to 7 | 4 |
| Peripheral neuritis | √ | - | - | - | - | - | √ | - | - | - | √ | - | √ | - | - | - | √ |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Personality disorder | - | √ | - | - | √ | - | √ | 8 | √ | - | √ | - | √ | - | √ | - | - |
| Psychological disturbance | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Psychomotor hyperactivity | - | - | - | - | - | - | - | - | - | - | - | 3 | - | - | - | - | - |
| Psychosis | - | √ | <2 | √ | √ | - | √ | - | √ | - | - | - | √ | - | √ | √ | - |
| Psychotic depression | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Reflexes decreased | - | - | - | - | √ | - | - | - | √ | - | - | - | √ | 2 | - | 4 to 5 | - |
| Reflexes increased | - | - | - | - | √ | - | - | 2 | √ | - | - | - | √ | - | - | 2 to 4 | √ |
| Respiratory depression | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Schizophrenic reaction | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | 2 |
| Sleep disorder | - | - | - | - | - | - | √ | - | √ | - | - | - | - | - | - | - | - |
| Somnolence | - | 19 to 30 | 15 to 27 | - | 8.4 to 21.4 | 5 to 8 | 9 to 17 | 4.4 to 23.0 | 5 to 36 | 7 to 18 | 3 to 28 | ≥5.0 to 24.3 | 18 to 19 | 9 to 29 | 19 to 30 | 22 to 26 | 17 |
| Speech disorder | √ | √* | - | - | √ | - | 3 | - | 1 to 3 | - | 1 to 7 | - | 4 | 13 | √ | - | 5 |
| Status epilepticus | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | 2 to 5 | - |
| Stupor | - | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | 2 | - | - | - |
| Suicide attempt | - | - | - | √ | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Thinking abnormal | - | 6 | - | - | 1.7 to 2.7 | - | 3 | - | 2 to 4 | - | 1 to 9 | - | √ | - | 6 | 3 to 7 | - |
| Tiredness | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 7 |
| Torticollis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Tremor | - | 19 to 57 | 3 to 12 | - | 6.8 | 4 to 12 | 4 to 10 | - | 3 to 16 | - | 1 to 11 | ≥5 | 9 to 21 | 9 | 19 to 57 | 15 to 16 | √ |
| Trismus | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Twitching | - | - | - | - | 1.3 | - | - | - | - | - | 1 to 5 | - | ≥1 | - | - | - | √ |
| Vertigo | - | √ | - | - | √ | 3 to 5 | 2 | 3 | 3 to 15 | 4 to 5 | 1 to 4 | 3 | √ | 1 | √ | 2 to 5 | √ |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dermatologic** | | | | | | | | | | | | | | | | | |
| Abnormal body odor | - | - | - | √ | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Abscess | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Acne | - | - | - | 3.4 | √ | - | √ | - | 1 to 2 | - | - | - | ≥1 | 2 to 3 | - | - | √ |
| Alopecia | √ | 6 to 24 | - | √ | √ | - | √ | - | √ | - | √ | - | √ | 2 to 5 | 6 to 24 | - | √ |
| Angioedema | - | - | - | - | - | - | √ | - | √ | - | √ | - | - | - | - | - | - |
| Bullous eruption | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Contact dermatitis | - | - | - | - | - | - | - | - | ✔ | - | - | - | √ | - | - | - | - |
| Cyst | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Desquamation | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Dry skin | - | √ | - | - | √ | - | - | - | - | - | √ | - | √ | - | √ | - | - |
| Eczema | - | - | - | - | √ | - | 2 | - | √ | - | √ | - | √ | 1 | - | - | √ |
| Erythema | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Exfoliative dermatitis | √ | - | - | - | - | - | √ | - | - | - | √ | - | √ | - | - | - | - |
| Folliculitis | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Fungal dermatitis | - | - | - | - | √ | - | √ | - | - | - | - | - | - | - | - | - | - |
| Furunculosis | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Heat rash | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Herpes simplex | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Herpes zoster | - | - | - | - | √ | - | √ | - | - | - | - | - | - | - | - | - | - |
| Hirsutism | √† | - | - | - | √ | - | √ | - | - | - | √ | - | √ | - | - | - | √ |
| Lichenoid dermatitis | - | - | - | √ | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Maculopapular rash | - | - | - | - | √ | - | √ | - | √ | - | - | - | √ | - | - | √ | √ |
| Melanosis | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Nail disorder | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Petechial rash | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Pruritus | √ | √ | - | √ | 1.3 | 2 to 3 | 2 to 3 | 2 | - | - | √ | 3 | 2 | 1 to 9 | √ | √ | √ |
| Psoriasis | - | - | - | - | √ | - | - | - | √ | - | - | - | √ | 2 | - | - | - |
| Purpuric rash | √ | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pustular rash | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | ✓ |
| Rash | - | 6 | - | 3.4 | 1.2 | - | 7 to 14 | - | 2 to 4 | - | - | 4 | 5 | 1 to 4 | 6 | 4 to 5 | 3 |
| Skin atrophy | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Skin benign neoplasm | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Skin carcinoma | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Skin discoloration | √ | - | - | - | √ | - | √ | 2 | - | - | - | - | √ | 1 | - | - | - |
| Skin necrosis | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Skin nodules | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Skin ulcer | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Stevens-Johnson syndrome | √ | √ | - | √ | - | - | √ | - | √ | - | √ | - | - | - | √ | - | - |
| Subcutaneous nodule | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Subcutaneous nodule | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Sweating | - | - | - | √ | √ | - | - | - | 3 | - | - | - | √ | 1 | - | - | √ |
| Toxic epidermal necrolysis | √ | √ | - | √ | - | - | - | - | √ | - | - | - | - | - | √ | - | - |
| Urticaria | √ | - | - | √ | √ | - | √ | - | √ | - | √ | - | √ | √ | - | - | √ |
| Vesiculobullous rash | - | - | - | - | √ | - | √ | 2 | - | - | √ | - | √ | - | - | - | √ |
| **Endocrine System** | | | | | | | | | | | | | | | | | |
| Cushingoid appearance | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Diabetes mellitus | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Goiter | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - | - | - |
| Hyperthyroidism | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Hypoestrogen | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Hypothyroidism | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - | - | - |
| Ovarian failure | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| **Gastrointestinal** | | | | | | | | | | | | | | | | | |
| Abdominal distention | - | - | - | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | 2 | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abdominal pain | √ | 9 to 23 | - | - | 2.7 | - | 5 to 10 | - | 3 to 13 | - | √ | - | 7 | 5 to 7 | 9 to 23 | 2 to 3 | 6 |
| Abdominal pain upper | - | - | - | - | - | - | - | - | - | - | - | 3 | - | - | - | 5 | - |
| Abnormal stools | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Anorexia | √ | 4 to 12 | - | - | √ | - | 2 | 3 to 13 | 5 to 3 | - | - | - | ≥1 | 9 to 15 | 4 to 12 | - | 13 |
| Aphthous stomatitis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Cholangitis | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Cholecystitis | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | √ |
| Cholelithiasis | - | - | - | - | √ | - | - | - | √ | - | √ | - | √ | - | - | - | √ |
| Cholestatic jaundice | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Colitis | - | - | - | - | √ | - | - | - | √ | - | √ | - | - | - | - | - | √ |
| Constipation | √ | √ | 1 to 5 | 6.9 | 1.5 to 3.9 | √ | 4 to 5 | 3 | 1 to 6 | 2 to 3 | 2 to 7 | 3 | ≥1 | 1 to 5 | √ | 5 to 8 | 2 |
| Decreased appetite | - | - | - | - | - | - | - | - | - | - | - | 5 | - | - | - | - | - |
| Diarrhea | √ | 13 to 23 | - | 5.2 | 5.7 | 3 to 5 | 6 to 11 | 8 | 2 to 7 | - | - | - | 7 | 2 to 11 | 13 to 23 | 10 to 6 | 5 |
| Duodenitis | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Dyspepsia | - | 8 to 11 | 2 to 3 | 8.6 | 2.2 | √ | 2 to 7 | - | 1 to 6 | - | - | 3 | ≥1 | 2 to 7 | 8 to 11 | 4 to 5 | 3 |
| Dysphagia | - | - | <3 | √ | √ | - | √ | - | √ | - | √ | - | √ | 1 | - | - | √ |
| Enteritis | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Eructation | - | √ | - | - | √ | - | √ | - | √ | - | - | - | √ | - | √ | - | - |
| Esophageal ulcer | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Esophagitis | - | - | - | √ | √ | - | - | - | √ | - | √ | - | √ | √ | - | √ | √ |
| Fecal incontinence | - | √‡ | - | - | √ | - | - | - | - | - | - | - | √ | - | √ | - | √ |
| Flatulence | - | √ | - | √ | 2.1 | - | √ | - | √ | - | 1 to 3 | - | ≥1 | 1 | √ | - | √ |
| Gastritis | - | - | - | √ | √ | - | √ | - | 1 to 2 | - | √ | - | √ | 3 | - | - | √ |
| Gastroduodenal ulcer | - | - | - | √ | √ | - | - | - | √ | - | - | - | - | - | - | - | √ |
| Gastroenteritis | - | √‡ | - | - | √ | - | - | 4 | - | - | √ | - | ≥1 | 2 to 3 | √ | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gastrointestinal hemorrhage | - | - | - | √ | - | - | √ | - | - | - | √ | - | √ | - | - | √ | - |
| Gamma-glutamyl transpeptidase elevated | - | - | - | √ | √ | - | √ | - | √ | - | - | - | - | 1 to 3 | - | - | - |
| Gingivitis | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | 1 | - | - | - |
| Glossitis | √ | √‡ | - | √ | √ | - | √ | - | - | - | - | - | √ | 1 | √ | - | √ |
| Gum hemorrhage | - | - | - | - | √ | - | √ | - | - | - | - | - | - | - | - | - | √ |
| Gum hyperplasia | - | - | - | - | - | - | √ | - | √ | - | - | - | √ | 1 | - | - | √ |
| Halitosis | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Hematemesis | - | √ | - | √ | - | - | √ | - | √ | - | - | - | - | - | √ | - | √ |
| Hepatomegaly | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Hyperammonemia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Increased appetite | - | √ | √ | √ | 1.1 | - | √ | - | √ | - | 1 to 7 | √ | 2 | - | √ | 1 to 5 | - |
| Increased salivation | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | 6 | - | - | - |
| Irritable bowel syndrome | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Melena | - | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | √ | - | - | √ |
| Nausea | √ | 15 to 48 | 6 to 9 | - | 3.9 to 8.4 | 6 to 16 | 7 to 25 | 5* | 15 to 29 | 3 to 8 | - | 7 to >10 | 11 | 6 to 14 | 15 to 48 | 2 to 10 | 9 |
| Pancreatitis | - | √ | - | √ | √ | - | - | - | - | - | √ | - | - | - | √ | - | - |
| Rectal hemorrhage | - | - | - | √ | √ | - | - | - | 2 | - | √ | - | √ | - | - | - | √ |
| Stomatitis | √ | - | - | - | √ | - | √ | - | √ | - | - | - | √ | √ | - | - | √ |
| Ulcerative stomatitis | - | - | - | √ | - | - | - | - | √ | - | - | - | √ | - | - | - | √ |
| Vomiting | √ | 15 to 27 | - | 8.6 | 3.3 to 8.4 | - | 5 to 20 | 15 | 5 to 36 | 2 to 4 | 1 to 3 | ≥5 to 17 | 7 | 1 to 3 | 15 to 27 | 7 to 9 | √ |
| **Genitourinary** | | | | | | | | | | | | | | | | | |
| Abnormal ejaculation | - | - | - | - | √ | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Abortion | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Acute kidney failure | - | - | - | √ | √ | - | √ | - | - | - | √ | - | - | - | - | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Albuminuria | √ | - | - | - | - | - | - | 4 | - | - | √ | - | - | √ | - | - | √ |
| Amenorrhea | - | √ | - | - | √ | - | 2 | - | - | - | √ | - | √ | 2 | √ | - | √ |
| Anorgasmia | - | - | - | - | √ | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Balanitis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Bladder calculus | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Bladder neoplasm | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Bladder pain | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Breast enlargement | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | √ | - | - |
| Breast pain | - | - | - | - | √ | - | - | - | - | - | - | - | √ | 4 | - | - | - |
| Cervicitis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Chromaturia | - | - | <3 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cystitis | - | √ | - | - | √ | - | √ | - | - | - | - | - | √ | 1 to 3 | √ | - | - |
| Decreased libido | - | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | √ | - | - | √ |
| Dysmenorrhea | - | √ | - | - | √ | - | 5 to 7 | - | - | - | √ | - | √ | - | √ | √ | - |
| Dyspareunia | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Dysuria | - | - | 1 to 4 | √ | √ | - | √ | - | √ | - | √ | √ | √ | - | - | - | √ |
| Enuresis | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | √ |
| Epididymitis | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Female lactation | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Fibrocystic breast | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Glomerulitis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Gynecomastia | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Hematuria | - | - | 1 to 2 | √ | √ | - | √ | - | √ | - | √ | √ | √ | 2 | - | - | √ |
| Impotence | √ | - | - | - | 1.5 | - | √ | - | - | - | √ | - | √ | - | - | - | √ |
| Incontinence | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - |
| Increased libido | - | - | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - |
| Intermenstrual bleeding | - | - | - | 3.4 | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Kidney calculus | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - | - | - |
| Kidney failure | √ | - | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Leukorrhea | - | - | - | - | √ | - | - | - | √ | - | √ | - | - | - | - | - | - |
| Mastitis | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Menorrhagia | - | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | 2 | - | - | - |
| Metrorrhagia | - | √ | - | - | - | - | - | - | - | - | √ | - | √ | - | √ | - | √ |
| Nephritis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Nephrolithiasis | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - |
| Nocturia | - | - | - | - | √ | - | √ | - | - | - | - | √ | √ | - | - | - | √ |
| Oliguria | √ | - | - | - | - | - | - | - | - | - | √ | - | - | √ | - | - | - |
| Ovarian disorder | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Papanicolaou smear suspicious | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Pollakiuria | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - |
| Polyuria | - | - | - | - | √ | - | √ | - | √ | - | - | √ | √ | √ | - | - | √ |
| Pyelonephritis | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Renal stone | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Salpingitis | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Urethritis | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Urinary abnormality | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Urinary frequency | √ | √ | - | - | √ | - | √ | - | 1 to 2 | - | √ | - | ≥1 | 1 | √ | - | √ |
| Urinary hesitation | - | - | 1 to 4 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Urinary incontinence | - | √ | - | - | √ | - | √ | - | - | - | 1 to 2 | √ | √ | 2 | √ | - | √ |
| Urinary retention | √ | - | - | √ | √ | - | √ | - | - | - | √ | - | √ | √ | - | - | √ |
| Urinary tract infection | - | √ | - | 3.4 | √ | - | 3 | - | 1 to 5 | - | - | - | ≥1 to 5 | 2 | √ | 4 to 5 | - |
| Urinary urgency | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - | - | √ |
| Vaginal hemorrhage | - | - | - | √ | √ | - | - | - | - | - | - | - | √ | 3 | - | - | - |
| Vaginitis | - | √ | - | - | - | - | 4 | - | - | - | - | - | √ | - | √ | - | - |
| **Hemopoietic and Lymphatic** | | | | | | | | | | | | | | | | | |
| Agranulocytosis | √ | √ | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Anemia | - | - | - | √ | √ | √ | √ | - | - | - | √ | √ | √ | 1 to 2 | - | - | √ |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antinuclear factor test positive | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Aplastic anemia | √ | √ | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Ecchymosis | - | 4 to 5 | - | - | √ | - | √ | 4 | 2 to 4 | - | √ | - | ≥1 | - | 4 to 5 | - | 2 |
| Eosinophilia | √ | - | - | √ | - | - | √ | - | - | - | √ | - | √ | - | - | - | - |
| Erythrocytes abnormal | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Granulocytopenia | - | - | - | √ | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Hypochromic anemia | - | - | - | √ | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Immunodeficiency | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Iron deficiency | - | - | - | - | - | - | √ | - | - | - | - | √ | - | - | - | - | - |
| Leukocytosis | √ | - | - | √ | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Leukopenia | √ | - | - | √ | 1.1 | - | √ | - | √ | - | √ | √ | √ | 2 | - | - | √ |
| Lymphadenopathy | √ | - | - | √ | √ | - | 2 | - | 2 | - | √ | √ | √ | - | - | - | √ |
| Microcytic anemia | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Myelofibrosis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Neutropenia | - | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - |
| Pancytopenia | √ | √ | - | √ | - | - | - | - | - | - | - | - | √ | - | √ | - | - |
| Petechia | - | √ | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | √ |
| Polycythemia | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Prothrombin decreased | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Purpura | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Qualitative platelet disorder | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Thrombocythemia | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Thrombocytopenia | √ | 1 to 24 | - | √ | √ | - | √ | - | √ | - | √ | √ | 1 | - | 1 to 24 | - | √ |
| **Metabolic and Nutritional Disorders** | | | | | | | | | | | | | | | | | |
| Alkaline phosphate increase | - | - | - | √ | √ | - | √ | - | - | - | - | - | - | √ | - | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alanine transaminase increase | - | - | √ | - | - | √ | √ | - | - | - | - | - | - | - | - | - | - |
| Aspartate aminotransferase increase | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Creatinine phosphokinase increase | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Dehydration | - | - | - | - | √ | - | - | 2 | - | - | - | - | √ | √ | - | - | √ |
| Diabetic ketoacidosis | - | 3 to 8 | - | - | √ | - | - | - | - | - | - | - | - | 2 | 3 to 8 | - | - |
| Edema | √ | - | √ | √ | √ | - | 2 | - | 1 to 2 | - | 1 to 6 | - | - | - | - | 5 to 7 | √ |
| Glucose tolerance decrease | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Gout | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Hypercholesterolemia | - | - | - | - | - | - | - | - | - | - | - | - | √ | √ | - | - | - |
| Hyperglycemia | - | √ | - | - | 1.2 | - | √ | - | √ | - | - | - | √ | √ | √ | - | - |
| Hyperlipidemia | - | - | - | - | - | - | - | - | - | - | - | - | √ | √ | - | - | - |
| Hypoglycemia | - | - | - | - | √ | - | - | - | √ | - | 1 to 3 | - | √ | 1 | - | - | √ |
| Hypokalemia | - | - | - | √ | - | - | - | - | √ | - | - | - | √ | √ | - | - | - |
| Hyponatremia | - | - | - | √ | - | - | - | - | 1 to 5 | <2 | - | - | √ | √ | - | - | √ |
| Hypophosphatemia | - | - | - | 3.4 | - | - | - | - | - | - | - | - | - | √ | - | - | - |
| Lactic dehydrogenase increase | - | - | - | √ | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Peripheral edema | - | - | - | - | 1.7 to 8.3 | - | - | - | - | <2 | 2 to 16 | - | - | - | - | - | √ |
| Serum glutamic oxaloacetic transaminase increased | - | √ | - | √ | - | - | - | - | - | - | - | - | - | √ | √ | - | √ |
| Serum glutamic pyruvic transaminase | - | √ | - | 5.2 | - | - | - | - | - | - | - | - | - | √ | √ | - | √ |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| increased | | | | | | | | | | | | | | | | | |
| Weight gain | - | 4 to 9 | 2 to 3 | √ | 1.8 to 2.9 | - | √ | - | 1 to 2 | 4 | 1 to 16 | - | √ | 1 | 4 to 9 | 6 to 14 | √ |
| Weight loss | - | 6 | - | 3.4 | √ | - | - | - | √ | - | - | - | √ | 6 to 21 | 6 | - | 3 |
| Urate crystalluria | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| **Musculoskeletal** | | | | | | | | | | | | | | | | | |
| Arthralgia | - | √ | - | - | √ | - | 2 | - | - | <2 | 2 to 6 | - | √ | 1 to 7 | √ | 5 to 10 | √ |
| Arthritis | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | √ | - | - | √ |
| Arthrosis | - | √‡ | - | - | √ | - | - | - | - | - | √ | - | √ | - | √ | - | - |
| Bursitis | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Chondrodystrophy | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Fracture | - | - | - | - | 1.1 | - | - | - | - | - | - | - | - | - | - | - | - |
| Generalized spasm | - | - | - | - | - | √ | - | - | - | - | √ | - | √ | - | - | - | - |
| Leg cramps | - | - | - | - | √ | - | √ | - | - | - | √ | - | √ | - | - | - | √ |
| Muscle spasms | - | - | - | - | - | - | - | - | - | - | 2 to 4 | - | - | - | - | - | - |
| Muscle weakness | - | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | - | - | - | - |
| Myalgia | - | √ | - | - | 2 | - | √ | - | - | 1 to 3 | √ | - | ≥1 to 5 | 2 | √ | 3 to 5 | √ |
| Myasthenia | - | √ | - | - | √ | - | √ | - | - | - | 1 | - | 1 | - | √ | - | √ |
| Neuropathy | - | - | - | - | - | - | - | - | - | - | 2 to 9 | - | - | - | - | - | √ |
| Sprains/strains | - | - | - | - | - | - | - | - | 2 | - | - | - | - | - | - | - | - |
| Tendinous contracture | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - | - | - |
| **Respiratory** | | | | | | | | | | | | | | | | | |
| Apnea | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | √ |
| Asthma | - | - | - | √ | √ | - | - | 2 | √ | - | - | - | √ | - | - | - | - |
| Atelectasis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Bronchiolitis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Bronchitis | - | 5 | - | - | √ | - | 2 to 7 | - | 3 | - | 1 to 3 | 3 | √ | 2 to 7 | 5 | 5 | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bronchospasm | - | - | - | - | √ | - | 2 | - | - | - | - | - | - | - | - | - | - |
| Cough | - | - | - | - | - | - | - | - | - | <4 | - | - | - | - | - | - | - |
| Cough increased | - | √ | - | - | 1.8 | - | 7 to 8 | 2 to 11 | 5 | - | - | - | 4 | 2 to 4 | √ | 2 to 14 | √ |
| Dyspnea | √ | 1 to 5 | - | √ | √ | - | 2 to 5 | - | √ | - | 1 | - | √ | 1 to 2 | 1 to 5 | - | √ |
| Epistaxis | - | √ | - | √ | √ | - | 2 to 5 | - | 4 | - | - | - | √ | 2 to 4 | √ | - | - |
| Hemoptysis | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | √ |
| Hiccups | - | - | - | - | √ | - | √ | - | √ | - | √ | - | √ | - | - | - | - |
| Hoarseness | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Hyperventilation | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - | - | - |
| Hypoxia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Laryngitis | - | - | - | - | √ | - | - | - | √ | - | - | - | √ | - | - | - | - |
| Laryngismus | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Limb injury | - | - | - | - | - | - | - | - | - | <2 | - | - | - | - | - | - | - |
| Lung edema | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Lung fibrosis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Mucositis | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Nasal obstruction | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Nasopharyngitis | - | - | - | - | - | - | - | 7* | - | - | - | ≥5 | - | - | - | 9 to 14 | - |
| Pharyngitis | - | 2 to 8 | - | - | 1.2 to 2.8 | - | 5 to 14 | 6 to 10 | 3 | - | - | - | 7 | 6 | 2 to 8 | - | √ |
| Pharyngolaryngeal pain | - | - | - | - | - | - | - | - | - | 2 | 1 to 3 | - | - | - | - | 7 to 14 | - |
| Pneumonia | √ | √ | - | √ | √ | - | - | - | 1 to 2 | - | - | - | √ | 5 | √ | - | - |
| Respiratory disorder | - | - | - | - | - | - | - | - | - | - | - | - | √ | 5 | - | - | - |
| Rhinitis | - | 5 | - | 6.9 | 4.1 | - | 7 to 14 | 4 to 13 | 2 to 10 | - | - | - | ≥1 | 2 to 7 | 5 | - | 2 |
| Sinusitis | - | √ | - | - | √ | - | 1 to 5 | 2 | 2 to 4 | - | 4 to 7 | 3 | ≥1 | 2 to 5 | √ | - | - |
| Snoring | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Upper respiratory infection | - | 12 to 20 | - | 8.6 | √ | - | - | - | 5 to 10 | 3 to 4 | - | - | - | 16 to 18 | 12 to 20 | 7 to 9 | - |
| Voice alteration | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Yawn | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| **Other** | | | | | | | | | | | | | | | | | |
| Abnormal vision | - | √ | - | - | √ | - | - | - | 2 to 14 | - | 1 to 5 | - | √ | 13 | √ | - | - |
| Abnormality of accommodation | - | - | - | - | √ | - | √ | - | 2 | - | √ | - | - | √ | - | - | - |
| Accidental injury | - | √* | - | - | 3.3 | - | 14 | 17 | - | - | 2 to 11 | - | ≥1 to 21 | 6 to 14 | √ | - | √ |
| Addiction | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Allergic reaction | - | √ | - | √ | √ | - | - | - | 2 | - | √ | - | √ | <1 to 2 | √ | - | √ |
| Amblyopia | - | √ | - | - | 2.7 to 4.2 | - | √ | 2 | - | - | - | - | - | - | √ | - | √ |
| Anaphylactoid reaction | - | √ | - | √ | - | - | - | - | - | - | √ | - | - | - | √ | - | - |
| Anisocoria | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Ascites | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Back pain | - | √ | - | - | 1.8 | - | 8 | - | 2 to 4 | 2 to 5 | 1 to 4 | 3 | ≥1 | 2 to 5 | √ | 4 to 7 | - |
| Birth defects | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - |
| Blepharitis | - | - | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Blindness | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Buccal mucous membrane swelling | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cellulites | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Chills | √ | √‡ | - | - | √ | - | - | - | - | - | √ | - | √ | - | √ | - | - |
| Conjunctivitis | √ | √‡ | - | - | 1.2 | - | √ | 3 | - | - | √ | - | ≥1 | 2 to 4 | √ | - | √ |
| Contusion | - | - | - | - | - | 2 to 4 | - | - | - | <2 | - | - | - | - | - | - | - |
| Corneal ulcer | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Deafness | - | √ | - | - | √ | - | √ | - | - | - | - | - | √ | 2 | √ | √ | √ |
| Diplopia | - | - | 6 to 8 | - | - | - | - | - | - | 1 to 3 | - | - | - | - | - | - | - |
| Dry eyes | - | - | - | - | √ | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Dry mouth | √ | - | √ | - | 1.7 to 4.8 | √ | 6 | - | 3 | - | 1 to 15 | - | ≥1 | - | - | - | 2 |
| Ear infection | - | √ | - | 3.4 | 1.2 | - | - | - | 2 | - | √ | 3 | √ | 1 to 2 | √ | - | - |
| Ear pain | - | - | - | - | √ | - | √ | 2 | 1 to 2 | - | - | - | √ | - | - | 5 | - |
| Exophthalmoses | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Extraocular palsy | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Extremity pain | - | - | - | - | - | - | - | - | - | <3 | - | - | - | - | - | - | - |
| Eye disorder | - | - | - | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | - | - |
| Eye hemorrhage | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Eye pain | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Facial edema | - | - | - | 3.4 | √ | - | 2 | 2 | - | - | 1 to 3 | - | √ | - | - | - | √ |
| Fall | - | - | - | - | - | √ | - | - | 4 | 2 to 10 | - | - | - | - | - | - | - |
| Feeling abnormal | - | - | - | - | √ | - | - | - | 1 to 2 | - | 1 to 3 | - | - | - | - | - | - |
| Feeling drunk | - | - | - | - | √ | √ | - | - | √ | - | 1 to 2 | - | - | - | - | - | - |
| Fetal death | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Fever | √ | 6 | - | - | 10.1 | - | 6 to 15 | - | 3 | - | √ | - | ≥1 | 1 to 9 | 6 | 4 to 7 | - |
| Flank pain | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ |
| Flu syndrome | - | 12 | - | √ | - | - | 7 | 3 | - | - | 1 to 2 | - | ≥1 to 9 | <1 to 3 | 12 | - | 4 |
| Fluid retention | - | - | - | - | - | - | - | - | - | - | 1 to 3 | - | - | - | - | - | - |
| Glaucoma | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ |
| Granuloma | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Hangover effect | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | - | - | - |
| Head injury | - | - | - | - | - | - | - | - | - | <3 | - | - | - | - | - | - | - |
| Hepatic failure | √ | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hepatitis | √ | - | - | √ | √ | - | √ | - | - | - | - | - | - | - | - | - | - |
| Hernia | - | - | - | - | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Hot flushes | - | - | - | - | - | - | - | - | 1 to 2 | - | - | - | - | 2 | - | - | - |
| Hyperacusis | - | - | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Hyperhidrosis | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hyperpyrexia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hypothermia | - | √ | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Infection | - | - | - | - | 5.1 | - | 5 to 20 | 13 | 2 to 7 | - | 3 to 14 | - | ≥1 to 19 | 2 to 7 | - | - | - |
| Influenza | - | - | 1 to 5 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Intentional injury | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Iritis | - | - | - | - | √ | - | - | - | - | - | √ | - | - | √ | - | - | √ |
| Keratitis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Keratoconjunctivitis | - | - | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Liver function tests abnormal | √ | - | - | - | √ | √ | √ | - | √ | - | - | - | √ | - | - | - | - |
| Lupus erythematosus | - | - | - | √ | - | - | - | - | √ | - | - | - | - | - | - | - | √ |
| Malaise | - | √ | √ | √ | √ | - | - | - | √ | - | √ | - | √ | - | √ | 5 | √ |
| Miosis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Mouth ulceration | - | - | - | - | - | - | √ | - | - | - | √ | - | 1 | - | - | - | √ |
| Mydriasis | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Neck pain | - | √‡ | - | - | √ | - | 2 | 2 to 8 | - | - | - | - | √ | - | √ | - | - |
| Neck rigidity | - | √‡ | - | - | - | - | - | - | - | - | √ | - | √ | - | √ | - | √ |
| Neoplasm | - | - | - | √ | - | - | - | - | - | - | - | - | √ | <1 to 2 | - | - | - |
| Night blindness | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Ophthalmoplegia | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Oral hypoesthesia | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - |
| Otic atrophy | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Overdose | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |


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| Adverse Event(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pain | - | - | - | - | - | - | 5 | 6 to 7 | - | - | 4 to 5 | - | 5 to 7 | - | - | - | - |
| Parosmia | - | - | - | - | - | - | √ | - | - | - | √ | - | √ | - | - | - | √ |
| Pelvic pain | - | - | - | - | √ | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Periodontal abscess | - | - | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Photophobia | - | √* | - | - | √ | - | √ | - | √ | - | √ | - | √ | √ | √ | - | √ |
| Photosensitivity reaction | √ | √ | - | √ | √ | - | 2 | - | √ | - | √ | - | √ | √ | √ | - | - |
| Ptosis | - | - | - | - | √ | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Pyrexia | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - |
| Retinal edema | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Rigors | - | - | - | √ | - | - | - | - | √ | - | - | - | - | 1 | - | - | - |
| Sepsis | - | - | - | √ | √ | - | - | - | - | - | - | - | √ | - | - | - | - |
| Shock | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Skin lacerations | - | - | - | - | - | 2 to 3 | - | - | - | <2 | - | - | - | - | - | - | - |
| Sudden death | - | - | - | √ | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Sudden infant death syndrome | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Suicide attempt | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Taste loss | - | - | - | - | √ | - | √ | - | - | - | √ | - | √ | 1 to 2 | - | - | - |
| Taste perversion | - | √ | - | - | √ | - | √ | - | 5 | - | √ | - | √ | 2 to 3 | √ | - | 2 |
| Thirst | - | - | - | - | √ | - | - | - | 2 | - | - | - | √ | 1 to 2 | - | 2 | √ |
| Tinnitus | √ | 1 to 7 | - | - | √ | √ | √ | - | √ | - | √ | - | √ | 4 to 2 | 1 to 7 | 2 | √ |
| Tongue edema | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Uveitis | - | - | - | - | - | - | √ | - | - | - | √ | - | - | - | - | - | - |
| Viral infection | - | √* | - | - | 10.9 | - | - | 2 | - | - | - | - | - | 4 to 9 | √ | - | - |
| Visual field defect | - | - | - | √ | - | - | √ | - | - | - | - | - | √ | - | - | - | √ |

√Percent not specified.
- Event not reported or incidence <1%.
* Extended-release tablets only.
† Extended-release capsules only.
‡Delayed-release tablets only.


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## Contraindications

**Table 7a. Contraindications-Barbiturates**[1,48-50,56]

| Contraindication(s) | Phenobarbital | Primidone |
|---|---|---|
| Hypersensitivity to phenobarbital | √ | √ |
| Patients with histories of manifest or latent porphyria | √ | √ |
| Patients with marked impairments of liver function or respiratory disease in which dyspnea or obstruction is evident | √ | - |

**Table 7b. Contraindications-Benzodiazepines**[1,25,28,45]

| Contraindication(s) | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| Acute narrow-angle glaucoma | - | √ | √ |
| Children less than six years of age | - | - | √ |
| Hypersensitivity | - | √ | √ |
| Significant liver disease | - | √ | - |

**Table 7c. Contraindications-Hydantoins**[1,47,51-54]

| Contraindication(s) | Ethotoin | Phenytoin |
|---|---|---|
| Coadministration with delavirdine | - | √ |
| Hematologic disorders | √ | - |
| Hepatic abnormalities | √ | - |
| Hypersensitivity | - | √ |

**Table 7d. Contraindications-Succinimides**[1,24,33,34]

| Contraindication(s) | Ethosuximide | Methsuximide |
|---|---|---|
| Hypersensitivity | √ | √ |


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**Table 7e. Contraindications-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Contraindication(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coadministration with nefazodone | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Concurrent use with monoamine oxidase inhibitors | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Concurrent use with delavirdine or other non-nucleoside reverse transcriptase inhibitors | √* | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hepatic dysfunction | - | √ | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| History of any blood dyscrasias | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| History of previous bone marrow depression | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hypersensitivity | √ | √ | - | √ | √ | - | √ | - | √ | - | √ | - | √ | - | √ | - | √ |
| Known urea cycle disorders | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Patients with familial short QT syndrome | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - |
| Patients with mitochondrial disease | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Pregnant Women | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

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## Boxed Warnings

### Boxed Warning for carbamazepine[1]

**WARNING**

Serious dermatologic reactions and HLA-B*1502 allele: Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported during treatment with carbamazepine. These reactions are estimated to occur in one to six per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be approximately 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing Stevens-Johnson syndrome/toxic epidermal necrolysis and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

Aplastic anemia and agranulocytosis: 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. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per 1 million population per year for agranulocytosis and two patients per one million population 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. However, the vast majority of the cases of leukopenia 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 hematological changes observed while monitoring patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, obtain complete pretreatment hematological testing as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, monitor the patient closely. Consider discontinuation of the drug if any evidence of significant bone marrow depression develops.

### Boxed Warning for divalproex, valproic acid[26,27,58,63,64]

**WARNING**

Hepatotoxicity
*General Population:* Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific 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 appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

Children under the age of two years 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 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. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.


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**WARNING**

*Patients with Mitochondrial Disease:* There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g., Alpers Huttenlocher Syndrome). Divalproex is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, divalproex should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with divalproex for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice.

Fetal Risk
Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following *in utero* exposure. Valproate is therefore contraindicated in pregnant women treated for prophylaxis of migraine. Valproate should only be used to treat pregnant women with epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable.

Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using.

A Medication Guide describing the risks 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 as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting and/or 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.

**Boxed Warning for ezogabine[55]**

**WARNING**

Retinal Abnormalities and Potential Vision Loss
Ezogabine can cause retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. Some patients with retinal abnormalities have been found to have abnormal visual acuity. It is not possible to determine whether ezogabine caused this decreased visual acuity, as baseline assessments are not available for these patients. Approximately one third of the patients who had eye examinations performed after approximately four years of treatment were found to have retinal pigmentary abnormalities. An earlier onset cannot be ruled out, and it is possible that retinal abnormalities were present earlier in the course of exposure to ezogabine. The rate of progression of retinal abnormalities and their reversibility are unknown. Ezogabine should only be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from ezogabine. All patients taking ezogabine should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. Testing should include visual acuity and dilated fundus photography. Additional testing may include fluorescein angiograms (FA), ocular coherence tomography (OCT), perimetry, and electroretinograms (ERG). If retinal pigmentary


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| WARNING |
| --- |
| abnormalities or vision changes are detected, ezogabine should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss. |

**Boxed Warning for felbamate[1]**

| WARNING |
| --- |
| Before prescribing felbamate, the health care provider should be thoroughly familiar with the details of this prescribing information.<br><br>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.<br><br>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 and/or continued on felbamate without consideration of appropriate expert hematologic consultation.<br><br>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., two to five 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.<br><br>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.<br><br>In managing patients on felbamate, the clinical manifestation of aplastic anemia may not be seen until after a patient has been taking felbamate for several months (e.g., onset of aplastic anemia among felbamate-exposed patients for whom data are available has ranged from five 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.<br><br>It is not known whether 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.<br><br>It is not known whether the dose of felbamate affects the incidence of aplastic anemia.<br><br>It is not known whether concomitant use of antiepileptic drugs and/or other drugs affects the incidence of aplastic anemia.<br><br>Aplastic anemia typically develops without premonitory clinical or laboratory signs; the full blown syndrome presents 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. Discontinue felbamate if any evidence of bone marrow depression occurs.<br><br>Hepatic failure: Evaluation of postmarketing experience suggests that acute liver failure is associated |


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**WARNING**

with the use of felbamate. The reported rate in the United States has been approximately six cases of liver failure leading to death or transplant per 75,000 patient-years of use. This rate is an underestimate because of underreporting, and the true rate could be considerably greater than this. For example, if the reporting rate is 10%, the true rate would be one case per 1,250 patient-years of use.

Of the cases reported, approximately 67% resulted in death or liver transplantation, usually within five weeks of the onset of signs and symptoms of liver failure. The earliest onset of severe hepatic dysfunction followed subsequently by liver failure was three weeks after initiation of felbamate. Although some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, gastrointestinal symptoms), in other reports it was not clear if any prodromal symptoms preceded the onset of jaundice.

It is not known whether 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 antiepileptic drugs and/or other drugs affects the incidence of hepatic failure.

Felbamate should not be prescribed for anyone with a history of hepatic dysfunction.

Treatment with felbamate should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proved that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. There is no information available that documents how rapidly patients can progress from normal liver function to liver failure, but other drugs known to be hepatotoxins can cause liver failure rapidly (e.g., from normal enzymes to liver failure in two to four weeks). Accordingly, monitoring of serum transaminase levels (aspartate aminotransferase and alanine aminotransferase) is recommended at baseline and periodically thereafter. While more frequent monitoring increases the chances of early detection, the precise schedule for monitoring is a matter of clinical judgment.

Discontinue felbamate if serum aspartate aminotransferase or serum alanine aminotransferase levels become increased at least two times the upper limit of normal, or if clinical signs and symptoms suggest liver failure. Patients who develop evidence of hepatocellular injury while taking felbamate and are withdrawn from the drug for any reason should be presumed to be at increased risk for liver injury if felbamate is reintroduced. Accordingly, such patients should not be considered for re-treatment.

**Boxed Warning for lamotrigine[1]**

**WARNING**

Skin reactions: Lamotrigine can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8/1,000) in pediatric patients (two to 16 years of age) receiving lamotrigine immediate release as adjunctive therapy for epilepsy and 0.3% (3/1,000) in adults receiving 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 pediatric patients (two to 16 years of age) with epilepsy taking adjunctive lamotrigine immediate release, there was one rash-related death. In worldwide postmarketing 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.


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| WARNING |
| --- |
| The risk of serious rash caused by treatment with lamotrigine extended-release is not expected to differ from that with the immediate-release formulation of lamotrigine. However, the relatively limited treatment experience with lamotrigine extended-release makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with lamotrigine extended-release. Lamotrigine extended-release is not approved for patients younger than 13 years.<br><br>Other than age, there are no known factors identified to predict the risk of occurrence or the severity of rash caused by 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.<br><br>Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within two to eight weeks of treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., six 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.<br><br>Although benign rashes also occur with lamotrigine, it is not possible to reliably predict which rashes will prove to be serious or life-threatening. Accordingly, 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. |

**Boxed Warning for perampanel[1]**

| WARNING |
| --- |
| Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking perampanel. Monitor patients for these reactions as well as for changes in mood, behavior, or personality that are not typical for the patient, particularly during the titration period and at higher doses. Perampanel should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening. |

**Boxed Warning for vigabatrin[1]**

| WARNING |
| --- |
| Vision loss: Vigabatrin causes permanent vision loss in infants, children, and adults. Because assessing vision loss is difficult in children, the frequency and extent of vision loss in infants and children are poorly characterized. For this reason, the following data are primarily based on the adult experience.<br><br>In adults, vigabatrin causes permanent bilateral concentric visual field constriction in 30% or more of patients; it ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, vigabatrin also can damage the central retina and may decrease visual acuity.<br><br>The onset of vision loss from vigabatrin is unpredictable and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years.<br><br>The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.<br><br>In infants and children, vision loss may not be detected until it is severe. Nonetheless, unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the SHARE program, assess vision to the extent possible at baseline (no later than four weeks after starting vigabatrin) and |


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**WARNING**

at least every three months during therapy. Vision assessment is also required about three to six months after the discontinuation of vigabatrin therapy. Once detected, vision loss caused by vigabatrin is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.

Consider drug discontinuation, balancing benefit and risk, if visual loss is documented. It is possible that vision loss can worsen despite discontinuing vigabatrin.

Because of the risk of vision loss, withdraw vigabatrin from patients who do not show substantial clinical benefit within two to four weeks of initiation when used in infants or children or within three months when used in adults, or sooner if treatment failure becomes obvious. Periodically reassess patient response to and continued need for vigabatrin.

Symptoms of vision loss from vigabatrin are unlikely to be recognized by the parent, patient, or caregiver before vision loss is severe. Vision loss of milder severity, although unrecognized by the patient or caregiver, may still adversely affect function.

Do not use vigabatrin in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from vigabatrin has not been well characterized, but is likely adverse.

Do not use vigabatrin with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.

Use the lowest dose and shortest exposure to vigabatrin that is consistent with clinical objectives.

The possibility that vision loss from vigabatrin may be more common, more severe, or have more severe functional consequences in infants and children than in adults cannot be excluded.

Because of the risk of permanent vision loss, vigabatrin is available only through a special restricted distribution program called SHARE by calling 1-888-457-4273. Only health care providers and pharmacies registered with SHARE may prescribe and distribute vigabatrin. In addition, vigabatrin may be dispensed only to patients who are enrolled in and meet all conditions of SHARE.

## Warnings/Precautions

**Table 8a. Warnings and Precautions-Barbiturates**[1,48-50,56]

| Warning(s)/Precaution(s) | Phenobarbital | Primidone |
|---|---|---|
| Acute or chronic pain; caution should be exercised when therapy is administered to patients with acute or chronic pain | √ | - |
| Controlled substance; schedule IV drug | √ | - |
| Dependence; prolonged, uninterrupted therapy, even in therapeutic doses, may result in psychic and physical dependence | √ | - |
| Habit forming; therapy may be habit forming | √ | - |
| Hazardous tasks; therapy may impair the mental or physical abilities required for the performance of potentially hazardous tasks | √ | - |
| Special risk patients; therapy should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or have a history of drug abuse | √ | - |
| Suicidal behavior and ideation; therapy may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication | - | √ |
| Synergistic effects; concomitant use with alcohol may produce | √ | - |


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| Warning(s)/Precaution(s) | Phenobarbital | Primidone |
|---|---|---|
| additive central nervous system-depressant effects | | |
| Withdrawal seizures; the abrupt withdrawal of therapy may precipitate status epilepticus | - | √ |

**Table 8b. Warnings and Precautions-Benzodiazepines**[1,25,28,45]

| Warning(s)/Precaution(s) | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| Abuse; the pharmacological profile is similar to that of other benzodiazepines, which leads to sedation, somnolence, and anxiolytics; therefore, therapy may be abused | √ | - | - |
| Controlled substance; schedule IV drug | √ | √ | √ |
| Cytochrome P450 2C19 poor metabolizers; concentrations of the active metabolite are higher in poor metabolizers compared to extensive metabolizers | √ | - | - |
| Dermatological reactions; serious skin reactions, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported, discontinue immediately if signs, symptoms of unexplained rash suggestive of SJS or TEN occur | √ | - | - |
| Dependence; risk of dependence is present even with the use of therapeutic doses after a few weeks | √ | √ | - |
| Discontinuation of therapy; avoid abrupt discontinuation, withdrawal gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus | √ | - | - |
| Hazardous tasks; therapy may impair the mental or physical abilities required for the performance of potentially hazardous tasks | √ | √ | √ |
| Hypersalivation; therapy may produce an increase in salivation | - | √ | - |
| Psychiatric disorders; therapy is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment | - | - | √ |
| Somnolence/sedation; therapy causes somnolence and sedation | √ | - | - |
| Suicidal behavior and ideation; therapy may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication | √ | √ | - |
| Withdrawal; abrupt discontinuation of therapy causes withdrawal symptoms | √ | √ | √ |
| Worsening of seizures; when used in patients in whom several different types of seizure disorders coexist, therapy may increase the incidence or precipitate the onset of generalized tonic-clonic/grand mal seizures | - | √ | √ |

**Table 8c. Warnings and Precautions-Hydantoins**[1,47,51-54]

| Warning(s)/Precaution(s) | Ethotoin | Phenytoin |
|---|---|---|
| Acute toxicity; serum levels sustained above the optimal range may produce confusional states | - | √ |
| Dermatologic effects; therapy can cause rare, serious skin adverse reactions, which can be fatal | - | √ |


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| Warning(s)/Precaution(s) | Ethotoin | Phenytoin |
|---|---|---|
| Enteral feeding; literature suggest that patients who received enteral feeding and/or related nutritional supplements had lower than expected plasma levels | - | √ |
| Hematologic effects; blood dyscrasias have been reported in patients receiving therapy | √ | - |
| Hyperglycemia; has been reported with therapy, therapy may also raise serum glucose levels in patients with diabetes | - | √ |
| Lymphadenopathy; there have been a number of reports suggesting a relationship between therapy and the development of lymphadenopathy | - | √ |
| Osteomalacia; has been associated with therapy and is considered to be caused by the agent's interference with vitamin D metabolism | - | √ |
| Other seizures; therapy is not indicated for seizures caused by hypoglycemic or other metabolic causes | - | √ |
| Porphyria; exercise with caution when administering therapy in patients suffering from this disease | - | √ |
| Slow metabolism; a small proportion of patients receiving therapy have been shown to metabolize the agent slowly | - | √ |
| Suicidal behavior and ideation; therapy may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication | √ | √ |
| Withdrawal seizures; the abrupt withdrawal of therapy may precipitate status epilepticus | - | √ |

**Table 8d. Warnings and Precautions-Succinimides**[1,24,33,34]

| Warning(s)/Precaution(s) | Ethosuximide | Methsuximide |
|---|---|---|
| Hazardous tasks; therapy may impair the mental or physical abilities required for the performance of potentially hazardous tasks | √ | √ |
| Hematologic effects; blood dyscrasias have been reported in patients receiving therapy | √ | √ |
| Mixed epilepsy disorder; therapy, when used alone in mixed types of epilepsy, may increase the frequency of tonic-clonic seizures in some patients | √ | √ |
| Suicidal behavior and ideation; therapy may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication | √ | √ |
| Systemic lupus erythematosus; cases have been reported with the use of therapy | √ | √ |
| Withdrawal seizures; the abrupt withdrawal of therapy may precipitate status epilepticus | √ | √ |


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**Table 8e. Warnings and Precautions-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Warning(s)/Precaution(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Absence seizures; use therapy with caution in patients with a mixed seizure disorder, therapy has been associated with increased frequency or generalized convulsions | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Acute multiorgan failure; multiorgan failure has been observed in patients receiving therapy | - | √ | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | - | - |
| Acute myopia and secondary angle-closure glaucoma; this syndrome has been reported with therapy | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - |
| Anaphylactic reactions and/or angioedema; rare cases have been reported in patients after taking the first or subsequent doses of therapy | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - | - | - |
| Anticholinergic effects; therapy has shown mild anticholinergic activity | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Aplastic anemia; therapy is associated with a marked increase in the incidence of aplastic anemia | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Aseptic meningitis; therapy increases the risk of developing aseptic meningitis | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Atrial fibrillation/flutter; therapy may predispose to atrial arrhythmias, especially in patients with diabetic neuropathy and/or cardiovascular disease | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - |
| Blood pressure effects; a significantly higher risk of at least one measured increase in diastolic blood pressure had been observed with therapy | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - |
| Central nervous system; therapy has been associated with central nervous system- | √ | - | - | - | - | √ | - | √ | √ | - | √ | √ | √ | √ | - | - | √ |


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| Warning(s)/Precaution(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| related adverse reactions | | | | | | | | | | | | | | | | | |
| Congestive heart failure; use with caution due to limited data in this patient population | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Controlled substance; schedule V drug | - | - | - | - | - | √ | - | - | - | - | √ | - | - | - | - | - | - |
| Creatine kinase levels; therapy was associated with creatine kinase elevations | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | √ |
| Dermatologic; severe dermatologic reactions have been reported | √ | - | - | - | - | - | √ | √ | √ | - | - | - | √ | - | - | - | √ |
| Discontinuation of therapy; avoid abrupt discontinuation to prevent the possibility of increasing seizure frequency | - | - | - | √ | √ | √ | √ | √ | √ | - | √ | - | √ | √ | - | √ | - |
| Dizziness and somnolence; dose-related increases in dizziness and somnolence have been reported with treatment | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Edema; therapy has been shown to cause edema in adults | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - |
| Electroencephalogram abnormalities; therapy may induce exacerbations of pre-existing electroencephalogram abnormalities | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Fall risk increased; serious injuries including head injuries and bone fracture have been reported | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - |
| Folic acid supplementation; supplementation prior to conception and during the first trimester of pregnancy may decreases the risk for congenital neural tube defects | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Generalized weakness; moderately severe to incapacitating generalized weakness has been reported with therapy | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Hazardous tasks; therapy may impair the mental or physical abilities required for the performance of potentially hazardous tasks | √ | √ | - | - | √ | √ | - | √ | √ | - | √ | - | √ | - | √ | √ | √ |


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| Warning(s)/Precaution(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hematologic effects; have been observed with therapy | √ | - | - | - | - | - | √ | √ | - | - | √ | √ | - | - | - | √ | √ |
| Hepatic failure; evaluation of postmarketing experience suggests that acute liver failure is associated with therapy | - | √ | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Human immunodeficiency virus; there are in vitro studies that suggest therapy stimulates the replication of the human immunodeficiency virus and cytomegalovirus under certain experimental conditions | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Hyperammonemia and encephalopathy associated with concomitant topiramate/valproic acid use; coadministration has been associated with hyperammonemia and encephalopathy | - | √ | - | - | - | - | - | - | - | - | - | - | - | √ | √ | - | - |
| Hypersensitivity reactions; have been reported | - | - | - | - | - | - | - | - | - | - | √ | √ | - | - | - | - | √ |
| Hyponatremia; has been reported with therapy | √ | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - |
| Kidney stones; have been reported with therapy | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | √ |
| Magnetic resonance imaging; abnormal magnetic resonance imaging signal changes have been observed in some infants treated for infantile spasms with therapy | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - |
| Melanin-containing tissues; product contains melanin, which could accumulate in melanin-rich tissues over time | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Metabolic acidosis; hyperchloremic, nonunion gab, metabolic acidosis is associated with therapy | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | √ |
| Neurologic symptoms, including dizziness, | | | | | | | | | | √ | | | | | | | |


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| Warning(s)/Precaution(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| gait disturbance, somnolence and fatigue occurred more frequently in clinical trials with active treatment compared to placebo | | | | | | | | | | | | | | | | | |
| Neuropsychiatric effects; use in children three to 12 years of age is associated with central nervous system-related adverse events | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Neuropsychiatric symptoms; confusional state, psychotic symptoms and hallucinations occurred more frequently in clinical trials with active treatment compared to placebo | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Neurotoxicity; has been observed in animal studies | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - |
| Oligohidrosis and hyperthermia; have been reported with therapy | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | √ |
| Ophthalmic effects; changes in vision occur and/or there may be a possibility of long-term ophthalmic effects | - | - | - | - | - | - | - | - | - | - | √ | - | √ | - | - | - | - |
| Pancreatitis; cases of have been reported with therapy | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | √ |
| Paresthesia; appears to be a common effect of therapy | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - |
| Peripheral edema; therapy may cause peripheral edema | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - |
| Peripheral neuropathy; therapy has been shown to cause symptoms of peripheral neuropathy in adults | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - |
| Phenylketonurics; oral solution contains aspartame | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - |
| Potential medication errors; medication errors have occurred with therapy | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| PR interval; therapy was associated with PR prolongation | - | - | - | - | - | √ | - | - | - | - | √ | - | - | - | - | - | - |


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| Warning(s)/Precaution(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Psychiatric and behavioral reactions; monitor patients during treatment and for at least one month following the last dose | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - |
| QT interval; therapy was associated with QT shortening | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - |
| QT interval: therapy was associated with QT prolongation | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Retinal abnormalities and potential vision loss; abnormalities seen in patients have funduscopic features similar to those seen in retinal pigment dystrophies that are known to result in damage to photoreceptors and vision loss, the rate of progression of retinal abnormalities and the reversibility after drug discontinuation are unknown | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Seizures in patients without epilepsy; postmarketing reports have shown that therapy use has been associated with new-onset seizures and status epilepticus in patients without epilepsy | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - |
| Skin discoloration; skin discoloration of blue, grey-blue or brown has been reported | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Special risk patients; prescribe therapy only after a critical benefit-to-risk appraisal in patients with a history of cardiac conduction disturbance; cardiac, hepatic, or renal damage; and adverse hematologic or hypersensitivity reaction to other drugs | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Status epilepticus; rare treatment-emergent events have been reported | - | - | - | - | - | - | √ | - | - | - | - | - | √ | - | - | - | √ |
| Sudden and unexplained death in patients with epilepsy; premarketing studies of | - | - | - | - | √ | - | √ | - | - | - | - | - | √ | √ | - | - | √ |


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| Warning(s)/Precaution(s) | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| gabapentin | | | | | | | | | | | | | | | | | |
| Suicide; the possibility of suicide attempt is inherent in bipolar disorder, accompany drug therapy with close supervision in high risk patients | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Suicidal behavior and ideation; therapy may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication | - | - | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | - | - | √ | √ |
| Syncope; syncope was reported in patients with diabetic neuropathy receiving therapy | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - |
| Thrombocytopenia; has been reported with therapy | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Urinary retention; has been reported with therapy | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Vision loss; the onset and progression of vision loss from therapy are unpredictable and may occur or worsen precipitously between assessments, once detected, vision loss caused by therapy is not reversible | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - |
| Weight gain; therapy may cause weight gain | - | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | √ | - |
| Withdrawal seizures; the abrupt withdrawal of therapy may precipitate status epilepticus | √ | √ | √ | - | - | - | - | - | - | √ | - | √ | - | - | - | - | √ |
| Women of childbearing potential; avoid due the risk fetal risk of neural tube defects and other major congenital malformations, unless the drug is essential to the management of medical condition | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

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## Drug Interactions

**Table 9a. Drug Interactions-Barbiturates**[1,48-50,56]

| Description | Phenobarbital | Primidone |
|---|---|---|
| Anticoagulants: barbiturates reduce the effects of anticoagulants. Patients receiving barbiturates will need modification of their anticoagulant dose. Monitor anticoagulant action and adjust doses as needed. Termination of barbiturate therapy will result in decreased anticoagulant requirements. Monitor patients for several weeks. Consider using a benzodiazepine. | √ | √ |
| β-blockers: When administered concomitantly, pharmacokinetic effects of metoprolol and propranolol may be reduced. If an interaction is suspected, consider a higher β-blocker dose during coadministration of barbiturates. | √ | √ |
| Carbamazepine: concomitant administration may result in decreased serum primidone, its metabolite, and carbamazepine concentrations. Monitor serum carbamazepine concentrations, and observe the patient for loss of carbamazepine efficacy. Consider discontinuing the barbiturate or adjusting the dose of carbamazepine as needed. | √ | √ |
| Clozapine: clozapine plasma concentrations may be reduced, decreasing the pharmacologic effects. Monitor clozapine therapy when phenobarbital is started or stopped. Observe the patient for clozapine toxicity when phenobarbital is stopped. | √ | - |
| Contraceptives, hormonal: loss of oral contraceptive efficacy, possibly resulting in unintended pregnancy. Alternate methods of contraception are recommended; ethinyl estradiol 80 µg may give good cycle control. | √ | √ |
| Corticosteroids: Decreased pharmacologic effects of corticosteroids may be observed. If possible, avoid this combination. Carefully monitor patients receiving corticosteroids when a barbiturate is added or discontinued. Increases in the corticosteroid dosage may be required to maintain the desired effect. | √ | √ |
| Doxycycline: concomitant administration may decrease doxycycline half-life and serum levels, resulting in a decreased therapeutic effect. The dose of doxycycline may need to be increased during barbiturate coadministration. Consider an alternative tetracycline. | √ | √ |
| Exemestane: plasma exemestane concentrations may be reduced, resulting in decreased efficacy. If phenobarbital is coadministered in patients receiving exemestane, the recommended dosage of exemestane is 50 mg once daily after a meal. If phenobarbital is discontinued, reduce the exemestane dosage to 25 mg once daily with a meal. | √ | √ |
| Felodipine: pharmacologic effects of felodipine may be decreased. Patients receiving long-term treatment with both drugs may require higher doses of felodipine. | √ | √ |
| Griseofulvin: serum griseofulvin levels are decreased. Separating drug administration times, giving the phenobarbital in divided doses, or increasing the griseofulvin dose may be helpful if therapeutic failures with griseofulvin occur. Also, consider stopping either drug or using alternative therapy. | √ | √ |
| Hepatitis C protease inhibitors: hepatitis C protease inhibitors plasma concentrations may be reduced, leading to loss of virologic response. Phenobarbital concentrations may be increased or decreased. Coadministration of boceprevir and phenobarbital is contraindicated. Coadminister telaprevir and phenobarbital with caution; close clinical and laboratory monitoring of phenobarbital concentrations is recommended. Dose titration is recommended to achieve the desired clinical response. | √ | - |
| Hydantoins: hydantoins may increase serum primidone concentrations. In patients requiring both primidone and a hydantoin, closely monitor serum concentrations of primidone and primidone metabolites following any alteration in hydantoin therapy. | - | √ |
| Lapatinib: plasma lapatinib concentrations may be reduced, resulting in decreased efficacy. | √ | √ |


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| Description | Phenobarbital | Primidone |
|---|---|---|
| Avoid coadministration of lapatinib and phenobarbital. If these agents must be used concurrently, gradually titrate the dosage of lapatinib from 1,250 to 4,500 mg/day based on tolerability. If phenobarbital is discontinued, reduce lapatinib to the indicated dose. | | |
| 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 coadministration of barbiturates. | √ | √ |
| Methoxyflurane: enhanced renal toxicity may occur with concomitant administration. If possible, do not administer methoxyflurane in the presence of enzyme inducers such as barbiturates. Because enzyme induction dissipates slowly, be wary of the combination for several weeks following withdrawal of barbiturates. Monitor renal function closely. | √ | √ |
| Metronidazole: concomitant administration results in therapeutic failure of metronidazole. Observe for metronidazole treatment failure in patients receiving a barbiturate concurrently, and if necessary, increase the metronidazole dose accordingly. Alternatively, use higher initial metronidazole doses in patients also receiving a barbiturate. | √ | √ |
| Nifedipine: serum nifedipine concentrations are decreased, resulting in reduced efficacy. Titrate dose according to response. A larger dose of nifedipine may be needed. | √ | √ |
| Progestins: loss of contraceptive efficacy, possibly leading to pregnancy. Inform women of the increased risk of contraceptive failure. Consider alternative or additional nonhormonal methods. | √ | √ |
| Quinidine: concomitant administration appears to reduce serum quinidine concentrations and its elimination half-life. Closely monitor serum concentrations in a patient who requires quinidine if barbiturate therapy is added to or removed from the patient's therapy. | √ | √ |
| Ranolazine: ranolazine plasma concentrations may be reduced, decreasing the pharmacologic effect. Coadministration of ranolazine and cytochrome P450 3A inducers such as phenobarbital is contraindicated. | √ | - |
| Rilpivirine: rilpivirine plasma concentrations may be reduced, resulting in a loss of virologic response and possible resistance. Coadministration of rilpivirine with phenobarbital is contraindicated. | √ | - |
| Succinimides: Concomitant administration may result in lower serum primidone concentrations. A patient who requires both primidone and a succinimide should have serum primidone and phenobarbital concentrations monitored whenever a change is made in the succinimide therapy. | - | √ |
| Tacrolimus: tacrolimus concentrations may be reduced. Monitor tacrolimus whole-blood concentrations and observe the clinical response of the patient when starting, stopping, or changing the barbiturate dose. Adjust the tacrolimus dose as needed. | √ | √ |
| Theophyllines: decreased theophylline levels may occur, resulting in reduced therapeutic effects. Increased theophylline dosages may be required with use of a barbiturate. Closely monitor plasma levels of theophylline when barbiturates are added to or removed from a patient's drug regimen; tailor dosage as needed. | √ | √ |
| Temsirolimus: plasma concentrations of sirolimus (a major metabolite of temsirolimus) may be reduced, decreasing the efficacy. Avoid coadministration of temsirolimus and phenobarbital. If these agents must be used concurrently, consider increasing the dosage to temsirolimus 50 mg/week and monitor sirolimus levels. If phenobarbital is discontinued, reduce temsirolimus to the indicated dose. | √ | √ |
| Valproic acid: plasma barbiturate concentrations may be elevated, increasing the pharmacologic and adverse effects. When valproic acid is added to the therapeutic regimen of a patient receiving a barbiturate, monitor the patient and the serum barbiturate concentration. Barbiturate dosage may need to be decreased in some patients. | √ | - |


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| Description | Phenobarbital | Primidone |
|---|---|---|
| Voriconazole: voriconazole plasma concentrations may be reduced, decreasing the therapeutic effect. Coadministration of voriconazole and long-acting barbiturates is contraindicated. | √ | - |

**Table 9b. Drug Interactions-Benzodiazepines**[1,25,28,45]

| Description | Clobazam | Clonazepam | Diazepam |
|---|---|---|---|
| Azole antifungal agents: increased and prolonged central nervous system depression and psychomotor impairment, possibly continuing for several days after the azole antifungal agent is stopped. When using fluconazole, consider giving a lower benzodiazepine dose or a benzodiazepine metabolized by glucuronidation (e.g., lorazepam, temazepam). Warn patients about increased and prolonged sedative effects. | - | √ | √ |
| Carbamazepine: the pharmacologic effects of certain benzodiazepines may be decreased. Monitor for a decrease in benzodiazepine clinical response during coadministration of carbamazepine. If an interaction is suspected, consider using a higher dose of the benzodiazepine. | - | √ | - |
| Clozapine: the pharmacologic or toxic effects of certain benzodiazepines may be increased. Consider monitoring vital signs and observing patients for excessive adverse reactions when clozapine and benzodiazepines are coadministered. | - | √ | √ |
| Diltiazem: effects of certain benzodiazepines may be increased, producing increased central nervous system depression and prolonged effects. Give a lower dose of the benzodiazepine. Caution the patient about increased and prolonged sedative effects. | - | - | √ |
| Hydantoin: serum hydantoin concentrations may be increased, resulting in toxicity, but data conflict. Monitor serum hydantoin levels and effects when benzodiazepines are started or stopped. In some situations, a larger benzodiazepine dose may be needed. | - | - | √ |
| Macrolide antibiotics: increased central nervous system depression and prolonged sedation. Caution patients about increased or prolonged sedation. Reduce the benzodiazepine dose as needed. Benzodiazepines undergoing conjugative metabolism, including lorazepam, oxazepam, and temazepam, are unlikely to interact. Azithromycin does not alter midazolam metabolism but may delay its absorption. | - | - | √ |
| Opioid analgesics: increased risk of sedation and life-threatening respiratory depression, especially with overdose. Use with caution in patients in methadone maintenance programs (e.g., supervised ingestion) or patients receiving opioids for pain management. Subjective and performance responses may be altered. Caution patients against driving or operating machinery while taking these agents. | - | √ | √ |
| Protease inhibitors: possibly severe sedation and respiratory depression. Certain benzodiazepines are contraindicated in patients taking protease inhibitors. | - | √ | √ |
| Rifamycins: The pharmacologic effects of certain benzodiazepines may be decreased. Monitor the clinical response to the benzodiazepine when starting or stopping a rifamycin. Adjust the dose as needed. | - | √ | √ |


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**Table 9c. Drug Interactions-Hydantoins**[1,47,51-54]

| Description | Ethotoin | Phenytoin |
|---|---|---|
| Acetaminophen: coadministration of chronic hydantoins may increase the potential hepatotoxicity of acetaminophen and the therapeutic effects of acetaminophen may be reduced. The risk of hepatotoxicity is greatest when chronic dosing or overdosage with acetaminophen accompanies regular hydantoin use. Generally, no special dosage adjustment or monitoring is required at the usual therapeutic doses of acetaminophen and hydantoins. | √ | √ |
| Amiodarone: hydantoins may decrease serum amiodarone levels and serum hydantoin concentrations may increase resulting in symptoms of toxicity. Monitor drug concentrations and observe the patient for toxicity or loss of therapeutic effect when this combination is used. Be prepared to adjust the dose of either agent. Because effects may be delayed for several weeks, long-term monitoring is necessary. | √ | √ |
| Anticoagulants: concomitant administration with anticoagulants may lead to increased serum hydantoin concentrations with possible toxicity. Increased prothrombin time and an increased risk of bleeding may also occur. Monitor patients for signs or symptoms of altered response to hydantoins or anticoagulants while receiving the combination or when starting or stopping either drug. | √ | √ |
| Antineoplastic agents: serum phenytoin concentrations may be decreased, resulting in a loss of therapeutic effect. Monitor phenytoin serum levels and adjust the phenytoin dosage appropriately. Intravenous phenytoin may be useful. | - | √ |
| Carbamazepine: phenytoin may decrease serum carbamazepine levels. Monitor serum concentrations of both drugs, particularly when starting or stopping one drug. Alter dose as needed to maintain therapeutic effects and avoid toxicity. | √ | √ |
| Chloramphenicol: increased serum phenytoin concentrations with potential toxicity. If chloramphenicol must be used in a patient taking phenytoin, closely monitor serum concentrations of both drugs and adjust the dose as needed. | √ | √ |
| Cimetidine: serum hydantoin levels may be elevated, resulting in an increase in the pharmacologic effects. Monitor serum hydantoin levels and observe the patient's response when starting or stopping cimetidine. Adjust the hydantoin dosage as needed. | √ | √ |
| Contraceptives, hormonal: serum hydantoin levels may be increased and the pharmacologic effects of hormonal contraceptives may be decreased. Monitor patients for loss of seizure control. Increased doses of estradiol (i.e., 50 or 80 µg) may provide adequate cycle control; however, consider alternate methods of contraception. | √ | √ |
| Corticosteroids: corticosteroid effects may be decreased with concomitant therapy. Dexamethasone may reduce phenytoin levels. A two-fold or more increase in the steroid dose may be needed. Greater than expected phenytoin doses may also be required. If unable to avoid this combination, monitor phenytoin levels and adjust the dose of either agent. | √ | √ |
| Cyclosporine: phenytoin decreases cyclosporine concentrations, resulting in a decrease in the immunosuppressive activity. Closely monitor cyclosporine concentrations during concurrent phenytoin administration; tailor cyclosporine dosage to maintain concentrations in the therapeutic range. | √ | √ |
| Diazoxide: serum phenytoin levels may be decreased, resulting in a possible decrease in the anticonvulsant actions of phenytoin. Monitor phenytoin serum levels and observe patients for a decrease in phenytoin activity or an increase in toxicity if diazoxide is added to or discontinued from the treatment regimen. Tailor the phenytoin dosage as needed. | - | √ |
| Disopyramide: phenytoin coadministration may decrease the serum levels, half-life, and bioavailability of disopyramide while increasing mono-N-dealkyldisopyramide, a metabolite of disopyramide, serum levels. Anticholinergic actions may be enhanced. The effects of this | √ | √ |


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| Description | Ethotoin | Phenytoin |
|---|---|---|
| interaction may persist for several days following phenytoin discontinuation. The dose of disopyramide may need to be increased during concurrent phenytoin therapy. If increased anticholinergic effects occur, consider an alternative to disopyramide. | | |
| Disulfiram: serum hydantoin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of hydantoins. Monitor serum hydantoin levels and observe patients for hydantoin toxicity or a decrease in hydantoin activity if disulfiram is added to or discontinued from the treatment regimen. Adjust the hydantoin dosage as needed. | √ | √ |
| Dopamine: coadministration of phenytoin during a dopamine infusion may result in profound hypotension and possible cardiac arrest. Use phenytoin with extreme caution in patients receiving a dopamine infusion. If phenytoin must be administered, carefully monitor blood pressure and discontinue the phenytoin infusion if hypotension occurs. | - | √ |
| Doxycycline: the half-life of doxycycline is decreased by the coadministration of phenytoin. Monitor clinical response closely when phenytoin is used concomitantly. Some researchers recommend doubling the daily dose of doxycycline to maintain adequate serum levels. | √ | √ |
| Erlotinib: hydantoin concentrations may be elevated, increasing the pharmacologic effects and adverse reactions. Plasma erlotinib levels may be decreased, resulting in decreased efficacy. Use of alternative treatment that lacks cytochrome P450 3A4-inducing activity is recommended. If alternative therapy is not available, consider increasing the erlotinib starting dose at two week intervals. If the dose of erlotinib is adjusted upward, reduce to the indicated starting dose immediately after stopping the hydantoin. In addition, monitor hydantoin concentrations and observe the clinical response of patients when starting, stopping, or changing the erlotinib dose. Adjust the hydantoin dose as needed. | √ | √ |
| Estrogens: a loss of seizure control has been suggested with concomitant therapy and breakthrough bleeding, spotting, and pregnancy have also resulted. Monitor patients for loss of seizure control. Increased doses of estradiol (i.e., 50 or 80 µg) may provide adequate cycle control; however, consider alternate methods of contraception. | √ | √ |
| Exemestane: plasma exemestane concentrations may be reduced, decreasing the efficacy. If phenytoin is coadministered in patients receiving exemestane, the recommended dosage of exemestane is 50 mg once daily after a meal. If phenytoin is discontinued, reduce the exemestane dosage to 25 mg once daily with a meal. | - | √ |
| Felbamate: serum hydantoin concentrations may be increased, resulting in an increase in the pharmacologic and toxic effects of hydantoins. Phenytoin may also decrease serum felbamate concentrations. During any change in drug therapy, monitor hydantoin and felbamate concentrations and observe for changes in seizure control. In addition, observe for hydantoin toxicity if felbamate is added to the treatment schedule. When adding felbamate to phenytoin therapy, consider reducing the phenytoin dose approximately 20%. | √ | √ |
| Felodipine: the pharmacologic effects of felodipine may be decreased. Patients receiving long-term treatment with hydantoins and felodipine may require higher doses of felodipine to achieve plasma levels equivalent to those of patients who are not receiving hydantoins concurrently. | √ | √ |
| Fluconazole: serum hydantoin concentrations may be increased, producing an increase in the pharmacologic and toxic effects of hydantoins. Monitor hydantoin serum concentrations and observe for hydantoin toxicity or a decrease in hydantoin activity if fluconazole is started or stopped. Adjust the hydantoin dosage as needed. | √ | √ |
| Folic acid: serum hydantoin concentrations may be decreased, resulting in a decreased pharmacologic effect. Monitor serum hydantoin concentrations and observe for decreased hydantoin activity or increased toxicity if folic acid is started or stopped. Adjust the hydantoin dosage as needed. | √ | √ |
| Isoniazid: serum phenytoin concentrations may be increased, resulting in an increase in the | √ | √ |


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| Description | Ethotoin | Phenytoin |
|---|---|---|
| pharmacologic and toxic effects of phenytoin. Monitor hydantoin serum concentrations and observe patients for hydantoin toxicity or a decrease in hydantoin activity if isoniazid is added to or discontinued from the treatment regimen. Adjust the hydantoin dosage as needed. | | |
| Itraconazole: the pharmacologic effects of itraconazole may be decreased, while the effects of hydantoins may be increased. Until more clinical data are available, avoid concomitant use of itraconazole and hydantoins, if possible. | √ | √ |
| Lapatinib: plasma lapatinib concentrations may be reduced, decreasing the efficacy. Avoid coadministration of lapatinib and hydantoins. If these agents must be used concurrently, gradually titrate the dose of lapatinib from 1,250 up to 4,500 mg/day based on tolerability. If the hydantoin is discontinued, reduce lapatinib to the indicated dose. | - | √ |
| Levodopa: the efficacy of levodopa may be reduced with coadministration. Use this combination with caution. If an interaction is suspected, consider changing the hydantoin therapy. | √ | √ |
| Methadone: the actions of methadone may be reduced with coadministration. A higher dose of methadone may be required during coadministration of hydantoins. | √ | √ |
| Metyrapone: subnormal pituitary-adrenal responses to oral metyrapone when concomitantly administered. Consider using oral metyrapone doses up to twice the usual dose when assessing pituitary-adrenal axis function in patients maintained on hydantoins. Discontinue hydantoins when possible. | √ | √ |
| Mexiletine: coadministration results in increased mexiletine clearance, leading to a lower steady-state plasma concentration and possible loss of efficacy. Monitor plasma mexiletine concentrations and observe for loss of mexiletine effectiveness during coadministration of hydantoins. Increase mexiletine dose according to plasma concentration changes and clinical requirements. | √ | √ |
| Mirtazapine: plasma mirtazapine concentrations may be reduced, decreasing the pharmacologic effects. In patients receiving mirtazapine, closely monitor the clinical response when starting, stopping, or changing the hydantoin dose. Adjust mirtazapine therapy as needed. | √ | √ |
| Nisoldipine: the pharmacologic effects of nisoldipine may be decreased. Monitor the cardiovascular status of patients receiving nisoldipine when hydantoins therapy is started, stopped, or adjusted in dose. Patients receiving long-term treatment with hydantoins may require larger doses of nisoldipine than patients who are not receiving hydantoins. | √ | √ |
| Nondepolarizing muscle relaxants: coadministration may lead to a shorter than expected duration or a decreased effect of nondepolarizing muscle relaxants. Nondepolarizing muscle relaxants dosage may need to be increased. Monitor for reduced effectiveness. | - | √ |
| Phenacemide: serum hydantoin levels may be increased, resulting in an increase in the pharmacologic and toxic effects. Monitor serum hydantoin levels and observe the patient for hydantoin toxicity or a decrease in hydantoin activity if phenacemide is added to or discontinued from the treatment regimen. Tailor the hydantoin dosage as needed. | √ | √ |
| Primidone: hydantoins may increase serum primidone, phenobarbital, and phenylethylmalonamide concentrations. In patients requiring both primidone and a hydantoin, closely monitor serum concentrations of primidone and primidone metabolites following any alteration in hydantoin therapy. | √ | √ |
| Quetiapine: plasma quetiapine concentrations and pharmacologic effects may be decreased. In patients receiving Quetiapine, monitor clinical response when starting, stopping, or changing the dose of phenytoin. Be prepared to change the dose of Quetiapine as needed. | - | √ |
| Quinidine: a decrease in the therapeutic effect of quinidine may occur. Frequent monitoring | - | √ |


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| Description | Ethotoin | Phenytoin |
|---|---|---|
| of serum quinidine concentrations is recommended; an increase in the quinidine dose may be required. | | |
| Ranolazine: plasma ranolazine concentrations may be reduced, decreasing the pharmacologic effect. Coadministration of ranolazine and cytochrome P450 3A inducers such as phenytoin is contraindicated. | - | √ |
| Rifamycins: serum hydantoin levels may be decreased, resulting in decreased pharmacologic effects. Monitor hydantoin serum levels and observe patients for a decrease in hydantoin activity or an increase in toxicity if rifampin is added to or discontinued from the treatment regimen. Tailor the hydantoin dosage as needed. | √ | √ |
| Selective serotonin reuptake inhibitors: serum hydantoin concentrations may be increased, producing an increase in the pharmacologic and toxic effects of hydantoins. Monitor serum hydantoin concentrations and observe the clinical response of the patient when sertraline therapy is started, stopped or changed in dosage. Adjust the hydantoin dose accordingly. | √ | √ |
| Sucralfate: the absorption of oral phenytoin may be administration with coadministration. Consider monitoring the patient for a change in phenytoin activity if sucralfate is added to or discontinued from the treatment regimen. Tailor the dose of phenytoin as needed. | - | √ |
| Sulfonamides: serum hydantoin levels may be increased, resulting in increased pharmacologic and toxic effects. Monitor serum hydantoin levels and observe the patient for hydantoin toxicity or a decrease in hydantoin activity if sulfonamides are added to or discontinued from the treatment regimen. Tailor the hydantoin dosage as needed. | √ | √ |
| Tacrolimus: serum phenytoin concentrations may be increased and serum tacrolimus concentrations may be decreased. Monitor serum concentrations of tacrolimus and phenytoin. Observe the clinical response of the patient during coadministration of these drugs. Adjust the doses as needed. | - | √ |
| Temsirolimus: plasma concentrations of sirolimus, a major metabolite of temsirolimus, may be reduced, resulting in decreased efficacy. Avoid temsirolimus and hydantoin coadministration. If these agents must be used concurrently, consider increasing the dosage to temsirolimus 50 mg/wk and monitor sirolimus levels. If the hydantoin is discontinued, reduce temsirolimus to the indicated dose. | - | √ |
| Theophylline: decrease or loss of pharmacologic effects of theophyllines or phenytoin may occur. When either medication is added to or deleted from a patient's regimen, monitor the plasma levels of each. Tailor dosages as needed. | - | √ |
| Ticlopidine: plasma hydantoin concentrations may be increased, resulting in an increase in adverse effects. Monitor hydantoin levels and observe the patient's clinical response when the dose of ticlopidine is started, stopped, or changed. Adjust the phenytoin dose as needed. | √ | √ |
| Trimethoprim: serum hydantoin concentrations may be increased, producing an increase in the pharmacologic and toxic effects. Monitor serum hydantoin concentrations and observe patients for hydantoin toxicity or a decrease in hydantoin activity if trimethoprim is added to or discontinued from the treatment regimen. Tailor the hydantoin dosage as needed. | √ | √ |
| Valproic acid: hydantoin effects may be enhanced, while those of valproic acid may be decreased. Monitor the free fraction of hydantoin and serum valproic acid levels. Interpret total hydantoin plasma levels, considering the increase in the free fraction of the drug. Observe patients for hydantoin toxicity or loss of therapeutic effects. Tailor the dose of either drug as needed. | √ | √ |


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**Table 9d. Drug Interactions-Succinimides**[1,24,33,34]

| Description | Ethosuximide | Methsuximide |
|---|---|---|
| Lamotrigine: serum lamotrigine concentrations may be reduced, decreasing the therapeutic effects. It may be necessary to adjust the dose of when starting, stopping, or changing the dose of succinimide therapy. Observe the clinical response of the patient and adjust the dose of lamotrigine as needed. | √ | √ |
| Primidone: coadministration may result in lower serum primidone and phenobarbital concentrations. A patient who requires both primidone and a succinimide should have serum primidone and phenobarbital concentrations monitored whenever a change is made in the succinimide therapy. | √ | √ |


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**Table 9e. Drug Interactions-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aripiprazole: plasma aripiprazole concentrations may be reduced, decreasing the pharmacologic effects. When carbamazepine is added to aripiprazole therapy, double the aripiprazole dosage. Make additional dosage adjustments based on clinical evaluation. When carbamazepine is discontinued, decrease the dosage of aripiprazole. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Azole antifungals: plasma carbamazepine concentrations may be elevated, resulting in increased clinical and adverse effects. Closely monitor carbamazepine concentrations and observe the clinical response when an azole antifungal agent is started or stopped. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Bupropion: serum bupropion concentrations may be decreased, reducing the pharmacologic effects. Observe the clinical response of the patient. If an interaction is suspected, adjust therapy as indicated. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Carbapenem antibiotics: plasma valproic acid levels may be decreased, leading to a loss of seizure control. Monitor anticonvulsant plasma concentrations and observe patients for seizure activity when starting a carbapenem antibiotic. If an interaction is suspected, it may be necessary to use alternative antibiotic therapy. If the carbapenem antibiotic is stopped, the valproic acid dose may need to be reduced. | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Central nervous system depressants; concomitant use of perampanel and central nervous system depressants including alcohol may increase central nervous system depression. | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - |
| Cholestyramine: serum valproic acid concentrations and bioavailability may be reduced, resulting in a decrease in therapeutic effects. Administer anticonvulsant therapy at least three hours before but not within three hours following | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| cholestyramine. Monitor the patient's clinical response and adjust the dose of anticonvulsant as needed. | | | | | | | | | | | | | | | | | |
| Cimetidine: plasma carbamazepine levels may be increased, resulting in toxicity. Monitor serum carbamazepine concentrations, and observe the patient for signs of toxicity after initiation of cimetidine therapy. Adjust the dose accordingly. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Contraceptives, hormonal: loss of oral contraceptive efficacy, possibly resulting in unintended pregnancy. Plasma lamotrigine and valproic acid concentrations may also be reduced, resulting in a decreased therapeutic effect. To help avoid unintended pregnancy, patients should use an alternative method of contraception. If larger doses of the hormonal contraceptive are being considered, titrate the hormonal contraceptive dose against breakthrough bleeding. | √ | √ | - | - | - | - | √ | - | √ | √ | - | - | - | - | √ | - | - |
| Cyclosporine: cyclosporine levels may be decreased, resulting in a reduction of pharmacologic effects. Monitor cyclosporine levels; observe patient for signs of rejection or toxicity if carbamazepine is added to or discontinued from the treatment regimen. Adjust the cyclosporine dose as needed. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cytochrome P450 inducers; concurrent use may reduce perampanel serum concentration by approximately 50 to 67% | - | - | - | - | - | - | - | - | - | √ | - | - | - | - | - | - | - |
| Danazol: serum carbamazepine concentrations may be increased, resulting in increased pharmacologic and toxic effects. Avoid this combination if possible. If both drugs are given, monitor carbamazepine serum levels and observe patients for signs of toxicity after initiating danazol therapy. In patients stabilized on carbamazepine, it may be | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| necessary to alter the dose when starting or stopping danazol. | | | | | | | | | | | | | | | | | |
| Diltiazem: serum carbamazepine concentrations may be increased, resulting in toxicity. Monitor serum carbamazepine levels, and observe patients for signs of carbamazepine toxicity or a loss of therapeutic effect if diltiazem is added to or discontinued from the treatment regimen. Be prepared to increase the carbamazepine dose if diltiazem is discontinued. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Divalproex sodium, valproate sodium, valproic sodium: increased and decreased valproic acid levels, resulting in toxicity or loss of seizure control. Variable changes in carbamazepine levels may also occur and lamotrigine levels may be increased. Monitor serum levels and observe patients for seizure activity and toxicity for at least one month after either drug is started or stopped. Alter dosage as needed. | √ | - | - | √ | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Doxycycline: coadministration may result in a decrease in the half-life of doxycycline, resulting in a reduction in efficacy. The dose of doxycycline may need to be increased during carbamazepine coadministration. Consider the use of another tetracycline. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Exemestane: plasma exemestane concentrations may be reduced, decreasing the efficacy. If carbamazepine is coadministered in patients receiving exemestane, the recommended dosage of exemestane is 50 mg once daily after a meal. If carbamazepine is discontinued, reduce the exemestane dosage to 25 mg once daily with a meal. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Estrogens: the efficacy of estrogens may be decreased. Inform women of the possible increased risk of estrogen failure during concomitant administration of topiramate. An | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| alternate method of contraception or an increased estrogen dose (greater than or equal to 35 µg ethinyl estradiol) should be considered. | | | | | | | | | | | | | | | | | |
| Felbamate: decreased serum carbamazepine or felbamate concentrations may occur, resulting in a loss of effectiveness. Serum valproic acid concentrations may be increased, possibly resulting in toxicity. During any change in drug therapy, observe patients for changes in seizure control. The epoxide metabolite is active and may pharmacodynamically balance the decrease in carbamazepine concentration. Also, in patients receiving felbamate, carefully monitor concentrations if therapy with carbamazepine is altered. | √ | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Felodipine: the pharmacologic effects of felodipine may be decreased. Patients receiving long-term treatment with carbamazepine and felodipine may require higher doses of felodipine to achieve plasma levels equivalent to those of patients who are not receiving carbamazepine concurrently. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Fluoxetine: serum carbamazepine levels may be increased, possibly leading to toxicity. Monitor serum carbamazepine levels during coadministration of fluoxetine. Adjust the dose of carbamazepine accordingly. Sertraline does not appear to interact with carbamazepine and may be an alternative. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Haloperidol: therapeutic effects of haloperidol may be decreased and increased for carbamazepine. If an interaction is suspected, consider adjusting the dose of therapy as indicated. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| HMG-CoA reductase inhibitors: plasma concentrations of certain HMG-CoA reductase inhibitors may be reduced, decreasing the therapeutic effect. If coadministration of | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| these agents cannot be avoided, closely monitor the clinical response of the patient. Pravastatin and rosuvastatin are less likely to interact with carbamazepine and may be suitable alternatives. | | | | | | | | | | | | | | | | | |
| Hydantoins: phenytoin may decrease serum carbamazepine, felbamate, and valproic acid levels. Monitor serum concentrations of both drugs, particularly when starting or stopping one drug. Alter dose as needed to maintain therapeutic effects and avoid toxicity. | √ | √ | - | √ | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Isoniazid: both carbamazepine toxicity and isoniazid hepatotoxicity may occur with coadministration. Monitor serum carbamazepine concentrations, and observe patients for toxicity. Adjust the dose of carbamazepine as needed. Monitor liver function and consider discontinuing isoniazid if hepatotoxicity occurs. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Lamotrigine: serum lamotrigine levels and efficacy may be reduced. Serum levels of the active metabolite of carbamazepine may be increased, resulting in toxicity. It may be necessary to adjust the dose of lamotrigine when the dose of carbamazepine is started, stopped, or changed. Observe clinical response and adjust the lamotrigine dose as needed. When adding lamotrigine to regimens including carbamazepine monitor for carbamazepine toxicity and reduce the dose if noted. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Lapatinib: plasma lapatinib concentrations may be reduced, decreasing the efficacy. Avoid coadministration of lapatinib and carbamazepine. If these agents must be used concurrently, titrate the dosage of lapatinib gradually from 1,250 to 4,500 mg/day based on tolerability. If carbamazepine is discontinued, reduce the lapatinib dose to the indicated dosage. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lithium: coadministration may result in adverse central nervous system effects. Monitor patients for signs of neurotoxicity. If these develop, one of the two drugs may need to be discontinued. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mebendazole: the pharmacologic effects of mebendazole may be decreased. No special precautions appear necessary. If an interaction is suspected, consider increasing the dose of mebendazole during coadministration of carbamazepine. Measure mebendazole plasma levels and adjust the dose accordingly. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Monoamine oxidase inhibitor: theoretical risk of severe adverse events with coadministration. On theoretical grounds, coadministration of carbamazepine and a monoamine oxidase inhibitor is contraindicated. Discontinue the monoamine oxidase inhibitor at least 14 days prior to administration of carbamazepine. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Nefazodone: serum carbamazepine levels may be elevated with possible increase in adverse events and lower serum nefazodone levels, resulting in a decrease in efficacy. Coadministration of carbamazepine and nefazodone is contraindicated. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Nondepolarizing muscle relaxants: coadministration may lead to a shorter than expected duration or a decreased effect of nondepolarizing muscle relaxants or an increased effect. Monitor patients for reduced muscle relaxant effectiveness and increase the dose of the nondepolarizing muscle relaxants accordingly. | √ | - | - | - | √ | - | - | - | - | - | - | - | - | - | - | - | - |
| Primidone: coadministration may result in decreased primidone, its metabolite, and carbamazepine serum concentrations. Plasma barbiturate concentrations may also be elevated, increasing the pharmacologic and | √ | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| adverse events. Monitor serum anticonvulsant concentrations, and observe the patient for loss of anticonvulsant efficacy. Consider discontinuing the barbiturate or adjusting the dose of anticonvulsant as needed. | | | | | | | | | | | | | | | | | |
| Propoxyphene: serum carbamazepine concentrations may be increased, resulting in toxicity. Because of the potential for toxicity and the availability of alternative analgesics, avoid propoxyphene. If this combination is used, monitor serum carbamazepine concentrations and observe patients for clinical signs of toxicity. Be prepared to adjust the carbamazepine dose as needed. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Protease inhibitors: carbamazepine levels may be elevated, increasing the risk of toxicity. Protease inhibitor levels may decrease, resulting in decreased efficacy. Closely monitor carbamazepine serum levels when starting, stopping, or changing the dose of the protease inhibitor and observe the clinical response to protease inhibitor therapy. Adjust the dose as needed. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Quetiapine: serum quetiapine levels may be decreased or increased. Plasma concentrations of carbamazepine active metabolite may be increased, resulting in toxicity. Observe patients for possible neurotoxicity or increased seizure activity if anticonvulsant therapy and quetiapine are coadministered. Consider monitoring anticonvulsant levels. Also, monitor for a decrease in quetiapine response. If an interaction is suspected, it may be necessary to discontinue anticonvulsant therapy or quetiapine. | √ | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Ranolazine: plasma ranolazine concentrations may be reduced, decreasing the pharmacologic effect. Coadministration of ranolazine and cytochrome P450 3A | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| inducers such as carbamazepine is contraindicated. | | | | | | | | | | | | | | | | | |
| Rifamycins: plasma lamotrigine levels may be reduced, decreasing the pharmacologic effects. It may be necessary to adjust the dose of lamotrigine when starting, stopping, or changing the dose of the rifamycin. Observe the clinical response of the patient and adjust the dose of lamotrigine as needed. | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Salicylates: coadministration may lead to increased free fraction of valproic acid, possibly leading to toxic effects. When aspirin is given to a patient taking valproic acid, monitor serum valproic acid concentrations (including free fraction if readily available), symptoms of valproic acid toxicity, and liver enzymes. | - | - | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Sertraline: the therapeutic effect of sertraline may be decreased or reversed. In patients receiving carbamazepine, consider administration of an antidepressant that is not affected by cytochrome P450 3A4 metabolism. In patients receiving sertraline, closely monitor patient response and be prepared to adjust the dose of sertraline when starting, stopping, or changing the dose of carbamazepine. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Succinimides: serum lamotrigine concentrations may be reduced, decreasing the therapeutic effects. It may be necessary to adjust the dose of lamotrigine when starting, stopping, or changing the dose of succinimide therapy. Observe the clinical response of the patient and adjust the dose of lamotrigine as needed. | - | - | - | - | - | - | √ | - | - | - | - | - | - | - | - | - | - |
| Temsirolimus: plasma concentrations of temsirolimus' active metabolite may be decreased, resulting in reduced efficacy. Avoid temsirolimus and carbamazepine coadministration. If these agents must be used | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| concurrently, consider increasing the dosage to temsirolimus 50 mg/week and monitor sirolimus levels. If carbamazepine is discontinued, reduce temsirolimus to the indicated dose. | | | | | | | | | | | | | | | | | |
| Topiramate: the pharmacologic effects of topiramate may be reduced. Monitor the clinical response to topiramate when starting, stopping, or changing the dose of carbamazepine. Adjust the dose as needed. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Verapamil: serum carbamazepine levels may be increased, resulting in an increase in the pharmacologic and toxic effects. Monitor serum carbamazepine levels, and observe the patient for signs of carbamazepine toxicity or loss of therapeutic effect if verapamil is added to or discontinued from the treatment regimen. carbamazepine dose may need to be decreased 40 to 50% when administered with verapamil. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Voriconazole: plasma voriconazole concentrations may be reduced, decreasing the therapeutic effect. Coadministration of voriconazole and carbamazepine is contraindicated. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Warfarin: coadministration may lead to a decreased anticoagulation effect of warfarin. Monitor coagulation parameters when starting or stopping carbamazepine therapy in patients receiving warfarin. Adjust the warfarin dose as needed. | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Zidovudine: the area under the curve of zidovudine may be increased, leading to toxicity. It may be necessary to adjust the dose of zidovudine when starting, stopping, or changing the dose of valproic acid. Monitor hemoglobin and hematocrit. | - | √ | - | - | - | - | - | - | - | - | - | - | - | - | √ | - | - |
| Ziprasidone: plasma ziprasidone concentrations may be | √ | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |


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| Description | Carbamazepine | Divalproex | Ezogabine | Felbamate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Pregabalin | Rufinamide | Tiagabine | Topiramate | Valproic acid | Vigabatrin | Zonisamide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| reduced, decreasing the therapeutic effect. Monitor the clinical response of the patient to ziprasidone when starting, stopping, or changing the dose of carbamazepine. Be prepared to change the ziprasidone dose as needed. | | | | | | | | | | | | | | | | | |


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## Dosage and Administration

**Table 10a. Dosing and Administration-Barbiturates**[1,48-50,56]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Phenobarbital | Anticonvulsant:<br>Injection: 4 to 6 mg/kg/day for seven to 10 days to blood level of 10 to 15 µg/mL or 10 to 15 mg/kg/day intramuscular or intravenous<br><br>Tablet: 50 to 100 mg two to three times daily<br><br>Emergency control of certain acute convulsive episodes:<br>Injection: 20 to 320 mg/kg over 10 to 15 minutes intravenous<br><br>Hypnotic:<br>Injection (bedtime): 100 to 320 mg intramuscular or intravenous<br><br>Sedative:<br>Elixir, tablet: 30 to 120 mg/day administered in two to three divided doses<br><br>Injection (daytime sedation): 30 to 120 mg/day administered in two to three divided doses<br><br>Injection (preoperative sedation): 100 to 200 mg 60 to 90 minutes before surgery<br><br>Partial and generalized seizures:<br>Elixir: 3 to 6 mg/kg/day or 60 to 200 mg/day | Anticonvulsant:<br>Tablet: 15 to 20 mg two to three times daily<br><br>Sedative:<br>Injection (preoperative sedation): 1 to 3 mg/kg intramuscular or intravenous<br><br>Tablet: 6 mg/kg/day in three divided doses<br><br>Partial and generalized seizures:<br>Elixir: 3 to 6 mg/kg/day or 60 to 200 mg/day<br><br>Status epilepticus: Injection: 15 to 20 mg/kg over 10 to 15 minutes intravenous | Elixir:<br>20 mg/5 mL<br><br>Injection:<br>65 mg/mL<br>130 mg/mL<br><br>Tablet:<br>15 mg<br>16.2 mg<br>30 mg<br>32.4 mg<br>60 mg<br>64.8 mg<br>97.2 mg<br>100 mg |
| Primidone | Control of grand mal, psychomotor, and focal epileptic seizures, used alone or concomitantly with other anticonvulsants:<br>Tablet (patients >8 years of age): initial, 100 to 125 mg at bedtime for three days then 100 to 125 mg twice daily for three days, then 100 to 125 mg three times daily for three days, then 250 mg three times daily; maintenance, 250 mg three to four times daily; maximum, 500 | Control of grand mal, psychomotor, and focal epileptic seizures, used alone or concomitantly with other anticonvulsants:<br>Tablet (patients >8 years of age): initial, 100 to 125 mg at bedtime for three days then 100 to 125 mg twice daily for three days, then 100 to 125 mg three times daily for three days, then 250 mg three times daily; maintenance, 250 mg three to four times | Tablet:<br>50 mg<br>250 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | mg four times daily | daily; maximum, 500 mg four times daily<br><br>Tablet (patients <8 years of age): initial, 50 mg at bedtime for three days, then 50 mg twice daily for three days, then 100 mg twice daily for three days, then 125 mg three times daily; maintenance, 125 to 250 mg three times daily or 10 to 25 mg/kg/day in divided doses | |

**Table 10b. Dosing and Administration-Benzodiazepine**[1,25,28,45]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Clobazam | Adjunctive treatment of seizures associated with LGS in patients two years of age or older:<br>Tablet: initial, 5 (≤30 kg) or 10 mg/day (>30 kg); maintenance, 10 to 20 (≤30 kg) or 20 to 40 mg/day (>30 kg) | Adjunctive treatment of seizures associated with LGS in patients two years of age or older:<br>Tablet: initial, 5 (≤30 kg) or 10 mg/day (>30 kg); maintenance, 10 to 20 (≤30 kg) or 20 to 40 mg/day (>30 kg) | Tablet:<br>5 mg<br>10 mg<br>20 mg |
| Clonazepam | Treatment of LGS (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy:<br>Orally disintegrating tablet, tablet: initial, not to exceed 1.5 mg/day divided into three doses; maintenance, increase until seizures are adequately controlled; maximum, 20 mg/day<br><br>Orally disintegrating tablet (pediatrics): initial, 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses; maintenance, 0.1 to 0.2 mg/kg/day<br><br>Treatment of panic disorder, with or without agoraphobia:<br>Orally disintegrating tablet, tablet: initial, 0.25 mg twice daily; maintenance, 1 mg/day | Treatment of LGS (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy:<br>Orally disintegrating tablet: initial, 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses; maintenance, 0.1 to 0.2 mg/kg/day | Orally disintegrating tablet:<br>0.125 mg<br>0.25 mg<br>0.5 mg<br>1 mg<br>2 mg<br><br>Tablet:<br>0.5 mg<br>1 mg<br>2 mg |
| Diazepam | Management of selected, refractory, patients with epilepsy, on stable regimens of | Management of selected, refractory, patients with epilepsy, on stable regimens | Rectal gel:<br>2.5 mg<br>10 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity:<br>Rectal gel: 0.2 to 0.5 mg/kg as a single dose; a second dose may be prescribed and administered four to 12 hours later | of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity:<br>Rectal gel: 0.2 to 0.5 mg/kg as a single dose; a second dose may be prescribed and administered four to 12 hours later | 20 mg |

LGS=Lennox-Gastaut Syndrome

**Table 10c. Dosing and Administration-Hydantoins**[1,47,51-54]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Ethotoin | Control of generalized tonic-clonic and complex partial seizures:<br>Tablet: initial, 1 g/day in four to six divided doses; maintenance, 2 to 3 g/day | Control of generalized tonic-clonic and complex partial seizures:<br>Tablet: initial, do not start >750 mg/day; maintenance, 500 mg to 1 g | Tablet:<br>250 mg |
| Phenytoin | Seizures:<br>Chewable tablet, extended-release capsule (treatment naïve adults): initial, 100 mg three times daily; maintenance, 100 to 200 mg three times daily<br><br>Suspension (treatment-naïve adults): 5 mL three times daily<br><br>Status epilepticus:<br>Injection: loading dose, 10 to 15 mg/kg; maintenance, 100 mg orally or intravenously every six to eight hours | Seizures:<br>Chewable tablet, extended-release capsules, suspension: initial, 5 mg/kg/day in two to three equally divided doses; maintenance, 4 to 8 mg/kg; maximum, 300 mg/day<br><br>Status epilepticus:<br>Injection: loading dose, 10 to 15 mg/kg; maintenance, 100 mg orally or intravenously every six to eight hours | Chewable tablet:<br>50 mg<br><br>Extended-release capsule:<br>30 mg<br>100 mg<br>200 mg<br>300 mg<br><br>Injection:<br>50 mg/mL<br><br>Suspension:<br>125 mg/5 mL |

**Table 10d. Dosing and Administration-Succinimides**[1,24,33,34]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Ethosuximide | Absence seizures:<br>Capsule, syrup: initial, 500 mg/day | Absence seizures in patients ≥3 years of age:<br>Capsule, syrup: initial, 250 or 500 mg/day; maintenance, 20 mg/kg/day | Capsule:<br>250 mg<br><br>Syrup:<br>250 mg/5 mL |
| Methsuximide | Absence seizures:<br>Capsule: initial, 300 mg/day for seven days; maintenance, increase at weekly intervals by 300 mg/day; maximum, 1,200 mg/day | Absence seizures:<br>Capsule: initial, 300 mg/day for seven days; maintenance, increase at weekly intervals by 300 mg/day; maximum, 1,200 mg/day | Capsule:<br>300 mg |


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**Table 10e. Dosing and Administration-Anticonvulsants, Miscellaneous**[1,23,26,27,31,32,35-44,46,55, 57-66]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Carbamazepine | Generalized tonic-clonic seizures, mixed seizure patterns, and partial seizures with complex symptomatology:<br>Chewable tablet, extended-release tablet, suspension, tablet: initial, 400 mg/day, maintenance, 800 to 1,200 mg/day<br><br>Generalized tonic-clonic seizures in children >12 years of age:<br>Chewable tablet, extended-release tablet, suspension, tablet: initial, 400 mg/day; maintenance, 800 to 1,200 mg/day; maximum, 1,000 to 1,200 mg/day<br><br>Bipolar disorder in adults:<br>Extended-release capsules: initial, 400 mg/day in divided doses twice daily; maximum, 1,600 mg/day<br><br>Trigeminal neuralgia in adults:<br>Chewable tablet, extended-release tablet, suspension, tablet: initial, 200 mg/day; maintenance, 400 to 800 mg/day; maximum, 1,200 mg/day | Generalized tonic-clonic seizures, mixed seizure patterns, and partial seizures with complex symptomatology in children <6 years of age:<br>Chewable tablet, extended-release tablet, suspension, tablet: initial, 10 to 20 mg/kg/day in divided doses; maintenance, <35 mg/kg; maximum, 35 mg/kg/day<br><br>Generalized tonic-clonic seizures in children six to 12 years of age:<br>Chewable tablet, extended-release tablet, suspension, tablet: initial, 200 mg/day; maintenance, 400 to 800 mg/day; maximum, 1,000 mg/day<br><br>Generalized tonic-clonic seizures in children >12 years of age:<br>Chewable tablet, extended-release tablet, suspension, tablet: initial, 400 mg/day; maintenance, 800 to 1,200 mg/day; maximum, 1,000 to 1,200 mg/day | Chewable tablet:<br>100 mg<br><br>Extended-release capsule:<br>100 mg<br>200 mg<br>300 mg<br><br>Extended-release tablet:<br>100 mg<br>200 mg<br>400 mg<br><br>Suspension:<br>100 mg/5 mL<br><br>Tablet:<br>200 mg |
| Divalproex | Complex partial and absence seizures:<br>Capsule, delayed-release tablet, extended-release tablet: initial, 10 to 15 mg/kg/day; maximum, 60 mg/kg/day<br><br>Bipolar disorder:<br>Delayed-release tablet: initial, 750 mg/day in divided doses; | Complex partial and absence seizures in children 10 years of age and older:<br>Capsule, delayed-release tablet, extended-release tablet: initial, 10 to 15 mg/kg/day; maximum, 60 mg/kg/day | Capsule (sprinkle):<br>125 mg<br><br>Delayed-release tablet:<br>125 mg<br>250 mg<br>500 mg<br><br>Extended-release tablet:<br>250 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | maximum 60 mg/kg/day<br><br>Extended-release tablet: initial, 25 mg/kg/day; maximum, 60 mg/kg/day<br><br>Migraine prophylaxis:<br>Delayed-release tablet: maintenance, 250 mg twice daily; maintenance, 1,000 mg/day<br><br>Extended-release tablet: initial, 500 mg once daily for seven days; maintenance, 1,000 mg/day | | 500 mg |
| Ezogabine | Partial seizures:<br>Tablet: initial, 100 mg three time daily; maintenance, 200 to 400 mg three times daily; maximum, 400 mg three times daily | The safety and effectiveness in children <18 years of age have not been established. | Tablet:<br>50 mg<br>200 mg<br>300 mg<br>400 mg |
| Felbamate | Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use:<br>Suspension, tablet: initial, 1,200 mg/day in three to four divided doses; maintenance, 2,400 to 3,600 mg/day | Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use:<br>Suspension, tablet: initial, 1,200 mg/day in three to four divided doses; maintenance, 2,400 to 3,600 mg/day<br><br>The safety and efficacy of felbamate in children, other than those with Lennox-Gastaut syndrome, have not been established. | Suspension:<br>600 mg/5 mL<br><br>Tablet:<br>400 mg<br>600 mg |
| Gabapentin | Partial seizures:<br>Capsule, solution, tablet (patients >12 years of age): initial, 300 mg three times daily; maintenance, 900 to 1,800 mg/day | Partial seizures in children ≥3 years of age:<br>Capsule, solution, tablet: initial, 10 to 15 mg/kg/ day | Capsule:<br>100 mg<br>300 mg<br>400 mg<br><br>Solution: |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | Capsule, solution, tablet (patients three to 12 years of age): initial, 10 to 15 mg/kg/ day administered in three divided doses; maintenance, 25 to 40 mg/kg/day<br><br>PHN:<br>Capsule, solution, tablet: initial, 300 mg once daily for one day, 300 mg twice daily for one day, and 300 mg three times daily for one day; maintenance, 1,800 mg/day divided three times daily | administered in three divided doses; maintenance, 25 to 40 mg/kg/day | 250 mg/5 mL<br><br>Tablet:<br>600 mg<br>800 mg |
| Lacosamide | Partial seizures:<br>Injection, solution, tablet: initial, 50 mg twice daily; maintenance, 200 to 400 mg/day | The safety and effectiveness in children <17 years of age have not been established. | Injection:<br>200 mg/20 mL<br><br>Solution:<br>10 mg/mL<br><br>Tablet:<br>50 mg<br>100 mg<br>150 mg<br>200 mg |
| Lamotrigine | Bipolar disorder:<br>Chewable tablet, orally disintegrating tablet, tablet: 200 mg/day (target dose)<br><br>LGS, and partial and primary generalized tonic-clonic seizures:<br>Chewable tablet, extended-release tablet, orally disintegrating tablet, tablet: initial dosage and dose titration is based on concurrent medications | Bipolar disorder in patients :<br>Safety and efficacy in children <18 years of age have not been established.<br><br>LGS, and partial and primary generalized tonic-clonic seizures in patients ≥2 years of age:<br>Chewable tablet, extended-release tablet, orally disintegrating tablet, tablet: initial dosage and dose titration is based on concurrent medications | Chewable tablet:<br>2 mg<br>5 mg<br>25 mg<br><br>Extended-release tablet:<br>25 mg<br>50 mg<br>100 mg<br>200 mg<br>250 mg<br>300 mg<br><br>Orally disintegrating tablet:<br>25 mg<br>50 mg<br>100 mg<br>200 mg<br><br>Tablet:<br>25 mg<br>50 mg<br>100 mg<br>150 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | | | 200 mg<br>250 mg |
| Levetiracetam | Myoclonic seizures in patients with juvenile myoclonic epilepsy:<br>Injection, solution, tablet: initial, 500 mg twice daily; maintenance, 1,500 twice daily<br><br>Partial seizures:<br>Extended-release tablet: initial, 1,000 mg once daily; maximum, 3,000 mg/day<br><br>Injection, solution, tablet: initial, 7 to 10 mg/kg or 500 mg twice daily; maintenance, 21 to 30 mg/kg or 1,500 mg twice daily<br><br>Primary generalized tonic-clonic seizures:<br>Injection, solution, tablet: initial, 10 mg/kg or 500 mg twice daily; maintenance, 30 mg/kg or 1,500 mg twice daily | Myoclonic seizures in patients with juvenile myoclonic epilepsy in patients ≥12 years of age:<br>Injection, solution, tablet: initial, 500 mg twice daily; maintenance, 1,500 twice daily<br><br>Partial seizures in patients ≥16 years of age:<br>Extended-release tablet: initial, 1,000 mg once daily; maximum, 3,000 mg/day<br><br>Partial seizures in patients ≥1 month of age:<br>Injection, solution, tablet: initial, 7 to 10 mg/kg or 500 mg twice daily; maintenance, 21 to 30 mg/kg or 1,500 mg twice daily<br><br>Primary generalized tonic-clonic seizures in patients ≥6 years of age:<br>Injection, solution, tablet: initial, 10 mg/kg or 500 mg twice daily; maintenance, 30 mg/kg or 1,500 mg twice daily | Extended-release tablet:<br>500 mg<br>750 mg<br><br>Injection:<br>500 mg/5mL<br><br>Solution:<br>100 mg/mL<br><br>Tablet:<br>250 mg<br>500 mg<br>750 mg<br>1,000 mg |
| Oxcarbazepine | Partial seizures:<br>Extended-release tablet: initial, 600 mg once daily; maintenance, dose dependent on body weight or 1,200 to 2,400 mg once daily<br><br>Suspension, tablet: initial, 8 to 10 mg/kg/day or 600 | Partial seizures in patients ≥6 years of age:<br>Extended-release tablet: initial, 8 to 10 mg/kg/ once daily; maintenance, dose dependent on body weight or 1,200 to | Extended-release tablet:<br>150 mg<br>300 mg<br>600 mg<br><br>Suspension:<br>300 mg/5 mL |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
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| | mg/day administered in two divided doses; maintenance, dose dependent on body weight or 1,200 to 2,400 mg/day | 2,400 mg once daily<br><br>Partial seizures in patients ≥2 years of age:<br>Suspension, tablet: initial, 8 to 10 mg/kg/day or 600 mg/day administered in two divided doses; maintenance, dose dependent on body weight or 1,200 to 2,400 mg/day | Tablet:<br>150 mg<br>300 mg<br>600 mg |
| Perampanel | Partial seizures:<br>Tablet: initial, 2 mg once daily at bedtime (4 mg if using enzyme-inducing AEDs); maintenance, 4 to 8 mg once daily at bedtime; maximum, 12 mg once daily at bedtime | Partial seizures in patients ≥12 years of age:<br>Tablet: initial, 2 mg once daily at bedtime (4 mg if using enzyme-inducing AEDs); maintenance, 4 to 8 mg once daily at bedtime; maximum, 12 mg once daily at bedtime | Tablet:<br>2 mg<br>4 mg<br>6 mg<br>8 mg<br>10 mg<br>12 mg |
| Pregabalin | Fibromyalgia:<br>Capsule: initial, 75 mg two times a day; maintenance, 300 to 450 mg/day<br><br>Management of neuropathic pain associated with DPN:<br>Capsule: initial, 150 mg divided three times daily; maintenance, 150 to 300 mg/day divided twice daily or three times daily; maximum, 300 mg/day divided twice daily or three times daily<br><br>Management of neuropathic pain associated with spinal cord injury:<br>Capsule: initial, 75 mg twice daily; maintenance,150 to 600 mg/day<br><br>Partial seizures:<br>Capsule: initial, not to exceed 150 mg/day; maintenance, 150 to 600 mg/day; maximum, 600 mg/day | The safety and effectiveness in children have not been established. | Capsule:<br>25 mg<br>50 mg<br>75 mg<br>100 mg<br>150 mg<br>200 mg<br>225 mg<br>300 mg<br><br>Solution:<br>20 mg/mL |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
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| | PHN:<br>Capsule: initial, 150 mg/day divided twice daily or three times daily; maintenance, 300 to 600 mg mg/day divided twice daily or three times daily; maximum, 600 mg/day divided twice daily or three times daily | | |
| Rufinamide | LGS:<br>Suspension, tablet: initial, 10 mg/kg/day or 400 to 800 mg/day administered in two divided doses; maintenance, 45 mg/kg/day or 3,200 mg/day | LGS in patients ≥4 years of age:<br>Suspension, tablet: initial, 10 mg/kg/day or 400 to 800 mg/day administered in two divided doses; maintenance, 45 mg/kg/day or 3,200 mg/day | Suspension:<br>40 mg/mL<br><br>Tablet:<br>200 mg<br>400 mg |
| Tiagabine | Partial seizures:<br>Tablet: initial, 4 mg/day; maintenance, 32 to 56 mg/day administered in two to four divided doses | Partial seizures in patients >12 years of age:<br>Tablet: initial, 4 mg/day; maintenance, up to 32 mg/day administered in two to four divided doses; maximum, 32 mg/day | Tablet:<br>2 mg<br>4 mg<br>12 mg<br>16 mg |
| Topiramate | Epilepsy monotherapy (patients ≥10 years of age):<br>Capsule (sprinkle), tablet: initial, 50 mg/day administered in two divided doses; maximum, 400 mg/day administered in two divided doses<br><br>Extended-release capsule: initial 50 mg once daily; maintenance, 400 mg once daily<br><br>Epilepsy adjunctive therapy (adults with partial onset seizure or LSG and primary generalized tonic-clonic seizures):<br>Capsule (sprinkle), tablet: initial, 25 to 50 mg/day; maintenance, 200 to 400 mg/day administered in two divided doses | Epilepsy monotherapy (children two to <10 years):<br>Capsule (sprinkle), tablet: initial, 25 mg/day administered for seven days; maintenance, daily doses in two divided doses based on weight<br><br>Epilepsy monotherapy (patients ≥10 years of age):<br>Capsule (sprinkle), tablet: initial, 50 mg/day administered in two divided doses; maximum, 400 mg/day administered in two divided doses<br><br>Extended-release | Capsule (sprinkle):<br>15 mg<br>25 mg<br><br>Tablet:<br>25 mg<br>50 mg<br>100 mg<br>200 mg<br><br>Extended-release capsule:<br>25 mg<br>50 mg<br>100 mg<br>200 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
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| | Extended-release capsule: Initial, 25 to 50 mg once daily; maintenance, 200 to 400 mg once daily<br><br>Migraine prophylaxis:<br>Capsule, tablet: initial, 25 mg/day administered nightly for seven days; maintenance, 100 mg/day administered in two divided doses | capsule: initial 50 mg once daily; maintenance, 400 mg once daily<br><br>Epilepsy adjunctive therapy (pediatrics with partial onset seizures, primary generalized tonic-clonic seizures, or LSG):<br>Capsule (sprinkle), tablet: initial, 25 mg/day administered at night for seven days; maintenance, 5 to 9 mg/day/day administered in two divided doses<br><br>Extended-release capsule: Initial, 25 to 50 mg once daily; maintenance, 200 to 400 mg once daily | |
| Valproic acid | Absence seizures:<br>Capsule, delayed-release capsule, solution: initial, 15 mg/kg/day; maintenance, increase until seizure control or limiting adverse events<br><br>Bipolar disorder:<br>Delayed-release capsule: initial, 750 mg/day; maintenance, increase rapidly to achieve lowest therapeutic dose or desired plasma level<br><br>Migraine prophylaxis:<br>Delayed-release capsule: 25 mg twice daily<br><br>Partial seizures:<br>Capsule, delayed-release capsule, solution: initial, 10 to 15 mg/kg/day; maintenance, increase to achieve optimal response | Absence seizures:<br>Capsule, delayed-release capsule, solution: initial, 15 mg/kg/day; maintenance, increase until seizure control or limiting adverse events<br><br>Partial seizures (patients >10 years of age):<br>Capsule, delayed-release capsule, solution: initial, 10 to 15 mg/kg/day; maintenance, increase to achieve optimal response | Capsule:<br>250 mg<br><br>Delayed-release capsule:<br>125 mg<br>250 mg<br>500 mg<br><br>Solution:<br>250 mg/5 mL |
| Vigabatrin | Partial seizures:<br>Tablet: initial, 500 mg twice | Infantile spasms (patients >1 month to | Solution (powder):<br>500 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
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| | daily; maintenance, 1.5 g twice daily | 2 years of age):<br>Solution: initial, 50 mg/kg/day twice daily; maximum, 150 mg/kg/day<br><br>Partial seizures:<br>Tablet: initial, 500 mg twice daily; maintenance, 1.5 g twice daily | Tablet:<br>500 mg |
| Zonisamide | Partial seizures:<br>Capsule: initial, 100 mg/day; maintenance, 100 to 600 mg/day | Safety and efficacy in children <16 years of age have not been established. | Capsule:<br>25 mg<br>50 mg<br>100 mg |

AED=antiepileptic drugs, DPN=diabetic peripheral neuropathy, LGS=Lennox-Gastaut Syndrome, PHN=postherpetic neuralgia

## Clinical Guidelines

**Table 11. Clinical Guidelines**

| Clinical Guideline | Recommendations |
|---|---|
| National Institute for Clinical Excellence: **The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care (2012)**[7] | Treatment of atonic or tonic seizures<br>• First-line treatment in children, young people, and adults with tonic or atonic seizure: sodium valproate.<br>• Offer lamotrigine as adjunctive treatment if sodium valproate is ineffective or not tolerated.<br>• Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin.<br><br>Treatment of generalized tonic-clonic seizures<br>• First-line treatment in children, young people, and adults with newly diagnosed focal seizures: sodium valproate.<br>• Offer lamotrigine if sodium valproate is unsuitable.<br>• Consider carbamazepine and oxcarbazepine.<br>• Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated.<br>• If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin.<br><br>Treatment of infantile spasms<br>• Discuss with, or refer to, a tertiary pediatric epilepsy specialist when an infant presents with infantile spasms.<br>• Offer a steroid or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis.<br>• Offer vigabatrin as first-line treatment to infant with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid.<br><br>Treatment of Lennox-Gastaut Syndrome (LGS) |


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| Clinical Guideline | Recommendations |
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| | • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected LGS.<br>• Offer sodium valproate as first-line treatment to children with LGS.<br>• Offer lamotrigine as adjunctive treatment if first-line treatments are ineffective or not tolerated.<br>• Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin.<br>• Only offer felbamate in centers providing tertiary epilepsy specialist care and when treatment with all of the antiepileptics listed above have proved ineffective or not tolerated.<br><br><u>Treatment of myoclonic seizures</u><br>• First-line treatment in children, young people, and adults with myoclonic seizures: valproate, unless unsuitable.<br>• Consider levetiracetam or topiramate if sodium valproate is unsuitable or not tolerated.<br>• Offer levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated.<br>• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist or consider clobazam, clonazepam, piracetam*, or zonisamide.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.<br><br><u>Treatment of absence seizures</u><br>• First-line treatment in children, young people, and adults with absence seizures: ethosuximide or sodium valproate. If there is a high risk of generalized tonic-clonic seizures, offer sodium valproate first, unless it is unsuitable.<br>• Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective, or not tolerated.<br>• If two first-line antiepileptics are ineffective, consider a combination of two of these three antiepileptics as adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate.<br>• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.<br><br><u>Treatment of focal seizures</u><br>• First-line treatment in children, young people, and adults with newly diagnosed focal seizures: carbamazepine or lamotrigine.<br>• Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic tried is ineffective, offer an alternative from the five antiepileptics noted above.<br>• Consider adjunctive treatment if a second well-tolerated antiepileptic is ineffective. |


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| Clinical Guideline | Recommendations |
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| | • For refractory focal seizures, offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment to all patients with focal seizures if first-line treatments are ineffective or not tolerated.<br>• For refractory focal seizures, if adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptics that may be considered by a specialist are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.<br><br>Treatment of Dravet syndrome<br>• Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Dravet syndrome.<br>• Consider sodium valproate or topiramate as first-line treatment in children with Dravet syndrome.<br>• Discuss with a tertiary epilepsy specialist if first-line treatments are ineffective or not tolerated, and consider clobazam or stiripentol as adjunctive treatment.<br>• Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.<br><br>Treatment of benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, or late-onset childhood occipital epilepsy (Gastaut type)<br>• Discuss with the child or young person, and their family and/or caretakers, whether antiepileptic drug treatment is indicated.<br>• Offer carbamazepine or lamotrigine as first-line treatment to children and young people.<br>• Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic drug tried is ineffective, offer an alternative from the five antiepileptics noted above.<br>• Consider adjunctive treatment if a second well-tolerated antiepileptic drug is ineffective.<br>• Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated.<br>• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptic drugs that may be considered are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.<br><br>Treatment of idiopathic generalized epilepsy<br>• First-line treatment in children, young people, and adults with idiopathic generalized epilepsy: sodium valproate.<br>• Offer lamotrigine if sodium valproate is unsuitable or not tolerated.<br>• Consider topiramate.<br>• Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated.<br>• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam or zonisamide.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, |


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| | pregabalin, tiagabine or vigabatrin.<br><br>Treatment of juvenile myoclonic epilepsy<br>• First-line treatment in children, young people, and adults with juvenile myoclonic epilepsy: sodium valproate.<br>• Consider lamotrigine, levetiracetam, or topiramate if sodium valproate is unsuitable or not tolerated.<br>• Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated.<br>• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, or zonisamide.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.<br><br>Treatment of epilepsy with generalized tonic-clonic seizures only<br>• First-line treatment in children, young people, and adults with epilepsy with generalized tonic-clonic seizures only: lamotrigine, sodium valproate.<br>• Consider carbamazepine or oxcarbazepine.<br>• Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated.<br><br>Treatment of childhood absence epilepsy, juvenile absence epilepsy, or other absence epilepsy syndromes<br>• First-line treatment in children, young people, and adults: ethosuximide, sodium valproate.<br>• Offer lamotrigine if first-line treatments are unsuitable, ineffective, or not tolerated.<br>• If two first-line antiepileptic drugs are ineffective, consider a combination of two of these three antiepileptic drugs adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate.<br>• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate, or zonisamide.<br>• Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. |
| American Academy of Neurology: **Evidence-Based Guideline Update: Medical Treatment of Infantile Spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)**[10] | • To date, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone (ACTH), and vigabatrin.<br>• Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.<br>• ACTH or vigabatrin may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over vigabatrin.<br>• There is insufficient evidence to recommend the use of dexamethasone, prednisolone and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms.<br>• The data is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for the treatment of infantile spasms.<br>• Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to |


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| | possibly improve developmental outcome.<br>• A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes. |
| Infantile Spasms Working Group: **Infantile Spasms: A U.S. Consensus Report (2010)**[11] | • To improve outcomes in infantile spasms, the goals include early recognition and diagnosis, short-term treatment with a first-line therapy, timely electroencephalography evaluation to assess treatment effectiveness and prompt treatment modification if indicated.<br>• Effective treatment should produce both cessation of spasms and resolution of hypsarrhythmia on electroencephalography.<br>• The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short amount of time as clinically indicated.<br>• There is insufficient evidence to recommend the best approach in events of relapse. Possible treatment options include using the previously effective agent and dose, using the previously effective agent at the maximum dose or using a new agent.<br>• ACTH is considered first-line therapy for infantile spasms. There is insufficient evidence to recommend the optimal dose and duration of treatment, although short duration is preferable to avoid adverse events. Treatment with the maximum dose of ACTH should be continued for two weeks followed by taper and evaluation of treatment response.<br>• Vigabatrin is considered first-line therapy for infantile spasms, especially in patients with comorbid tuberous sclerosis complex. Vigabatrin should be initiated at 50 mg/kg/day and increased up to 100 to 150 mg/kg/day if indicated. Efficacy should be assessed within two weeks following dose titration. Responders to treatment may continue therapy for six to nine months, with continued ophthalmic evaluation.<br>• No recommendations can be given with regard to oral corticosteroids in the treatment of infantile spasms.<br>• Ketogenic diet may be considered as second-line therapy when first-line therapies fail or are inappropriate.<br>• Patients with refractory spasms, concomitant partial seizures or focal abnormalities on the electroencephalography may be evaluated for surgery. |
| European Federation of Neurological Societies: **European Federation of Neurological Societies Guideline on the Management of Status Epilepticus (2010)**[200] | <u>Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus</u><br>• The preferred treatment is intravenous administration of lorazepam 0.1 mg/kg; however, depending on the patients' general medical condition, treatment can be started at a lower dose of 4 mg, to be repeated if seizures continue for >10 minutes after first injection.<br>• If lorazepam is not available, diazepam 10 mg (route of administration not specified) directly followed by phenytoin (15 to 18 mg/kg) or equivalent fosphenytoin.<br>• General management of refractory status epilepticus includes treatment in an intensive care unit.<br><br><u>Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus</u><br>• Immediate infusions of anesthetic doses of midazolam, propofol or barbiturates are recommended due to the progressive risk of brain and systemic damage.<br>• If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours. Simultaneous initiation of the |


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| | chronic medication the patient with be treated with in the future should be initiated.<br>• For elderly patients in whom intubation and artificial ventilation would not be justified, further non-anesthetizing anticonvulsants may be tried.<br><br>Pharmacological treatment for refractory non-convulsive status epilepticus<br>• Due to poor evidence and lack of any head-to-head trials, no recommendations can be made regarding which of the non-anaesthetizing anticonvulsants should be the drug of choice.<br>• Recommendations include phenobarbital, valproic acid and levetiracetam.<br>• If treatment regimen includes the administration of anesthetics, use the same protocol as refractory generalized convulsive status epilepticus. |
| American Academy of Neurology/American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy (2004)**[5] | • At this time, there are no studies that assessed the efficacy and tolerability of the new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide) in adults with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy.<br>• Lamotrigine can be included in the treatment options for children with newly diagnosed absence seizures. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide in children with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy.<br>• Patients with newly diagnosed partial or mixed seizure disorders who require treatment can be initiated on carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate or valproic acid. The choice of drug will depend on individual patient characteristics. At this time, there is insufficient evidence to determine effectiveness in newly diagnosed patients for levetiracetam, tiagabine and zonisamide. |
| American Academy of Neurology/American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2004)**[6] | • Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children. At this time, there is insufficient evidence to recommend use of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine or zonisamide for refractory generalized tonic-clonic seizures in adults and children.<br>• Lamotrigine and topiramate may be used to treat drop attacks associated with LGS in adults and children.<br>• Lamotrigine, oxcarbazepine and topiramate can be used as monotherapy in adults with refractory partial epilepsy. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine or zonisamide in monotherapy for refractory partial epilepsy.<br>• Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide are appropriate treatment options as adjunctive therapy for refractory partial epilepsy in adults.<br>• Gabapentin, lamotrigine, oxcarbazepine and topiramate may be used as adjunctive treatment of refractory partial seizures in children. At this time, there is insufficient evidence to recommend levetiracetam, tiagabine or zonisamide as adjunctive treatment of refractory partial seizures in children. |
| International League Against Epilepsy: **Updated ILAE** | Adults with partial onset seizures<br>• Carbamazepine, levetiracetam, phenytoin, and zonisamide are established treatments as initial monotherapy for adults with newly |


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| **Evidence Review of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes (2013)**[201] | diagnosed or untreated partial-onset seizures. Valproic acid is probably effective and gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are possibly effective for partial onset seizures. Clonazepam and primidone are potentially efficacious/effective.<br><br>Children with partial-onset seizures<br>• Oxcarbazepine is established as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures. Carbamazepine, phenobarbital, phenytoin, topiramate, valproic acid and vigabatrin may be effective and clobazam, clonazepam, lamotrigine and zonisamide are potentially efficacious/ effective.<br><br>Elderly adults with partial-onset seizures<br>• Gabapentin and lamotrigine are effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures. Carbamazepine may be effective and topiramate and valproic acid are potentially efficacious/ effective.<br><br>Adults with generalized-onset tonic-clonic seizures<br>• Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures. Gabapentin, levetiracetam and vigabatrin are potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.<br><br>Children with generalized-onset tonic-clonic seizures<br>• Carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective for children with newly diagnosed or untreated generalized onset tonic-clonic seizures. Oxcarbazepine is potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.<br><br>Children with absence seizures<br>• Ethosuximide and valproic acid are established treatments for children with newly diagnosed or untreated absence seizures. Lamotrigine is possibly efficacious/effective as initial monotherapy. Gabapentin is inefficacious/ineffective for children with absence seizures.<br>• Based on scattered reports, the following AEDs may precipitate or aggravate absence seizures: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin. No conclusion can be made about levetiracetam efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative.<br><br>Children with benign childhood epilepsy with centrotemporal spikes (BECTS)<br>• Carbamazepine and valproic acid are possibly effective as initial monotherapy for children with BECTS. Gabapentin, levetiracetam, oxcarbazepine, and sulthiame* are potentially efficacious/effective.<br><br>Juvenile myoclonic epilepsy<br>• Topiramate and valproic acid are potentially efficacious/effective for patients with newly diagnosed juvenile myoclonic epilepsy. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and |


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| | vigabatrin may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic-clonic seizures. There has been a report that lamotrigine may exacerbate seizures in juvenile myoclonic epilepsy. |
| Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for Management of Bipolar Disorder in Adults (2010)**[13] | Bipolar mania or mixed bipolar disorder:<br>• Pharmacotherapy for bipolar mania or mixed episode should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar manic episodes while minimizing the potential risks. Agents that are most likely to be beneficial for mania are the following: lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone. In addition, lithium or valproate may be combined with an atypical antipsychotic.<br>• Agents most likely to be beneficial for the treatment of a mixed bipolar episode are valproate, carbamazepine, aripiprazole, olanzapine, risperidone, or ziprasidone.<br>• Agents that are unlikely to be beneficial either for bipolar mania or mixed bipolar are lamotrigine, topiramate, or gabapentin.<br>• Clozapine, haloperidol and oxcarbazepine may be considered in patients with mania or mixed episode. Lithium or quetiapine may be considered in patients with mixed episode.<br>• Treatment response should be evaluated at four to eight weeks after initiation of treatment, after each change in treatment, and periodically until full remission is achieved. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence.<br>• Patients who have failed monotherapy may consider switching to another monotherapy, combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotics (SGA).<br>• Clozapine, with its more serious adverse event profile, may be combined with valproate or lithium as a treatment of severe mania or mixed episode, if it has been successful in the past or if other antipsychotics have failed.<br><br>Pharmacotherapy for bipolar depression<br>• Pharmacotherapy for bipolar depression should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar depressive episodes, while minimizing the potential risks.<br>• Quetiapine, lamotrigine, or lithium monotherapy should be considered as first-line treatment for adult patients with bipolar depression.<br>• Olanzapine/fluoxetine combination should be considered for treatment of bipolar depression, but its adverse effects (weight gain, risk of diabetes, hypertriglyceridemia) places this combination as a second-line treatment. Olanzapine alone may also be considered for bipolar depression, but adverse effects require caution.<br>• Agents that had been effective in treating prior episodes of depression should be considered.<br>• There is insufficient evidence to recommend for or against the use of valproate, carbamazepine, topiramate, risperidone, ziprasidone, or clozapine for bipolar disease depression.<br>• Aripiprazole is not recommended for monotherapy in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of |


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| | treatment refractory depression.<br>• Combining lithium with lamotrigine can be considered for patients with bipolar depression who do not respond to monotherapy.<br>• When patients do not respond to treatment options that have shown better efficacy, antidepressant augmentation with selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, and monoamine oxidase inhibitors can be considered for short-term treatment, monitoring closely for triggering of manic symptoms.<br>• Clozapine may be considered for augmentation, using caution regarding metabolic or other adverse effects.<br>• There is insufficient evidence to recommend for or against use of augmentation with aripiprazole, olanzapine, risperidone, haloperidol, oxcarbazepine, topiramate, ziprasidone, valproate, or carbamazepine for the treatment of bipolar depression.<br>• Gabapentin and the tricyclic antidepressants are not recommended for monotherapy or augmentation in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression.<br>• If there is no response within two to four weeks on an adequate dose of medication, therapy should be adjusted by either augmenting with additional agents, discontinuing switching to another effective medication or electroconvulsive therapy if multiple medication trials have been ineffective. |
| American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007)**[14] | • Youth with suspected bipolar disorder must also be carefully evaluated for other associated problems, including suicidality, comorbid disorders (including substance abuse), psychosocial stressors, and medical problems.<br>• The diagnostic validity of bipolar disorder in young children has yet to be established. Caution must be taken before applying this diagnosis in preschool children.<br>• For mania in well-defined DSM-IV-TR bipolar I disorder, pharmacotherapy is the primary treatment.<br>  o Standard therapy, based on adult literature, includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated.<br>  o The choice of medication should be based on 1) evidence of efficacy, 2) illness phase, 3) presence of confounding symptoms, 4) adverse events, 5) patient's medication response history, 6) patient and family preferences.<br>  o Clozapine is reserved for treatment-refractory cases because of its adverse event profile.<br>  o Antidepressants may be used as adjunctive therapy for bipolar depression.<br>• Most youths with bipolar I disorder will require ongoing medication therapy to prevent relapse; some individuals will need lifelong treatment.<br>• Psychopharmacological interventions require baseline and follow-up symptoms, adverse event (including patient's weight), and laboratory monitoring as indicated.<br>  o A six to eight week trial of a mood-stabilizing agent is recommended, using adequate doses, before adding or substituting other mood stabilizers.<br>• For severely impaired adolescents with manic or depressive episodes in |


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| | bipolar I disorder, electroconvulsive therapy may be used if medications either are not helpful or cannot be tolerated.<br>• Psychotherapeutic interventions are an important component of a comprehensive treatment plan for early-onset bipolar disorder.<br>• The treatment of bipolar disorder not otherwise specified generally involves the combination of psychopharmacology with behavioral/psychosocial interventions. |
| National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence: **Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary And Secondary Care (2006)**[15] | Acute manic episode in adults<br>• An antipsychotic or valproate should be used for severe manic symptoms marked by a behavioral disturbance. Lithium may be used if symptoms are not severe due to its slower onset of action.<br>• For an acute manic episode while on lithium or valproate, dose should be optimized, then olanzapine, quetiapine or risperidone should be added on if there are no signs of improvement.<br><br>Acute depressive episode in adults<br>• Patients with an incomplete response to antidepressant monotherapy may be managed by increasing the dose, switching antidepressants (e.g., mirtazapine or venlafaxine), adding an antipsychotic (olanzapine or quetiapine) or adding lithium.<br>• Patients with concurrent depressive and psychotic symptoms may be managed with olanzapine, quetiapine, or risperidone if the depressive illness is severe.<br><br>Long-term management<br>• Lithium, olanzapine, or valproate should be considered for long-term treatment of bipolar disorder.<br>• Long-acting intramuscular antipsychotic injections should not be used routinely.<br>• Quetiapine or lamotrigine can be considered for the management of patients with chronic and recurrent depressive symptoms.<br><br>Acute manic episode in children and adolescents<br>• An antipsychotic or valproate should be used for severe manic symptoms marked by behavioral disturbance. Lithium may be used if symptoms are not severe due to its slower onset of action.<br>• If there is an inadequate response to an antipsychotic, adding lithium or valproate should be considered.<br>• For an acute manic episode while on lithium or valproate, dose should be optimized, then if there are no signs of improvement, olanzapine, quetiapine or risperidone may be added.<br>• Valproate should be avoided in girls and young women because of risks during pregnancy and risk of polycystic ovary syndrome.<br>• At the start of therapy and periodically thereafter, height, weight and prolactin levels should be measured.<br>• When considering an antipsychotic, the risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered.<br><br>Acute depressive episode in children and adolescents<br>• Patients with mild depressive symptoms, not requiring immediate treatment should be monitored.<br>• Children and adolescents with depressive symptoms needing treatment should be treated by specialists. |


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| | • A structured psychological therapy aimed at treating depression should be considered in addition to prophylactic medication.<br>• When prescribing an antidepressant, an antimanic agent should also be prescribed.<br>• Patients with an incomplete response to antidepressant therapy may be managed by increasing the dose, switching antidepressants (e.g., mirtazapine or venlafaxine), adding an antipsychotic (olanzapine or quetiapine) or adding lithium.<br>• Patients with concurrent depressive and psychotic symptoms may be managed with olanzapine, quetiapine, or risperidone if the depressive illness is severe. |
| The Texas Medication Algorithm Project: **Texas Implementation of Medication Algorithms Procedural Manual: Bipolar Disorder Algorithms (2007)**[16] | Treatment of hypomanic or manic episodes<br>• Stage 1 treatment options for euphoric symptoms include: lithium, valproate, aripiprazole, quetiapine, risperidone, and ziprasidone.<br>• Stage 1 treatment options for mixed symptoms include: valproate, aripiprazole, risperidone, and ziprasidone.<br>• Stage 1b, olanzapine and carbamazepine are potential alternatives to stage 1 agents.<br>• Stage 2 treatment options include a combination with two of the following: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not two antipsychotics).<br>• Stage 3 treatment options include a different combination than that tried in Stage 2, with additional options including carbamazepine, oxcarbazepine, aripiprazole, and a typical antipsychotic.<br>• Stage 4 treatment options include clozapine or three-drug combinations (include lithium, an anticonvulsant mood stabilizer [valproate, carbamazepine, or oxcarbazepine], plus an atypical antipsychotic).<br><br>Treatment of depression<br>• Stage 1 recommended treatment is lamotrigine monotherapy for those patients without a recent and/or severe history of manic symptoms. Others should receive lamotrigine plus a mood stabilizer.<br>• Stage 2 treatment options include quetiapine monotherapy or the olanzapine/fluoxetine combination treatment.<br>• For Stage 3 and beyond, evidence-based medicine is limited to case series, open-label studies and expert clinical consensus. A variety of treatment options are suggested.<br>• For intolerance or unresponsiveness to agents used in a particular Stage, it is recommended to try an alternative mood stabilizer within that Stage. |
| American Psychological Association: **Practice Guideline for the Treatment of Patients With Bipolar Disorder (2002)**[12] | Treatment of acute manic or mixed episodes<br>• Adjunctive antipsychotic treatment is recommended for manic or mixed manic episodes with psychotic features.<br>• SGAs are preferable over first generation antipsychotics because of their adverse event profile.<br><br>Treatment of acute depressive episodes<br>• Patients presenting with psychotic features would require adjunctive treatment with an antipsychotic medication or electroconvulsive therapy.<br><br>Treatment of acute rapid cycling<br>• A combination regimen containing a SGA may also be used. |


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| | Maintenance treatment for manic/depressive episode<br>• Ongoing adjunctive antipsychotic therapy should be reassessed, and slowly tapered, unless required for control of persistent psychosis or prophylaxis against recurrence. |
| American Academy of Neurology/American Headache Society: **Evidence-based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (2012)**[17] | • The following medications are established as effective; therefore, should be offered for migraine prevention:<br>o Antiepileptic drugs: divalproex sodium, sodium valproate, topiramate.<br>o β-blockers: metoprolol, propranolol, timolol.<br>o Triptans: frovatriptan for short term menstrually associated migraine prevention.<br>• The following medications are probably effective; therefore, should be considered for migraine prevention:<br>o Antidepressants: amitriptyline, venlafaxine.<br>o β-blockers: atenolol, nadolol.<br>o Triptans: naratriptan, zolmitriptan for short term menstrually associated migraine prevention.<br>• The following medications are possibly effective; therefore, may be considered for migraine prevention:<br>o Angiotensin converting enzyme inhibitors: lisinopril.<br>o Angiotensin receptor blockers: candesartan.<br>o α-agonists: clonidine, guanfacine.<br>o Antiepileptic drugs: carbamazepine.<br>o β-blockers: nebivolol, pindolol.<br>• Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention: gabapentin, fluoxetine, fluvoxamine, protriptyline, acenocoumarol, warfarin, picotamide, bisoprolol, nicardipine, nifedipine, nimodipine, verapamil, acetazolamide, cyclandelate.<br>• Ineffective medications for migraine prevention:<br>o Lamotrigine is established as ineffective and should not be offered.<br>o Clomipramine is probably ineffective and should not be considered.<br>• Acebutolol, clonazepam, nabumetone, oxcarbazepine, and telmisartan are possibly ineffective and may not be considered. |
| American Academy of Family Physicians/ American College of Physicians-American Society of Internal Medicine: **Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache (2002)**[202] | Prevention of migraines<br>• Generally accepted indications for migraine prevention include the following: at least two attacks per month that produce disability lasting at least three days per month; contraindication to, or failure of, acute treatments; use of abortive medication at least two times per week; or presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction. Other factors to consider are adverse events with acute therapies, patient preference and the cost of both acute and preventive therapies.<br>• Although many agents are available for the preventive treatment of migraine, only a few have proven efficacy. Once an agent has been chosen, clinicians should initiate therapy with a low dose and titrate the dose slowly up until clinical benefits are achieved in the absence of adverse events or until limited by adverse events. Because a clinical benefit may take as long as two to three months to manifest, each treatment should be given an adequate trial. After a period of stability, clinicians should consider tapering or discontinuing treatment. |


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| | • Recommended first-line agents for the prevention of migraine headache are amitriptyline, divalproex sodium, propranolol, sodium valproate, and timolol. |
| American Academy of Neurology/United States Headache Consortium: **Practice Parameter: Evidence-Based Guidelines for Migraine Headache (2000)**[203] | • The goals of migraine preventive therapy are to reduce attack frequency, severity, and duration; improve responsiveness to treatment of acute attacks; and improve function and reduce disability.<br>• One or more of the following helps guide management decisions on the use of preventive therapies: recurring migraines that significantly interfere with daily routines, despite acute treatment; frequent headaches; contraindication to or failure or overuse of acute therapies; adverse events with acute therapies; presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction; patient preference and cost of both acute and preventive therapies. Also, consider coexisting conditions and medications.<br>• Initiate therapy with medications that have the highest level of evidence-based efficacy and at the lowest effective dose. Increase the dose slowly until clinical benefits are achieved in the absence of, or until limited by, adverse events. Since it may take two to three months to achieve clinical benefit, give each drug an adequate trial. Use of a long-acting formulation may improve compliance. Re-evaluate therapy and after three to six months headaches are well controlled, consider tapering or discontinuing treatment.<br>• The following medications have proven high efficacy for the prevention of migraine and mild-to-moderate adverse events: amitriptyline, divalproex sodium, fluoxetine, gabapentin, propranolol and timolol.<br>• This summary only focused on preventive therapy for migraines. |
| European Federation of Neurological Societies: **European Federation of Neurological Societies Guideline on the Drug Treatment of Migraine-Revised Report of an European Federation of Neurological Societies Task Force (2009)**[204] | Prevention of migraines<br>• Prophylactic drug treatment of migraine should be considered and discussed with the patient when: the quality of life, business duties, or school attendance are severely impaired; frequency of attacks per month is at least two; migraine attacks do not respond to acute drug treatment; or frequent, very long, or uncomfortable auras occur.<br>• A migraine prophylaxis regimen is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% within three months.<br>• The drugs of first choice for migraine prophylaxis are flunarizine*, metoprolol, propranolol, topiramate, and valproic acid. Drugs of second choice include amitriptyline, bisoprolol, naproxen, petasites*, and venlafaxine. |
| European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[205] | Painful polyneuropathy<br>• Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus-induced neuropathy.<br>• Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine).<br>• Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain.<br>• Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. |


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| | • In human immunodeficiency virus-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful.<br><br>Postherpetic neuralgia (PHN)<br>• Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin.<br>• Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications.<br>• Strong opioids and capsaicin cream are recommended as second-line therapies. |
| American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[18] | Anticonvulsants<br>• If clinically appropriate, pregabalin should be offered for treatment.<br>• Gabapentin and sodium valproate should be considered for treatment.<br>• There is insufficient evidence to support or refute the use of topiramate for treatment.<br>• Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment.<br><br>Antidepressants<br>• Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another.<br>• Venlafaxine may be added to gabapentin for a better response.<br>• There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy.<br><br>Opioids<br>• Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other.<br><br>Other pharmacologic options<br>• Capsaicin and isosorbide dinitrate spray should be considered for treatment.<br>• Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment.<br>• Lidocaine patch may be considered for treatment.<br>• There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment.<br><br>Nonpharmacologic options<br>• Percutaneous electrical nerve stimulation should be considered for treatment.<br>• Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment.<br>• Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment. |
| American Association of Clinical | Neuropathy<br>• All patients with type 2 diabetes should be assessed for neuropathy at the |


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| Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[206] | time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients.<br>• Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene.<br>• Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament.<br>• Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes.<br>• Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy.<br>• When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized.<br>• Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities.<br>• Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms.<br>• Maintain a referral network for podiatric and peripheral vascular studies and care. |
| American Diabetes Association: **Diabetic Neuropathies (2005)**[207] | Algorithm for the management of symptoms diabetic polyneuropathy<br>• Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral. |
| American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[19] | • Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN.<br>• There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another.<br>• Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine.<br>• Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin.<br>• In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN.<br>• Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit.<br>• The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN.<br>• There is insufficient evidence to make any recommendations on the long-term effects of these treatments. |
| European League | • Tramadol is recommended for the management of pain in fibromyalgia. |


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| Against Rheumatism: **Evidence-based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[20] | • Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia.<br>• Corticosteroids and strong opioids are not recommended.<br>• Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia.<br>• Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia. |
| American Academy of Neurology/European Federation of Neurological Societies: **Diagnostic Evaluation and Treatment of Trigeminal Neuralgia (2008)**[21] | • To control pain in patients with trigeminal neuralgia: carbamazepine should be offered; oxcarbazepine should be considered; baclofen, lamotrigine and pimozide* may be considered; and topical ophthalmic anesthesia should not be considered.<br>• For patients with trigeminal neuralgia refractory to medical therapy: early surgical therapy may be considered; and percutaneous procedures on the Gasserian ganglion, gamma knife and microvascular decompression may be considered. |

*Agent not currently available in the United States.

## Conclusions

The anticonvulsants consist of agents from the following pharmacologic classes: barbiturates, benzodiazepines, hydantoins, succinimides, and miscellaneous anticonvulsants.[1,2] The majority of agents are available in a generic formulation, and there is at least one generic agent available within each pharmacologic class.[1] Over the past decade, many new anticonvulsants have become available in the United States. Overall, the second generation anticonvulsants (e.g., gabapentin, lamotrigine, topiramate, levetiracetam, oxcarbazepine and zonisamide) have a number of potential advantages compared to older anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine and valproate) including a lower rates of adverse events, minimal or no need for serum monitoring, once or twice daily dosing and fewer drug interactions.[4-6]

Based on available clinical trial data, the safety and efficacy of the anticonvulsants for the management of seizure disorders are well established. At this time, there is insufficient evidence to suggest that one agent is more efficacious than another, or that one dosage formulation is more efficacious than another.[67-157] Despite a lack of demonstrated superiority compared to other available anticonvulsant dosage formulations within clinical trials, diazepam rectal gel provides a beneficial route of administration compared to other agents in the class. Overall, this agent offers a clinical advantage over other anticonvulsants included in this review. Diazepam rectal gel is Food and Drug Administration (FDA)-approved for the management of selected, refractory patients with epilepsy, who are receiving a stable anticonvulsant regimen, and who require intermittent use of diazepam to control bouts of increased seizure.[28] Results from several placebo-controlled trials support that diazepam rectal gel is beneficial in aborting an episode of acute repetitive seizures and reducing the recurrence of seizure shortly thereafter.[117,139-142] Furthermore, current clinical guidelines recognize the anticonvulsants as the standard of care for the management of seizure disorders.[5,6,7,10,11,200,201]

Epilepsy pharmacotherapy requires individualization, and should be focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life.[4] Recommendations from current treatment guidelines for the management of seizure disorders are comprehensive and disorder-specific. Carbamazepine and lamotrigine are considered first-line for the treatment of patients with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated anticonvulsant also proves inadequate. Sodium valproate is recommended first-line


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for the treatment of patients with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate should be offered to all patients if first-line therapies prove inadequate.[7] Vigabatrin oral solution is the only anticonvulsant FDA-approved for the management of infantile spasm.[1,57] There is insufficient evidence to support the use of agents other than adrenocorticotropic hormone (ACTH) and vigabatrin for the treatment of infantile spasms. Evidence suggests that ACTH may be preferred over vigabatrin for short term management.[10] Vigabatrin is also available as a tablet that is FDA-approved as adjunctive therapy for adult patients with refractory complex partial seizures. Use of vigabatrin is associated with progressive and permanent bilateral concentric visual field constriction, and may also reduce visual acuity.[57]

Sodium valproate is recognized as first-line for the treatment of Lennox-Gastaut Syndrome (LGS), with lamotrigine recommended as adjunctive therapy if needed.[7] Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are all FDA-approved for the treatment of LGS.[1,23,25,41,42,45,60] Clobazam was most recently approved by the FDA in 2011; however, this agent has been available internationally for several years for the treatment of anxiety and epilepsy. Some of the anticonvulsant agents hold additional FDA-approved indications that are unrelated to seizures disorders, including, but not limited to, prevention of migraines, and management of bipolar disorder (acute and maintenance treatment), fibromyalgia, neuropathic pain and trigeminal neuralgia.[1] Treatment guidelines recommend recognize valproate and carbamazepine as potentially beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine should be considered as a potential first-line option for the management of bipolar depression in adults, and patients who do not respond to initial monotherapy should receive combination therapy with lithium.[12-16] Treatment guidelines recommend the use of divalproex, topiramate, and valproic acid for migraine prophylaxis.[17] If clinically appropriate, treatment guidelines recommend pregabalin for the treatment of diabetic peripheral neuropathy. Gabapentin and sodium valproate are other anticonvulsants that should be considered.[18] According to treatment guidelines, first-line therapies for the management of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, opioids and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.[19] The use of anticonvulsants in the management of fibromyalgia is not addressed within treatment guidelines.[20] According to treatment guidelines, carbamazepine should be offered to patients experiencing pain associated with trigeminal neuralgia.[21]


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