



PART ONE

An Overview of Medications Used in Epilepsy

Parents, families and caregivers, as well as persons with epilepsy, frequently have questions about medications and often turn to the Internet for information about medications and other treatment options. This method is, at best, flawed and not completely reliable, depending on the websites that are used.

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Epilepsy is one of the more common neurological disorders and is particularly common in persons with developmental delays, cerebral palsy, autism and mental retardation. These same persons often suffer from seizures that are difficult to control with medications, resulting in the need for treatment with more than one medication.

The goals of treatment are to suppress the abnormal electrical activity in the brain enough to prevent seizures while avoiding side effects of medication.

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The following is an overview, in laymen's terms, of the most common anti-seizure medications. Information included here is based on recent research. Of course, your provider should always be contacted with questions about medication and side effects and no medications should be changed, increased or stopped without speaking to the provider.

As a general rule, all women of child-bearing age taking anti-epileptic drugs should be on folic acid supplementation

(5mg/day.) Calcium and vitamin D should also be supplemented.

Another general rule is that everyone with seizures should have a rescue medication available (diastat, midazolam, klonopin,) with instructions for its use and should be wearing Medalert identification.

Information includes generic name, brand name, year approved for use in the United States, FDA approved indications; advantages/disadvantages in clinical use; mechanism of action; need for monitoring of blood levels; side effects; use in pregnancy and breastfeeding and interactions with other medications especially anti-epileptic medications.

CARBAMAZEPINE (TEGRETOL, CARBATROL) (1964)

- approved by FDA for treatment of partial seizures, generalized seizures and mixed seizure types
- most useful for treatment of partial seizures and can worsen certain types of generalized seizures, including atonic, absence and myoclonic
- also used for TMJ and bipolar disorder
- acts on sodium channels
- therapeutic drug blood levels: 4-12

Interactions: phenobarbital and phenytoin(Dilantin) can increase clearance and valproic acid can elevate carbamazepine levels and increase side effects

- adverse effects worsen with higher doses and include- dizziness, double vision, nausea, vomiting, sedation (usually early on in treatment), weight gain, severe rash, cardiac issues, hypertension, anemias and liver issues, as well as low sodium,
- jaundice and blood clots.
- reduces the effectiveness of oral contraceptives
- pregnancy - can cause congenital malformations

CLOBEZAM (FRISIUM-ONFI) (2012)

- approved as adjunctive therapy for generalized seizures, focal seizures and focal seizures with secondary generalization
- Rapid onset - wide spectrum of effectiveness
- enhances GABA (neurotransmitter)
- Rare side effects
- No interactions
- Subject to tolerance
- rare side effects include sleepiness, fatigue, behavioral issues, sedation, and cognitive impairment
- does not interact with contraceptives



- use with central nervous system depressants, such as alcohol and barbiturates can worsen side effects
- no negative indicators to date in pregnancy and breastfeeding
- therapeutic blood levels not indicated

CLONAZEPAM

- FDA approved for use for seizures associated with Lennox-Gastaut syndrome, for akinetic and myoclonic seizures and absence seizures that fail to respond to other medications
- Increases GABA

The mainstay of treatment for epilepsy is medications. The goal of any therapy is to control seizures with minimal side effects and to achieve it by using as few medications as possible. When seizure control is not achieved, it is time to rethink the regimen and look at alternative treatments.

Side effects: sedation behavioral and cognitive impairment, drowsiness, ataxia; personality and behavioral change in children- hyperactivity, blurred vision aggressiveness, and irritability (usually dose-related)

- Titrated slowly- larger dose at night to avoid side effects
- Dosing solely at night often effective for myoclonic jerks (and may be first choice)
- Drug monitoring not recommended in asymptomatic individuals (therapeutic range 20-0mgg/L
- Withdrawal symptoms if a dose is missed including increased pulse, tremor and general feeling of being unwell
- Do not use with glaucoma or liver dysfunction
- Benefits of breastfeeding thought to outweigh risks
- Pregnancy-data limited but no increase in major malformations in some small studies

DIAZEPAM (VALIUM)

- Rescue medication - used in the community setting
- Available in oral, IV, IM, rectal gel
- Used in status epileptic and acute repetitive seizures

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- Shorter duration of action than lorazepam but reaches brain more rapidly - IV lorazepam is first choice for status epilepticus when available

- Therapeutic drug monitoring not indicated

- Adverse reactions are common and include confusion, ataxia, dizziness, dysarthria, restlessness, irritability (paradoxical)

- Repeated administration can increase the risk of respiratory depression, sedation and hypotension

- Pregnancy- class D - use in the first trimester increases the risk of major malformations and cleft palate- use just before delivery places the infant at risk for respiratory depression, hypotonia, feeding difficulties, temperature instability and neonatal withdrawal syndrome

- Should not be used when breastfeeding because it causes feeding difficulties in the infant

- No effect on oral contraceptives but oral contraceptives reduce the clearance of diazepam

ESLICARBAZEPINE ACETATE

- Not yet available in the US

- Adjunctive therapy for complex partial seizures in adults

- Inhibits sodium channels

- No therapeutic range established yet

Adverse effects: headache, dizziness, double vision, nausea and vomiting

- No serious reactions noted yet

- Reduces efficacy of oral contraceptives

ETHOSUXIMIDE (ZARONTIN) (1958)

- Indicated for childhood absence seizures- not effective for generalized tonic-clonic or partial seizures

- Adverse effects usually mild and dose-dependent but gastrointestinal side

effects are fairly common

- Blood levels 40-100 mcg/mL but routine monitoring is not useful

FELBAMATE (FELBATOL) (1996)

- Indicated in patients with Lennox-Gastaut syndrome whose seizures are not controlled with other medications

- Also used for refractory partial seizures with or without secondary generalization

- Show significant effects in seizure reduction

- Severe adverse reactions include life-threatening aplastic anemia and liver failure - this is common if the patient female, has a history of allergy or anemia on previous anti-epileptic medications or has a history of immune disorders, especially SLE

- Common side effects include anorexia, nausea, vomiting, and weight loss, insomnia and irritability in children; and are most likely to occur within the first 3 months of treatment

- medication should be given at 8am and noon to avoid side effect of insomnia

- If patient is on the ketogenic diet, tablet should be used instead of liquid because there is a large amount of sorbitol in liquid

- Bloods should be checked before initiating treatment and monitored at regular intervals

- Felbamate Increases phenytoin levels

GABAPENTIN (NEURONTIN) (1999)

- Indicated for adjunctive therapy in adults and children over 3 years old for partial seizures

- Side effects include central nervous system depression (drowsiness, sedation) and are generally short-lived- other side effects include side emotional lability and hostility and a rare rash

- No drug to drug interaction, including oral contraceptives and anti-epileptic medications

- No need for therapeutic drug monitoring of blood

- Not to be used in pregnancy

- Limit use while breastfeeding

- Seems to increase GABA and decrease glutamate but mechanism not fully understood

LACOSAMIDE (VIMPAT)

- Approved as adjunctive treatment for partial onset seizures in patients over 16 years old

- Advantages- works in refractory patients

- Mechanism of action- works on slow sodium channels

- Low potential for interactions with other drugs

- No rashes or weight changes in clinical trials

- Side effects- dizziness,

- No need for drug level monitoring

- Can cause EKG changes in patients with cardiac conduction problems or cardiac issues

- Should not be used in pregnancy or breastfeeding

- Does not interact with oral contraceptives

LAMOTRIGINE (LAMICTAL) (1995)

- Indicated for adjunctive therapy for partial onset seizures in adults and children; monotherapy in partial onset seizures, monotherapy for generalized seizures associated with Lennox-Gastaut syndrome and tonic-clonic seizures in generalized epilepsy

- Frequently used to treat absence seizures in children and adolescents

- Acts on sodium channels thereby blocking release of glutamate (excitatory neurotransmitter)

- Advantages- well-tolerated, does not worsen cognition, synergistic with valproic acid
- Disadvantages- risk of severe rash (lower risk with slow initiation and titration)
- Levels reduced by tegretol, phenytoin and other enzyme inducing anti-epileptic drugs
- Rare indications for following blood levels, except in pregnancy
- Common side effects- dizziness, ataxia, somnolence, headache, double vision, blurred vision, nausea, vomiting, insomnia,
- Use in pregnancy - slight increase in risk of congenital malformations, including oral clefts
- Breastfeeding- no adverse effects
- Can lower efficacy of oral contraceptives

LEVETIRACETEM (KEPPRA) (2001)

- Indicated for monotherapy in the treatment of partial onset seizures in adults and children over 6 years old
- Adjunctive therapy for partial onset seizures in adults and children over 1 month old
- Used for myoclonic seizures, photosensitive seizures, status epilepticus and neonatal seizures
- Works on modulating the activity of the SVA2 protein
- Well tolerated when used with steroids (as in patients with brain tumors)

Side effects: sleepiness, irritability, nausea, headaches, depression, emotional lability (mostly with higher doses and previous history of behavioral problems or psychiatric diagnosis)- no effect on cognition

- Pregnancy - decreases blood concentration- after delivery, maternal serum concentrations increase rapidly, so blood levels should be monitored during pregnancy and dose decreased soon after delivery

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- Few observations of major congenital defects
- Breastfeeding- concentrations are low in neonate but elimination is longer
- Oral contraceptives- no interactions

LORAZEPAM (ATIVAN)

- Indicated as first line treatment for status epilepticus—usually given IV or IM
- also used in adults for anxiety and sedation
- Enhances action of GABA
- Less risk of hypotension than with diazepam (which is also used for status epilepticus)
- Tendency for development of tolerance
- Common reactions- respiratory depression, sedation, dizziness, vertigo, weakness and unsteadiness
- Less common- disorientation, depression,
- Pregnancy use - only in life-threatening situations
- Not to be used in breastfeeding
- Oral contraceptives- may need to increase dose

MIDAZOLAM

- Licensed in the United States for conscious sedation, anesthesia and sedation in intensive care units
- Benzodiazepine that is used for treatment of status epilepticus and given nasally, intravenously or through buccal mucosa
- Alternative to Diastat (rectal valium)
- Short-lasting
- Rescue medication- used in the community setting -fewer relapses in one hour than with diazepam
- Easier to use inpatients in wheelchairs than rectal valium
- Most pediatric neurologists do not recommend a test dose administered inpatient
- Severe adverse reactions of respiratory depression and variations in blood pressure and pulse are only reported with intravenous use in an inpatient settings
- Side effects include gastrointestinal disturbances, jaundice, anaphylaxis, drowsiness, hallucinations, laryngospasm, drowsiness, ataxia, amnesia, fatigue, dizziness and vertigo,
- Pregnancy - no specific evidence of fetal malformations
- Breastfeeding - readily crosses into breast milk but no evidence of harm
- no interaction with oral contraceptives

OXCARBAZEPINE (TRILEPTAL) (1991)

- Indications- monotherapy and adjunctive therapy for partial-onset seizures
- Multiple mechanisms of action including acting on sodium, potassium and calcium channels
- Not associated with serious anemia and agranulocytosis as with carbamazepine
- No cognitive impairment in drug tri-

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als- fewer drug interactions due to low protein binding

Side effects: drowsiness and low sodium (more in adults) -

- Serious reactions include anaphylaxis, angioedema, rash, and anemia
- Major congenital malformation rates are comparable to rate in pregnancies in women with epilepsy on or off antiepileptic medications
- Blood levels should be monitored with renal impairment, to rule out non-compliance and during pregnancy because levels increase and increased markedly after delivery so doses may need to be changed
- Breastfeeding - effects are unknown
- Oral contraceptives reduce the efficacy of oxcarbazepine

PHENOBARBITOL (1912)

- Used for febrile seizures, tonic-clonic seizures, status epilepticus and eclampsia
- First line for treatment of partial and generalized tonic-clonic seizures in developing countries because of its low cost and ability to administer once daily
- Increases GABA and glutamate
- Blood levels 15-40mcg/mL
- Common side effects include drowsiness, mood changes, impairment of cognition and memory- at high doses may develop nystagmus, ataxia, slurred speech, disinhibition, anemias and tolerance with long-term use
- Serious reaction - respiratory depression
- Pregnancy - baby may experience withdrawal and trouble breathing - risk of congenital malformation
- Should not be taken when breastfeeding
- Interacts with oral contraceptives, causing contraceptive failure and breakthrough bleeding
- Valproate increases phenobarbital

concentration

- Interacts with a variety of medications, including steroids, warfarin, some antibiotics and antihistamines
- Blood level monitoring is recommended when the patient is on multiple anti-epileptic medications

PHENYTOIN (DILANTIN-FOSPHENYTOIN-CEREBYX) (1938)

- Used for partial onset and generalized seizures and for status epilepticus (phosphenytoin and cerebyx)
- Blocks sodium channels
- Advantage-inexpensive, long half-life
- Must closely monitor blood levels, although levels often fluctuate - therapeutic level is 10-20 mcg/mL

Side effects: gum hyperplasia, hirsutism, ataxia, slurred speech anemias, impotence; long-term use can lead to peripheral neuropathy and osteoporosis

- Pregnancy - preferably should not be on phenytoin- if needed, lowest dose possible should be used
- Usually considered safe in breastfeeding
- Multiple drug interactions including (but NOT limited to) psychiatric medications, calcium channel blockers, digoxin, cholesterol-lowering agents, warfarin, antifungals, antibiotics, felbamate, INH, topiramate, carbamazepine, phenobarbital and vigabatrin
- Phenytoin increases blood levels of felbamate, oxcarbazepine, and topiramate
- Phenytoin lowers blood levels of benzodiazepines,
- Carbamazepine, phenobarbital and vigabatrin increase the blood levels of phenobarbital

PREGABALIN

- Indicated as adjunctive treatment for focal epilepsies in adults and children

over 12 years old

- Also used for neuropathic pain
- Works on calcium channels
- Adverse reactions are mild to moderate and include sedation, dizziness, weight gain, gastrointestinal side effects and myoclonus (should not be used in generalized epilepsies)
- Not recommended for use in pregnancy
- Should be cautiously in breastfeeding, as no studies are available
- Does not interact with oral contraceptives
- Low interaction with other meds except for carbamazepine, which may lower pregabalin blood concentrations

PRIMIDONE (MYSOLINE) (1954)

- Treatment of generalized tonic-clonic seizures and complex partial seizures - second line treatment for juvenile myoclonic epilepsy
- Partially metabolized to phenobarbital
- Plasma levels 5-12 mcg/mL
- Common (but usually transient) side effects of drowsiness, listlessness, visual disturbances, nausea, headaches, dizziness, vomiting, nystagmus and ataxia
- Serious reactions include anemias, elevated liver enzymes, arthralgia and osteomalacia
- Pregnancy - can cause low folate levels and coagulation disorders in neonates and there is some evidence for congenital malformations
- Breastfeeding - can cause somnolence and drowsiness in nursing newborns
- Interacts with oral contraceptives-causing breakthrough bleeding and failure of contraceptive therapy
- Interacts with numerous medications, similarly to phenobarbital

RUFINAMIDE (BANZEL) (2008)

- Adjunctive treatment for partial onset

seizures and seizures associated with Lennox-Gastaut syndrome

- Main mechanism of action is unknown but thought to act on sodium channels
- Common side effects are dizziness, fatigue, nausea, vomiting, double vision and somnolence
- Can cause shortening of QT interval (cardiac)
- Valproic acid increases rufinamide concentration
- Does not decrease seizure activity when used with carbamazepine
- Rufinamide increases the serum concentration of carbamazepine, lamotrigine, and phenobarbital
- Decreases efficacy of oral contraceptives
- No need for blood level monitoring
- Not indicated for use during pregnancy
- Should not be taken when breastfeeding

STIRIPENTOL

- Not available in the United States
- Used in severe myoclonic epilepsy in infancy (Dravet's syndrome)
- Enhances GABA
- May need to decrease dosing of clobazam and should decrease dose of carbamazepine
- No indication for blood monitoring
- Common side effects are anorexia, weight loss, drowsiness, ataxia, nausea, lethargy, vomiting, tremor and in rare cases aplastic anemia
- Complete blood count and liver functions should be checked before treatment and every 6 months during treatment
- No studies on use in pregnancy and breastfeeding

TIAGABINE (GABATRIL)

- Indicated for adjunctive therapy for partial seizures with or without secondary generalization in adults and children over 12

Other treatments include surgery, ketogenic diet, and devices such as vagal nerve stimulators and deep brain stimulators.

- Increases GABA levels
- Disadvantages- requires slow titration because of potential adverse side effects and can aggravate generalized seizures
- No evidence to recommend routine monitoring of blood levels but patients seem to respond best with trough levels greater than 20 mcg/mL and even better at trough levels of 40 mcg/mL

Side effects: dizziness, weakness, nervousness, tremor, diarrhea, depression and emotional lability- usually can be managed by slow titration and dosing multiple times per day

- Not recommended in pregnancy
- Women who are taking tiagabine and breastfeeding should monitor their infants for adverse events
- Does not interact with oral contraceptives
- Minimal interaction with other anti-epileptic drugs

TOPIRAMATE (TOPAMAX) (1996)

- Indicated as monotherapy for partial onset and primary generalized tonic-clonic seizures in patients 10 years of age and older; adjunctive therapy for partial seizures in adults and pediatric patients 2-16 years old; adjunctive therapy in primary generalized tonic-clonic seizures in adults and pediatric patients 2-16 years old and seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older

- Several mechanisms of action include actions on sodium channels, calcium channels, inhibition of carbonic anhydrase and decrease in glutamate activity

Side effects: cognitive dulling (word finding difficulties and memory disturbances,) somnolence, dizziness, ataxia, nervousness, and fatigue- tend to be worse while titrating and reduce over time

- Minimal drug interactions although phenytoin and carbamazepine may increase topiramate levels
- Increased rate of congenital malformations when used in pregnancy
- Excreted in high concentrations in breast milk if taken at doses higher than 200mg/day

VALPROATE (DEPAKOTE, DEPAKENE, STAVZOR)

- FDA approved for monotherapy and adjunctive therapy for partial seizures, simple and complex absence seizures and as adjunctive therapy for multiple seizure types including absence, photosensitive and generalized tonic-clonic, absence and myoclonic status epilepticus, status epilepticus
- Enhances GABA, works on sodium and calcium channels and works on stabilizing mood by its action on dopamine and serotonin neurotransmitters
- Severe (rare) adverse events-pancreatitis, hepatic (liver) dysfunction,

Side effects: weight gain, nausea, vomiting, diarrhea, anorexia, abdominal pain, tremors, dizziness, agitation, hair loss, osteomalacia

- Pregnancy -increased risk of major congenital malformations, delayed intellectual development in children, craniofacial abnormalities (fetal valproate syn-

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drome.) neuronal tube defects- must have folic acid supplementation

- Breastfeeding -not contraindicated
- Valproate has no effect on oral contraceptives

VIGABATRIN (SABRIL) (2009)

- FDA approved as monotherapy for infantile spasms and adjunctive therapy for refractory complex partial seizures
- Inhibitor of transaminase - increases GABA
- Advantages- very effective for two severe types of seizures - infantile spasms and refractory partial seizures
- Adverse effects- visual field loss (of peripheral vision, worse towards the nose)

Side effects: rare cognitive issues, may worsen myoclonic and absence epilepsy, MRI changes in deep gray and white matter, usually transient and asymptomatic, weight gain, fatigue, somnolence, irritability, behavioral changes, psychosis, depression, ataxia; hyperactivity and agitation in children

- Pregnancy - studies in animals have

shown intrauterine growth retardation, minor congenital malformations and delays in skeletal development

- Breastfeeding - secreted in breast milk in low quantities
- No interaction with oral contraceptives

ZONISAMIDE (ZONEGRAN) (2000)

- FDA approved for adjunctive treatment of partial seizures - widely used for generalized seizures, Lennox-Gastaut syndrome and infantile spasms
- Works on sodium and calcium channels
- Adverse effects- cognitive side effects, risk of renal stones, rash (rare)

Side effects: ataxia, dizziness, nausea, fatigue, somnolence, agitation, irritability and anorexia (dose-related, titrate slowly)

- Advantages- once daily dosing , does not interact with other anti-epileptic drugs
- Pregnancy-limited data but no higher risk than with other anti-epileptic meds-should be used only if potential benefits outweigh the risks
- Breastfeeding - extensively secreted

in breast milk but limited data, so infant should be closely monitored for sedation or irritability

- Oral contraceptives- no clinically significant interactions

There are other medications that are not strictly anti-epileptic drugs but are widely used for certain syndromes and hard to control seizures. They are briefly mentioned here:

ACTH (ADRENOCORTICOTROPIC HORMONE) & PREDNISONE (STERIODS)

- Used for infantile spasms and Landau-Kleffer syndrome, Lennox-Gastaut syndrome, absence epilepsy, progressive myoclonic epilepsy, Rasmussen's syndrome, epilepsia partialis continua

IVIG

- Used in epilepsy syndromes with a presumed immune-mediated pathogenesis.

Other treatments include surgery, ketogenic diet, and devices such as vagal nerve stimulators and deep brain stimulators.

In conclusion, the mainstay of treatment for epilepsy is medications. The goal of any therapy is to control seizures with minimal side effects and to achieve it by using as few medications as possible. When seizure control is not achieved, it is time to rethink the regimen and look at alternative treatments. •

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