GABAPENTIN

**Therapeutics**

**Brands**
- Neurontin
- Horizant
*see index for additional brand names*

**Generic?** Yes (not for extended release)

**Class**
- Neuroscience-based Nomenclature: glutamate, voltage-gated calcium channel blocker (Glu-CB)
- Anticonvulsant, antineuralgic for chronic pain, alpha 2 delta ligand at voltage-sensitive calcium channels

**Commonly Prescribed for**
*bold for FDA approved*
- Partial seizures with or without secondary generalization (adjunctive)
- Postherpetic neuralgia
- Restless leg syndrome (extended release)
- Neuropathic pain/chronic pain
- Anxiety (adjunctive)
- Bipolar disorder (adjunctive)

**How the Drug Works**
- Is a leucine analogue and is transported both into the blood from the gut and also across the blood-brain barrier into the brain from the blood by the system L transport system
  ✽ Binds to the alpha 2 delta subunit of voltage-sensitive calcium channels
- This closes N and P/Q presynaptic calcium channels, diminishing excessive neuronal activity and neurotransmitter release
- Although structurally related to gamma-aminobutyric acid (GABA), no known direct actions on GABA or its receptors

**How Long Until It Works**
- Should reduce seizures by 2 weeks
- Should also reduce pain in posttherapeutic neuralgia by 2 weeks; some patients respond earlier
- May reduce pain in other neuropathic pain syndromes within a few weeks
- If it is not reducing pain within 6–8 weeks, it may require a dosage increase or it may not work at all
- May reduce anxiety in a variety of disorders within a few weeks

**If It Works**
- The goal of treatment is complete remission of symptoms (e.g., seizures)
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of chronic neuropathic pain most often reduces but does not eliminate symptoms and is not a cure since symptoms usually recur after medicine stopped
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists

**If It Doesn’t Work (for neuropathic pain or bipolar disorder)**
- ✽ May only be effective in a subset of bipolar patients, in some patients who fail to respond to other mood stabilizers, or it may not work at all
- Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of pain or mood
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider biofeedback or hypnosis for pain
- Consider the presence of noncompliance and counsel patient
- Switch to another agent with fewer side effects
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- ✽ Gabapentin is itself an augmenting agent to numerous other anticonvulsants in treating epilepsy; and to lithium, atypical...
antipsychotics and other anticonvulsants in the treatment of bipolar disorder
• For postherpetic neuralgia, gabapentin can decrease concomitant opiate use
  ✴ For neuropathic pain, gabapentin can augment TCAs and SNRIs as well as tiagabine, other anticonvulsants and even opiates if done by experts while carefully monitoring in difficult cases
• For anxiety, gabapentin is a second-line treatment to augment SSRIs, SNRIs, or benzodiazepines

Tests
• None for healthy individuals
• False positive readings with the Ames N-Multistix SG® dipstick test for urinary protein have been reported when gabapentin was administered with other anticonvulsants

SIDE EFFECTS

How Drug Causes Side Effects
• CNS side effects may be due to excessive blockade of voltage-sensitive calcium channels

Notable Side Effects
✴ Sedation (dose-dependent), dizziness
✴ Ataxia (dose-dependent), fatigue, nystagmus, tremor
• Peripheral edema
• Blurred vision
• Vomiting, dyspepsia, diarrhea, dry mouth, constipation, weight gain
• Additional effects in children under age 12: hostility, emotional lability, hyperkinesia, thought disorder, weight gain

Life-Threatening or Dangerous Side Effects
• Anaphylaxis and angioedema
• Sudden unexplained deaths have occurred in epilepsy (unknown if related to gabapentin use)
• Rare activation of suicidal ideation and behavior (suicidality)

Weight Gain
• Occurs in significant minority

Sedation
• Many experience and/or can be significant in amount
• Dose-related; can be problematic at high doses
• Can wear off with time, but may not wear off at high doses

What to Do About Side Effects
• Wait
• Wait
• Wait
• Take more of the dose at night to reduce daytime sedation
• Lower the dose
• Switch to another agent

Best Augmenting Agents for Side Effects
• Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range
• 900–1,800 mg/day in 3 divided doses (immediate-release)

Dosage Forms
• Capsule 100 mg, 300 mg, 400 mg, 800 mg
• Tablet 100 mg, 300 mg, 400 mg, 600 mg, 800 mg
• Tablet extended-release 300 mg, 600 mg
• Liquid 250 mg/5 mL – 470 mL bottle

How to Dose
• Postherpetic neuralgia (immediate-release): 300 mg on day 1; on day 2 increase to 600 mg in 2 doses; on day 3 increase to 900 mg in 3 doses; maximum dose generally 1,800 mg/day in 3 doses
• Postherpetic neuralgia (extended-release): 600 mg in the morning on day 1; on day 4 increase to 600 mg twice daily
• Restless leg syndrome (extended-release): 600 mg once daily at about 5 pm
• Seizures (ages 12 and older): initial 900 mg/day in 3 doses; recommended dose generally 1,800 mg/day in 3 doses; maximum dose generally 3,600 mg/day;
Gabapentin

### Pharmacokinetics
- Gabapentin is not metabolized but excreted intact renally
- Not protein bound
- Elimination half-life approximately 5–7 hours

### Drug Interactions
- Antacids may reduce the bioavailability of gabapentin, so gabapentin should be administered approximately 2 hours before antacid medication
- Naproxen may increase absorption of gabapentin
- Morphine and hydrocodone may increase plasma AUC (area under the curve) values of gabapentin and thus gabapentin plasma levels over time

### Other Warnings/Precautions
- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- Dizziness and sedation could increase the chances of accidental injury (falls) in the elderly
- Pancreatic acinar adenocarcinomas have developed in male rats that were given gabapentin, but clinical significance is unknown
- Development of new tumors or worsening of tumors has occurred in humans taking gabapentin; it is unknown whether gabapentin affected the development or worsening of tumors
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately

### Overdose
- No fatalities; slurred speech, sedation, double vision, diarrhea

### Long-Term Use
- Safe

### Habit Forming
- No

### How to Stop
- Taper over a minimum of 1 week
- Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt
  - Rapid discontinuation may increase the risk of relapse in bipolar disorder
  - Discontinuation symptoms uncommon

### Time Between Any 2 Doses
- Not exceed 12 hours
- Seizures (under age 13): see Children and Adolescents

### Dosing Tips
- Gabapentin should not be taken until 2 hours after administration of an antacid
- If gabapentin is added to a second anticonvulsant, the titration period should be at least a week to improve tolerance to sedation
- Some patients need to take immediate-release gabapentin only twice daily in order to experience adequate symptomatic relief for pain or anxiety
- At the high end of the dosing range, tolerability may be enhanced by splitting immediate-release dose into more than 3 divided doses
- Half-tablets not used within several days of breaking the scored tablet should be discarded
- Do not break or chew extended-release tablets, as this could alter controlled-release properties
- Extended-release tablets should be taken with food
- For intolerable sedation, can give most of the dose at night and less during the day
- To improve slow-wave sleep, may need to take gabapentin only at bedtime

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### Do Not Use
- If there is a proven allergy to gabapentin or pregabalin
SPECIAL POPULATIONS

Renal Impairment
• Gabapentin is renally excreted, so the dose may need to be lowered

<table>
<thead>
<tr>
<th>Immediate-Release</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Creatinine</td>
<td></td>
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<tr>
<td>Clearance (mL/min)</td>
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</tr>
<tr>
<td>30–59</td>
<td>400–1,400 mg/day in 2 doses</td>
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<tr>
<td>16–29</td>
<td>200–700 mg/day in 1 dose</td>
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<tr>
<td>&lt;16</td>
<td>100–300 mg/day in 1 dose</td>
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<tr>
<td>&lt;16 on hemodialysis</td>
<td>May need supplemental doses following dialysis</td>
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Cardiac Impairment
• No specific recommendations

Elderly
• Some patients may tolerate lower doses better
• Elderly patients may be more susceptible to adverse effects, including peripheral edema and ataxia

Children and Adolescents
• Approved for use starting at age 3 as adjunct treatment for partial seizures
• Ages 5–12: initial 10–15 mg/kg per day in 3 doses; titrate over 3 days to 25–35 mg/kg per day given in 3 doses; maximum dose generally 50 mg/kg per day; time between any 2 doses should usually not exceed 12 hours
• Ages 3–4: initial 10–15 mg/kg per day in 3 doses; titrate over 3 days to 40 mg/kg per day; maximum dose generally 50 mg/kg per day; time between any 2 doses should usually not exceed 12 hours

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
• Antiepileptic Drug Pregnancy Registry: (888) 233–2334
• Taper drug if discontinuing
• Seizures, even mild seizures, may cause harm to the embryo/fetus

Can be removed by hemodialysis; patients receiving hemodialysis may require supplemental doses of gabapentin
• Use in renal impairment has not been studied in children under age 12

Hepatic Impairment
• No available data but not metabolized by the liver and clinical experience suggests normal dosing

Extended-Release for Restless Leg Syndrome
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Extended-Release for Postherpetic Neuralgia
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GABAPENTIN

Potential Advantages
- Has few pharmacokinetic drug interactions
- Treatment-resistant bipolar disorder

Potential Disadvantages
- Usually requires 3 times a day dosing
- Poor documentation of efficacy for many off-label uses, especially bipolar disorder

Primary Target Symptoms
- Seizures
- Pain
- Anxiety

Pearls
- Gabapentin is generally well-tolerated, with only mild adverse effects
- Well studied in epilepsy and postherpetic neuralgia
- Most use is off label
- Off-label use for first-line treatment of neuropathic pain may be justified
- Off-label use for second-line treatment of anxiety may be justified
- Off-label use as an adjunct for bipolar disorder may not be justified
- Misperceptions about gabapentin’s efficacy in bipolar disorder have led to its use in more patients than other agents with proven efficacy, such as lamotrigine
- Off-label use as an adjunct for schizophrenia may not be justified
- May be useful for some patients in alcohol withdrawal
- One of the few agents that enhances slow-wave delta sleep, which may be helpful in chronic neuropathic pain syndromes
- May be a useful adjunct for fibromyalgia
- Drug absorption and clinical efficacy may not necessarily be proportionately increased at high doses, and thus response to high doses may not be consistent

Breast Feeding
- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- If drug is continued while breast feeding, infant should be monitored for possible adverse effects
- If infant becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis
- Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
- Atypical antipsychotics and anticonvulsants such as valproate may be safer and more effective than gabapentin during the postpartum period when treating a nursing mother with bipolar disorder

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Chronic neuropathic pain
- Has relatively mild side effect profile
Suggested Reading


