**Brands**
- Topamax
- Epitomax
- Topamac
- Topimax
- Trokendi XR
- Qsymia

*see index for additional brand names*

**Generic?**  Yes (not for Qsymia)

**Class**
- Anticonvulsant, voltage-sensitive sodium channel modulator

**Commonly Prescribed for**
(bold for FDA approved)
- Partial onset seizures (for immediate-release: adjunctive for adults and pediatric patients 2–16 years of age; for extended-release: monotherapy for patients 10 years and older, adjunctive for patients 6 years and older)
- Primary generalized tonic-clonic seizures (adjunctive; adults and pediatric patients 2–16 years of age)
- Seizures associated with Lennox-Gastaut Syndrome (2 years of age or older for immediate-release, 6 years of age and older for extended-release (adjunct))
- Migraine prophylaxis
- Chronic weight management (adjunct to reduced calorie diet and increased physical activity) in adults with an initial body mass index (BMI) of at least 30 kg/m² (obese) or at least 27 kg/m² (overweight) in the presence of at least one weight-related comorbid condition (in combination with phentermine (Qsymia))
- Bipolar disorder (adjunctive; no longer in development)
- Psychotropic drug-induced weight gain
- Binge eating disorder

**How the Drug Works**
- Blocks voltage-sensitive sodium channels by an unknown mechanism
- Inhibits release of glutamate
- Potentiates activity of gamma-aminobutyric acid (GABA)
- Carbonic anhydrase inhibitor

**How Long Until It Works**
- Should reduce seizures by 2 weeks
- Not clear that it has mood-stabilizing properties, but some bipolar patients may respond and if so, it may take several weeks to months to optimize an effect on mood stabilization

**If It Works**
- The goal of treatment is complete remission of symptoms (e.g., mania, seizures, migraine)
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists
- Continue treatment indefinitely to avoid recurrence of mania, seizures, and headaches

**If It Doesn’t Work (for bipolar disorder)**
- May be effective only in a subset of bipolar patients, in some patients who fail to respond to other mood stabilizers, or it may not work at all
- Consider increasing dose or switching to another agent with better demonstrated efficacy in bipolar disorder

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Topiramate is itself a second-line augmenting agent for numerous other anticonvulsants, lithium, and antipsychotics in treating bipolar disorder

**Tests**
- Baseline and periodic serum bicarbonate levels to monitor for hyperchloremic, non-anion gap metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis)

**SIDE EFFECTS**

**How Drug Causes Side Effects**
- CNS side effects theoretically due to excessive actions at voltage-sensitive sodium channels
- Weak inhibition of carbonic anhydrase may lead to kidney stones and paresthesias
• Inhibition of carbonic anhydrase may also lead to metabolic acidosis

**Notable Side Effects**

* Sedation, asthenia, dizziness, ataxia, paraesthesia, nervousness, nystagmus, tremor
* Nausea, appetite loss, weight loss
* Blurred or double vision, mood problems, problems concentrating, confusion, memory problems, psychomotor retardation, language problems, speech problems, fatigue, taste perversion

**Life-Threatening or Dangerous Side Effects**

* Metabolic acidosis
* Kidney stones
* Secondary angle-closure glaucoma
* Oligohidrosis and hyperthermia (more common in children)
* Sudden unexplained deaths have occurred in epilepsy (unknown if related to topiramate use)
* Rare activation of suicidal ideation and behavior (suicidality)

**Weight Gain**

• Unusual
• Common
• Problematic

• Reported but not expected
• Patients may experience weight loss

**Sedation**

• Unusual
• Common
• Problematic

• Many experience and/or can be significant in amount

**What to Do About Side Effects**

• Wait
• Wait
• Wait
• Take at night to reduce daytime sedation
• Increase fluid intake to reduce the risk of kidney stones
• Switch to another agent

**Best Augmenting Agents for Side Effects**

• Many side effects cannot be improved with an augmenting agent

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**Dosage and Use**

**Usual Dosage Range**

• Adults, immediate-release: 200–400 mg/day in 2 divided doses for epilepsy; 50–300 mg/day for adjunctive treatment of bipolar disorder
• Adults, extended-release: 200–400 mg/day as adjunct for partial onset seizures; 400 mg/day as adjunct for primary generalized tonic clonic seizures; 400 mg/day as monotherapy for seizures

**Dosage Forms**

• Tablet 25 mg, 100 mg, 200 mg
• Sprinkle capsule 15 mg, 25 mg
• Extended-release capsule 25 mg, 50 mg, 100 mg, 200 mg

**How to Dose**

• Adults (immediate-release): initial 25–50 mg/day; increase each week by 50 mg/day; administer in 2 divided doses; maximum dose generally 1,600 mg/day
• Adults (extended-release, adjunct for seizures): initial 25–50 mg once daily; increase weekly by 25–50 mg
• Seizures (extended-release, monotherapy, patients ages 10 and older): initial 50 mg once daily; increase by 50 mg weekly for 4 weeks, increase by 100 mg weekly for weeks 5 and 6; recommended dose 400 mg/day
• Seizures (immediate-release, ages 2–16): see Children and Adolescents

**Dosing Tips**

• Adverse effects may increase as dose increases
• Topiramate is available in a sprinkle capsule formulation, which can be swallowed whole or sprinkled over approximately a teaspoon of soft food (e.g., applesauce); the mixture should be consumed immediately
• Bipolar patients are generally administered doses at the lower end of the dosing range
• Slow upward titration from doses as low as 25 mg/day can reduce the incidence of unacceptable sedation
• Many bipolar patients do not tolerate more than 200 mg/day
• Weight loss is dose-related but most patients treated for weight gain receive
Topiramate may reduce the effectiveness of oral contraceptives.
Reports of hyperammonemia with or without encephalopathy in patients taking topiramate combined with valproate, though this is not due to a pharmacokinetic interaction; in patients who develop unexplained lethargy, vomiting, or change in mental status, an ammonia level should be measured.

Other Warnings/Precautions

- If symptoms of metabolic acidosis develop (hyperventilation, fatigue, anorexia, cardiac arrhythmias, stupor), then dose may need to be reduced or treatment may need to be discontinued.
- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- Use with caution when combining with other drugs that predispose patients to heat-related disorders, including carbonic anhydrase inhibitors and anticholinergics.
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately.

Do Not Use

- Within 6 hours prior to and 6 hours after alcohol use (extended-release).
- In patients with metabolic acidosis who are taking metformin (extended-release).
- If there is a proven allergy to topiramate.

Drug Interactions

- Carbamazepine, phenytoin, and valproate may increase the clearance of topiramate, and thus decrease topiramate levels, possibly requiring a higher dose of topiramate.
- Topiramate may increase the clearance of phenytoin and thus decrease phenytoin levels, possibly requiring a higher dose of phenytoin.
- Topiramate may increase the clearance of valproate and thus decrease valproate levels, possibly requiring a higher dose of valproate.
- Topiramate may increase plasma levels of metformin; also, metformin may reduce clearance of topiramate and increase topiramate levels.
- Topiramate may interact with carbonic anhydrase inhibitors to increase the risk of kidney stones.

SPECIAL POPULATIONS

Renal Impairment

- Topiramate is renally excreted, so the dose should be lowered by half.
- Can be removed by hemodialysis; patients receiving hemodialysis may require supplemental doses of topiramate.

Hepatic Impairment

- Drug should be used with caution.

Cardiac Impairment

- Drug should be used with caution.

Long-Term Use

- Probably safe.
- Periodic monitoring of serum bicarbonate levels may be required.

How to Stop

- Taper.
- Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt.
- Rapid discontinuation may increase the risk of relapse in bipolar patients.
- Discontinuation symptoms uncommon.

Pharmacokinetics

- Elimination half-life approximately 21 hours.
- Renally excreted.

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Doses at the lower end of the dosing range.

Overdose

- No fatalities have been reported in monotherapy; convulsions, sedation, speech disturbance, blurred or double vision, metabolic acidosis, impaired coordination, hypotension, abdominal pain, agitation, dizziness.

Habit Forming

- No.

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- Can be removed by hemodialysis; patients receiving hemodialysis may require supplemental doses of topiramate.

Hepatic Impairment

- Drug should be used with caution.

Cardiac Impairment

- Drug should be used with caution.
For bipolar patients, topiramate should generally be discontinued before anticipated pregnancies

Antiepileptic Drug Pregnancy Registry: • (888) 233–2334

Taper drug if discontinuing

For bipolar patients, given the risk of relapse in the postpartum period, mood stabilizer treatment, especially with agents with better evidence of efficacy than topiramate, should generally be restarted immediately after delivery if patient is unmedicated during pregnancy

Atypical antipsychotics may be preferable to topiramate if treatment of bipolar disorder is required during pregnancy

Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

Seizures, even mild seizures, may cause harm to the embryo/fetus

Breast Feeding

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 shows signs of irritability or sedation, 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 topiramate during the postpartum period when treating nursing mother with bipolar disorder

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Treatment-resistant bipolar disorder
- Patients who wish to avoid weight gain

Potential Disadvantages

- Efficacy in bipolar disorder uncertain
• Patients with a history of kidney stones or risks for metabolic acidosis

**Primary Target Symptoms**
• Incidence of seizures
• Unstable mood

**Pearls**
• Side effects may actually occur less often in pediatric patients
• Has been studied in a wide range of psychiatric disorders, including bipolar disorder, PTSD, binge eating disorder, obesity, and others
• Some anecdotes, case series, and open-label studies have been published and are widely known suggesting efficacy in bipolar disorder

✹ However, randomized clinical trials do not suggest efficacy in bipolar disorder; unfortunately these important studies have not been published by the manufacturer, who has dropped topiramate from further development as a mood stabilizer, though this is not widely known

✹ Misperceptions about topiramate’s efficacy in bipolar disorder have led to its use in more patients than other agents with proven efficacy, such as lamotrigine

✹ Due to reported weight loss in some patients in trials with epilepsy, topiramate is commonly used to treat weight gain, especially in patients with psychotropic drug-induced weight gain

✹ Weight loss in epilepsy patients is dose-related with more weight loss at high doses (mean 6.5 kg or 7.3% decline) and less weight loss at lower doses (mean 1.6 kg or 2.2% decline)

✹ Changes in weight were greatest in epilepsy patients who weighed the most at baseline (>100 kg), with mean loss of 9.6 kg or 8.4% decline, while those weighing <60 kg had only a mean loss of 1.3 kg or 2.5% decline

✹ Long-term studies demonstrate that weight losses in epilepsy patients were seen within the first 3 months of treatment and peaked at a mean of 6 kg after 12–18 months of treatment; however, weight tended to return to pretreatment levels after 18 months

✹ Some patients with psychotropic drug-induced weight gain may experience significant weight loss (>7% of body weight) with topiramate up to 200 mg/day for 3 months, but this is not typical, is not often sustained, and has not been systemically studied

• Early studies suggest potential efficacy in binge eating disorder
• The combination of topiramate and phentermine is approved as a treatment for obesity (see phentermine-topiramate); the combination is also being studied in diabetes and sleep apnea

**Suggested Reading**


