**TOPIRAMATE**

**Therapeutics**

**Brands**
- Topamax, Epitomax, Topamac

**Generic?**
- Yes

**Class**
- Antiepileptic drug (AED)

**Commonly Prescribed for** (FDA approved in bold)
- Partial-onset seizures (adjunctive; adults and pediatric patients age 2–16)
- Primary generalized tonic-clonic seizures (adjunctive; adults and pediatric patients age 2–16)
- Migraine prophylaxis
- Drop attacks associated with Lennox-Gastaut syndrome
- Obesity
- Bipolar disorder
- Binge-eating disorder/bulimia
- Cluster headache prophylaxis
- Idiopathic intracranial hypertension
- Alcohol dependence
- Essential tremor

**How the Drug Works**

There are multiple mechanisms of action, and it is uncertain which of these give the drug its effectiveness

- Augmentation of the GABA-A receptor
- Sodium channel blocker
- Carbonic anhydrase inhibitor, isoenzymes II and IV
- Glutamate receptor (specifically the AMPA/kainate subtype) antagonist
- May work by inhibiting protein kinase activity
- Possible serotonin activity on 5-HT2C receptors

**How Long Until It Works**

- Seizures – may decrease by 2 weeks
- Migraines – may decrease in as little as 2 weeks, but can take up to 3 months on a stable dose to see full effect

**If It Works**

- Seizures – goal is the remission of seizures. Continue as long as effective and well-tolerated. Consider tapering slowly, stopping after 2 years without seizures, depending on the type of epilepsy
- Migraine – goal is a 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy

**If It Doesn’t Work**

- Increase to highest tolerated dose
- Epilepsy: consider changing to another agent, adding a second agent or referral for epilepsy surgery evaluation
- Migraine: address other issues, such as medication-overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent

**Best Augmenting Combos for Partial Response or Treatment-Resistance**

- For some patients with epilepsy or migraine, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy
- Epilepsy: keep in mind drug interactions and their effect on levels
- Migraine: consider beta-blockers, antidepressants, natural products, other AEDs, and non-medication treatments such as biofeedback to improve headache control

**Tests**

- Mild to moderate decreases in bicarbonate can occur with topiramate, but are uncommon reasons for discontinuation. Routine screening for metabolic acidosis is not recommended

**Adverse Effects (AEs)**

**How Drug Causes AEs**

- CNS AEs may be caused by sodium channel blockade or GABA-A receptor augmentation
- Carbonic anhydrase inhibition causes paresthesias, metabolic acidosis; may lead to kidney stones

**Notable AEs**

- Sedation, cognitive problems, especially word-finding difficulties, mood problems, paresthesias
- Anorexia, diarrhea, weight loss
• Pallinopsia – a visual disturbance that causes persistence of images (rare and frightening for the patient but benign)

**Life-Threatening or Dangerous AEs**
- Metabolic acidosis
- Kidney stones (calcium phosphate)
- Narrow angle-closure glaucoma (rare)
- Fever, dehydration and lack of sweating (more common in children)

**Weight Gain**
- Unusual

**Sedation**
- Common

**What to Do About AEs**
- AEs often decrease or remit after a longer time on a stable dose
- Paresthesias may respond to high potassium diets or potassium tablets
- Cognitive AEs tend to improve with small decreases in dose
- For patients with kidney stones, check the type of stone. Topiramate usually causes calcium phosphate stones

**Best Augmenting Agents for AEs**
- Paresthesias related to topiramate may improve with high potassium diet or tablets
- Other AEs are more likely to improve by lowering dose

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**How to Dose**
- Adults: increase by 50 mg/week for epilepsy or as tolerated, and by 25 mg/week for migraine until goal dose
- Pediatrics – see children and adolescents

**Dosing Tips**
- Adverse events increase with dose increases
- Weight loss is often dose related, but patients on lower doses (50 mg) still lose weight
- Slow titration minimizes sedation and other AEs
- Some patients need higher doses for migraine or cluster headache prophylaxis

**Overdose**
- Convulsions, drowsiness, sleep disturbance, blurred vision, diplopia, stupor, hypotension, abdominal pain, agitation, dizziness, lethargy, depression, and metabolic acidosis. No reported deaths except with poly-drug overdoses

**Long-Term Use**
- Safe for long-term use

**Habit Forming**
- No

**How to Stop**
- Taper slowly
- Abrupt withdrawal can lead to seizures in patients with epilepsy. Tremor is also common
- Headaches may return within days to months of stopping, but patients often continue to do well for 6 or more months after stopping

**Pharmacokinetics**
- Renally excreted. Peak levels at 2 hr and half-life 21 hours

**Drug Interactions**
- Phenytoin, carbamazepine, valproic acid, and pioglitazone can increase topiramate clearance and decrease topiramate levels
- Lamotrigine and hydrochlorothiazide may increase topiramate levels
- Topiramate may increase levels of amitriptyline
**Topiramate**

- Can decrease levels of lithium, digoxin, and valproic acid
- Carbonic anhydrase inhibitors such as acetazolamide increase the risk of kidney stones
- Topiramate can interact with CNS depressants and alcohol with neuropsychiatric and cognitive consequences
- Higher-dose topiramate (> 200 mg) can decrease plasma concentrations of estrogens and progestins in patients taking oral contraceptives. Use a higher dose of estrogen or consider alternative methods of contraception

**Other Warnings/Precautions**
- Patients taking a ketogenic diet for seizures are more likely to experience severe metabolic acidosis on topiramate

**Do Not Use**
- Patients with a proven allergy to topiramate

**Special Populations**

**Renal Impairment**
- Topiramate is renally excreted and removed by hemodialysis. Lower dose and give an extra dose after dialysis sessions

**Hepatic Impairment**
- May be decreased in patients with significant liver disease

**Cardiac Impairment**
- No known effects

**Elderly**
- Elderly patients may be more susceptible to AEs

**Children and Adolescents**
- Approved for treatment of children over age 2 for epilepsy management
- Starting dose 1–3 mg/kg/day at night, increasing every 1–2 weeks by 1–3 mg/kg/day until goal dose of 5–9 mg/kg/day in 2 divided doses
- Paresthesias and cognitive AEs are less common in children

**Pregnancy**
- Risk category C. Teratogenic in animal studies but no studies in humans
- Associated with hypospadias in male infants
- Risks of stopping medication must outweigh risk to fetus for patients with epilepsy. Seizures and potential status epilepticus place the woman and fetus at risk and can cause reduced oxygen and blood supply to the womb
- Patients with migraine should generally stop topiramate before considering pregnancy. Migraine usually improves in the last 2 trimesters
- Supplementation with 0.4 mg of folic acid before and during pregnancy is recommended

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Generally recommendations are to discontinue drug or bottle feed
- If topiramate is used, then need to monitor infant for sedation, poor feeding or irritability

**Potential Advantages**
- Effectively treats both migraine and epilepsy. Usually causes weight loss, unlike many other medications for epilepsy and migraine

**Potential Disadvantages**
- Cognitive AEs. Weight loss in thin patients can be troublesome. Kidney stones and metabolic acidosis

**Primary Target Symptoms**
- Seizure frequency and severity
- Migraine frequency and severity

**Pearls**
- For epilepsy, higher doses may be needed. AEs are more common when using in combination with other drugs that can produce CNS depression
- Broad-spectrum AED effective against almost all seizure types (maybe even infantile spasms)
For migraine, the individual dose may vary widely. Some patients benefit from doses as low as 25 mg/day but others may require much higher doses than the 100 mg/day approved for migraine prophylaxis.

Topiramate may be effective in treating idiopathic intracranial hypertension (pseudotumor cerebrii) and is often easier to tolerate with more weight loss than acetazolamide.

Topiramate is not a first-line medication for cluster headache.

Topiramate is used for treatment of manic symptoms in bipolar disorder, but its efficacy was not established in clinical trials.

Topiramate is useful for essential tremor, although often higher doses are needed to see an effect.

Suggested Reading


