# NEURO-LOGICAL™

- Broad-Spectrum Efficacy
- Established Safety Record
- Well Tolerated

**TOPAMAX®**
(topiramate)

**Your logical choice**


## Multiple Mechanisms of Action

| TOPAMAX | |
|---|---|
| Blocks non-NMDA subtype (AMPA/kainate) of glutamate receptor | ✓ |
| Enhances effect of GABA | ✓ |
| Blocks $Na^+$ channels | ✓ |
| Activates $K^+$ channel conductance[1] | ✓ |
| Blocks $Ca^{++}$ channels[2] | ✓ |
| Carbonic anhydrase inhibition | ✓ |

- Multiple mechanisms of action may contribute to antiseizure efficacy

## Approved for a Broad Spectrum of Patients

*TOPAMAX is indicated as adjunctive therapy for patients in a broad range of age categories*

- Children as young as 2 years of age
- Adults

# Documented Broad-Spectrum Efficacy

| | FDA-Approved Indication—Adjunctive Therapy | | | | |
|---|---|---|---|---|---|
| | Partial-Onset Seizures in Adults | Partial-Onset Seizures in Patients ≥2 Years of Age | Primary Generalized Tonic-Clonic Seizures in Adults | Primary Generalized Tonic-Clonic Seizures in Patients ≥2 Years of Age | Seizures of Lennox-Gastaut Syndrome in Children and in Adults |
| **TOPAMAX** | ✓ | ✓ | ✓ | ✓ | ✓ |
| divalproex sodium | ✓ | ✓* | | | |
| oxcarbazepine | ✓ | ✓† | | | |
| lamotrigine | ✓ | ✓ | | | ✓‡ |
| levetiracetam | ✓ | | | | |

- Some first-generation antiepileptic drugs are not included in this table. Additional indications are:
  - "Carbamazepine has been found useful in: the management of psychomotor (temporal lobe) epilepsy and, as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication. As an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs."[3]
  - "Dilantin[§] (phenytoin) is indicated for the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures."[4]

*Patients ≥10 years of age.
†Patients ≥4 years of age.
‡Indicated for generalized seizures of Lennox-Gastaut syndrome.
§Dilantin is a registered trademark of Parke-Davis, a Warner-Lambert Division, a Pfizer Company.

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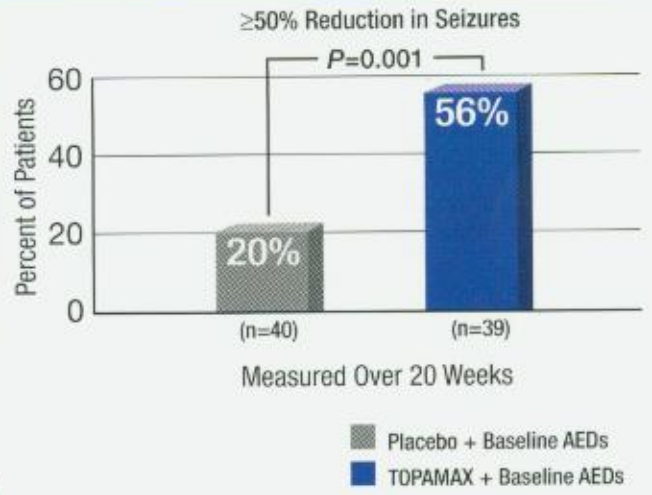
## Proven Efficacy Across Seizure Types in Adults and Children

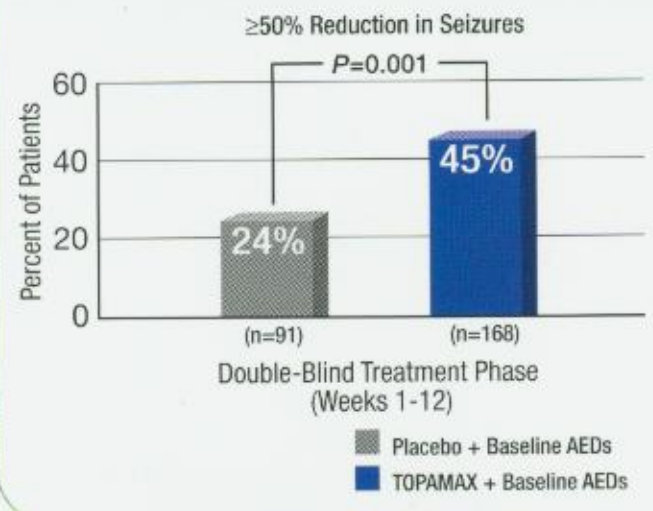
### *Primary Generalized Tonic-Clonic Seizures*

**Primary Generalized Tonic-Clonic Seizures in Adults and Children[5]**

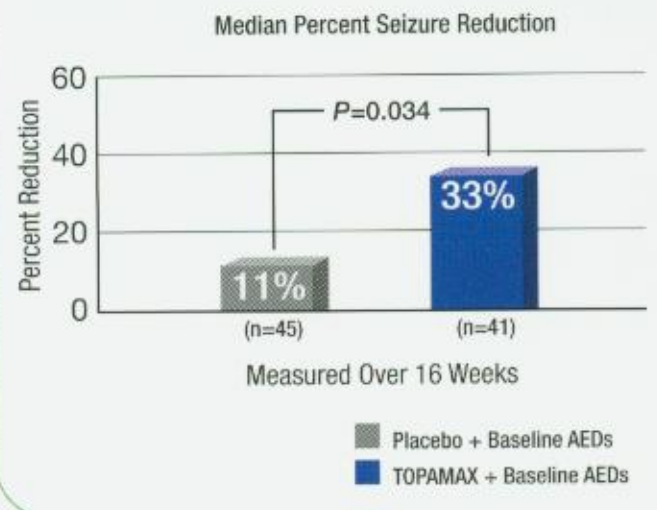



### *Partial-Onset Seizures*

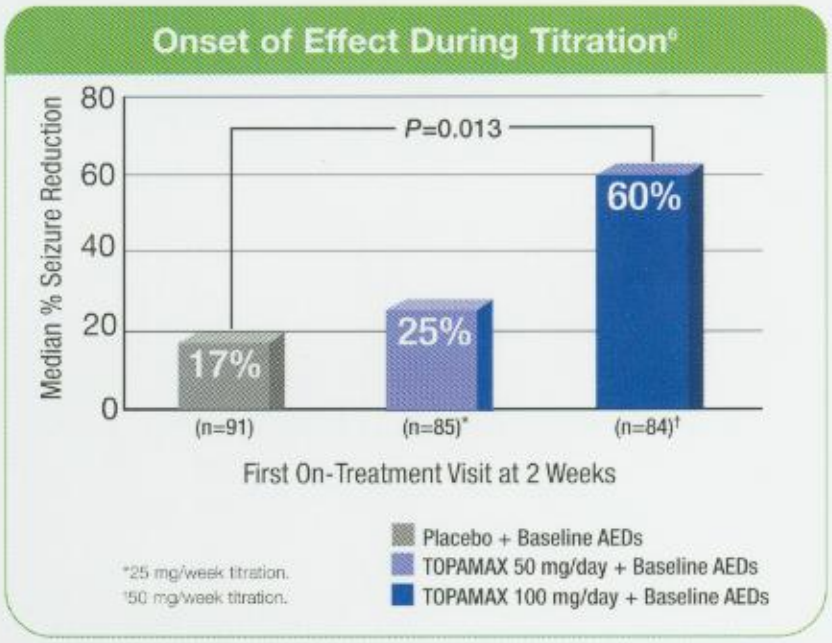
**Partial-Onset Seizures in Adults[6]**




**Partial-Onset Seizures in Children 2 to 16 Years of Age[7]**



# Efficacy as Early as 2 Weeks[6]




- Therapeutic effect shown as early as 2 weeks after start of TOPAMAX treatment[6]
- TOPAMAX at 200 mg/day is effective as adjunctive therapy when added to enzyme-inducing AEDs in adults with refractory partial-onset seizures[6]

Please see pages 8 and 9 for additional efficacy data.

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## Established Safety Record

- 3 million patients treated[8]
- Favorable pharmacokinetics
  - —Linear dose-plasma concentration relationship
  - —No autoinduction
- Minimal drug interactions
  - —Low protein binding
  - —Low potential for P450 enzyme induction[9]
- No significant interaction between TOPAMAX and combination oral contraceptives* at TOPAMAX doses up to 200 mg/day†[10]
- No black box warnings
- Not associated with drug-induced weight gain
- Not associated with unfavorable changes in lipids

*Containing norethindrone 1 mg and ethinyl estradiol 35 µg.

† Although there was a dose-dependent decrease in ethinyl estradiol exposure for doses between 200 to 800 mg/day, the clinical significance of the changes exerted is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.



Please see pages 10 and 11 for additional safety considerations.

# NEURO-LOGICAL™

## Well Tolerated at 200 mg/day[6]

| Most Common Adverse Events[1,6] | | |
|---|---|---|
| | Percent of Patients | |
| | Placebo (n=92) | TOPAMAX 200 mg/day (n=171) |
| Somnolence | 9 | 15 |
| Anorexia | 7 | 9 |
| Fatigue | 4 | 9 |
| Paresthesia | 2 | 9 |
| Nervousness | 2 | 9 |
| Weight decrease | 4 | 8 |
| Dizziness | 4 | 7 |

[1]Adverse events more frequent in TOPAMAX-treated patients with reported incidence >5%. Patients in these add-on trials were receiving 1 to 2 concomitant AEDs in addition to TOPAMAX or placebo.

## Flexible Dosing

| Commonly Used BID Titration Schedule for Adults | | | | | |
|---|---|---|---|---|---|
| | Week 1 | Week 2 | Week 3 | Week 4 | After Week 4 |
| AM Dose | | 25 | 25 | 50 | Increase in weekly increments of 25 to 50 mg/day to effect |
| PM Dose | 25 | 25 | 25 25 | 50 | |

- Initiate therapy with a PM dose of 25 to 50 mg of TOPAMAX
- Recommended daily dose of TOPAMAX in adults is 200 to 400 mg/day in two divided doses
- In children (ages 2 to 16 years), the recommended daily dose is approximately 5 to 9 mg/kg/day in two divided doses

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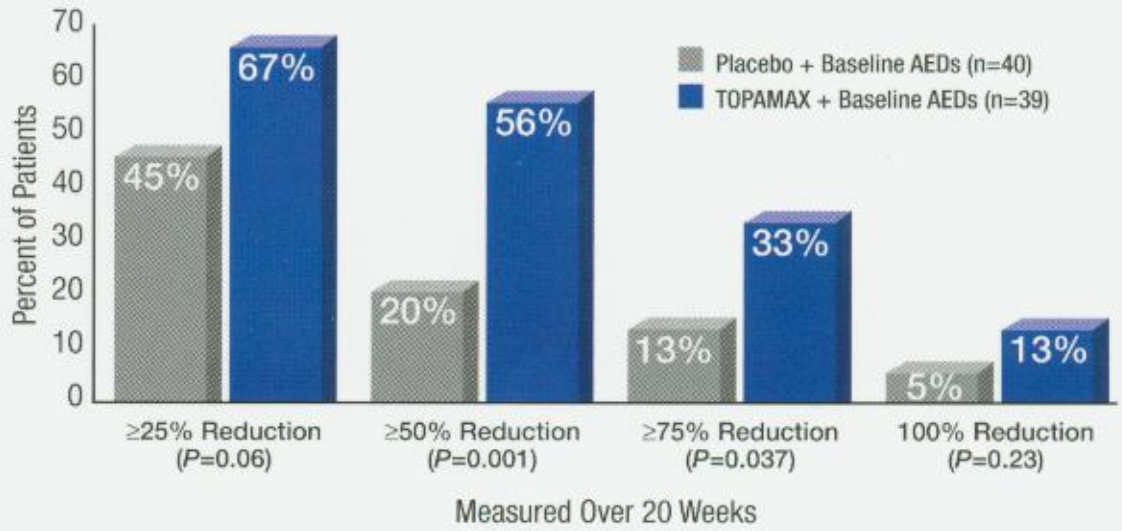
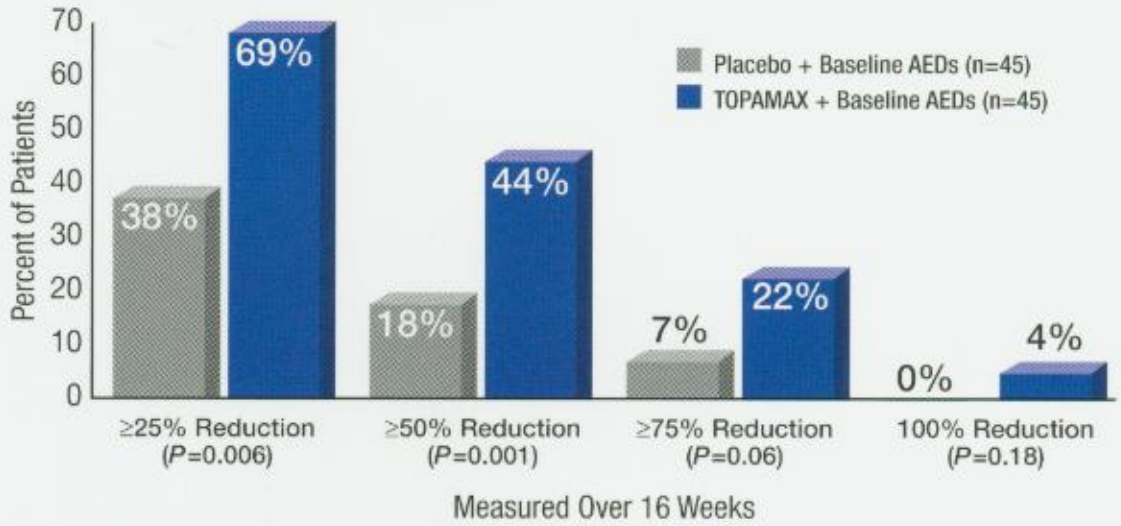
## Proven Efficacy

### Primary Generalized Tonic-Clonic Seizures in Adults[5,8]




### Partial-Onset Seizures in Adults[8,11]



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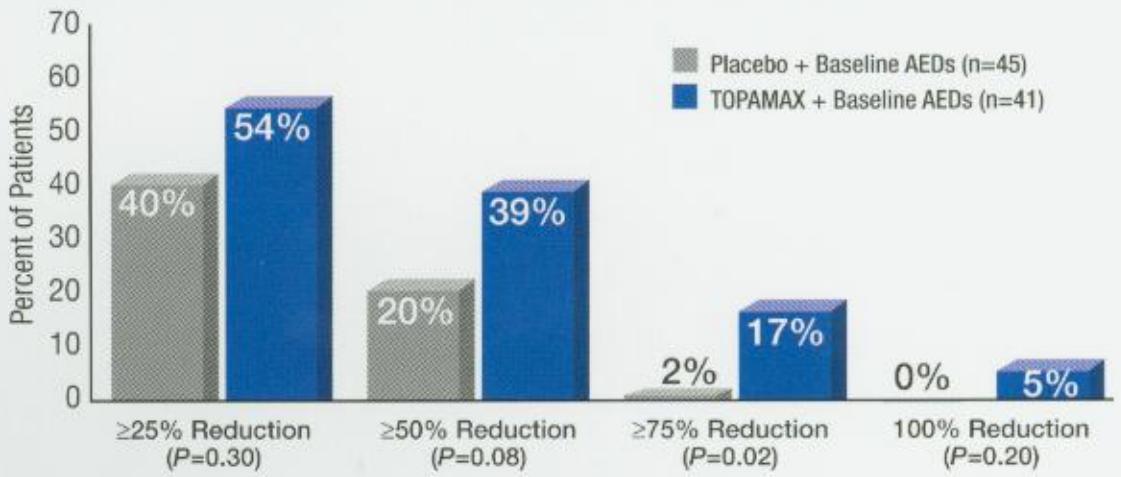
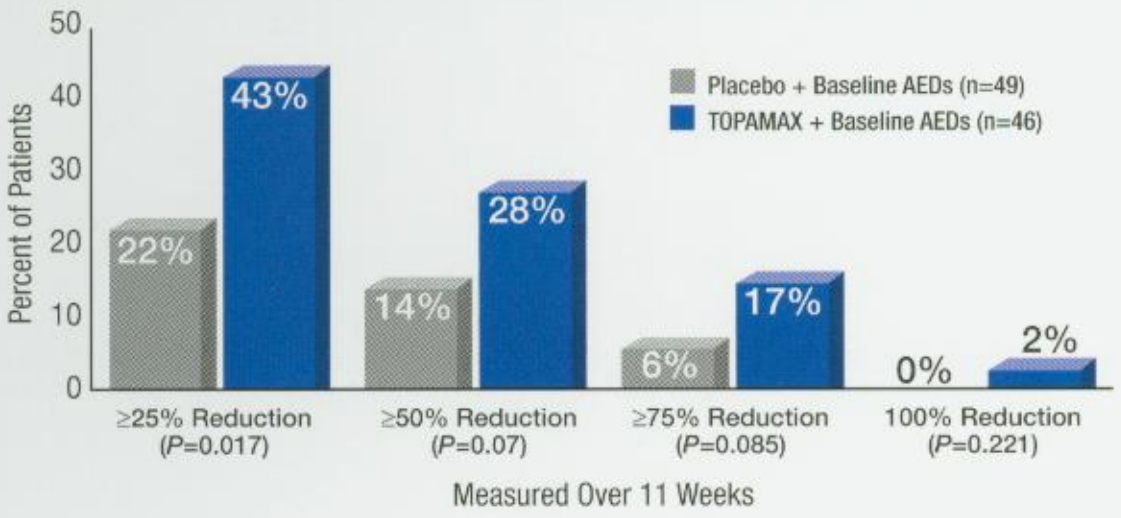
## Partial-Onset Seizures in Children 2 to 16 Years of Age[7,8]




Measured Over 16 Weeks

## Drop Attacks Associated With Lennox-Gastaut Syndrome[8,12]




Measured Over 11 Weeks

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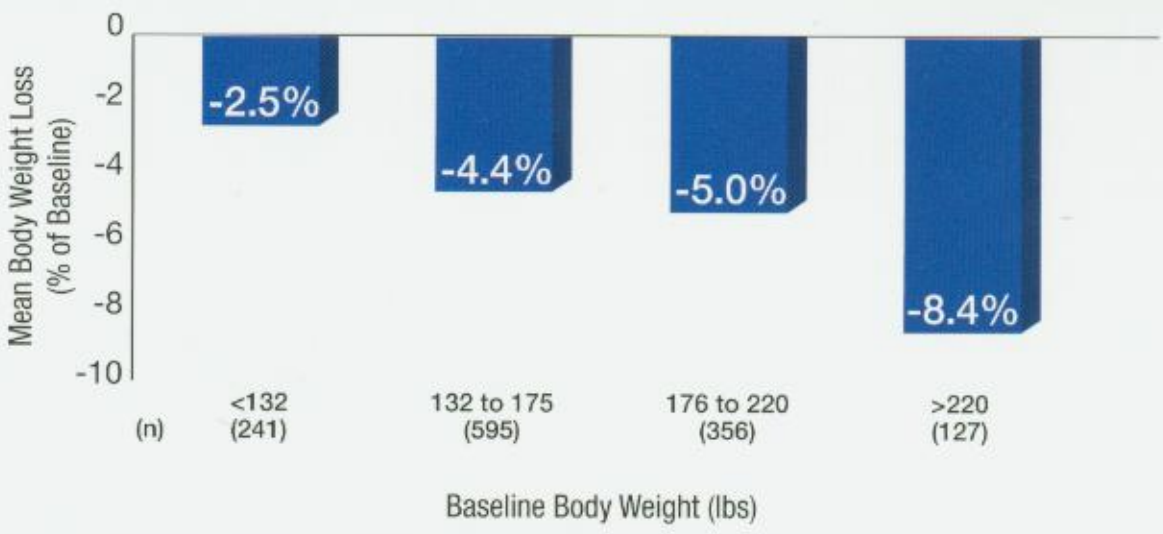
# Additional Safety Considerations

"Even small gains in weight within the range of healthy weights can carry health risks..."[13]

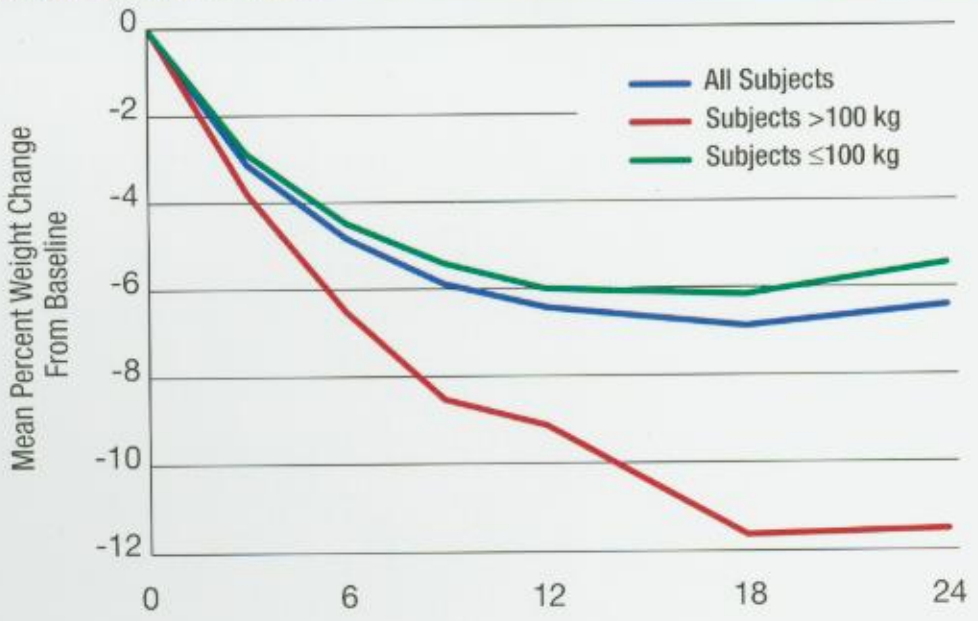
## *Weight Change Observations in Epilepsy Clinical Trials*[8]

**Weight Change Versus Baseline Body Weight[8]**




- In double-blind studies among adults, less than 1% of patients treated with TOPAMAX discontinued due to weight loss[8]

## Stabilization of Weight Loss Over Time[6]



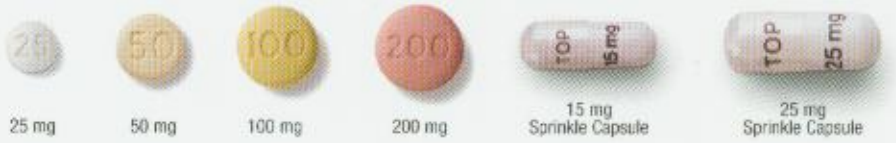

- In adjunctive clinical trials with children[8]:
  - After 6 months, mean weight loss was 0.6% of baseline body weight in patients treated with TOPAMAX; mean weight in children treated with TOPAMAX returned to baseline levels by month 7
  - After 14 to 19 months, children treated with TOPAMAX had a net weight gain of 8.5% (6 lbs)
  - No children permanently discontinued TOPAMAX due to weight loss

TOPAMAX® (topiramate)

Your logical choice

# NEURO-LOGICAL™

- **Broad-Spectrum Efficacy**
  - — Primary generalized tonic-clonic seizures
  - — Partial-onset seizures
  - — Seizure types associated with Lennox-Gastaut syndrome
- **Established Safety Record**
- **Well Tolerated**




25 mg | 50 mg | 100 mg | 200 mg | 15 mg Sprinkle Capsule | 25 mg Sprinkle Capsule

## TOPAMAX® (topiramate)

## Your logical choice

Indicated as adjunctive therapy for patients ≥2 years of age with primary generalized tonic-clonic seizures, partial-onset seizures, or seizures associated with Lennox-Gastaut syndrome.

In combination with other traditional antiepileptic drugs (AEDs), the most common side effects of TOPAMAX in adults (200 to 400 mg/day) were somnolence, dizziness, ataxia, speech disorders and related problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, and diplopia; and in children (5 to 9 mg/kg/day), somnolence, anorexia, fatigue, nervousness, difficulty with concentration/attention, weight decrease, aggressive reaction, and memory difficulty.

Serious as well as minor side effects have been reported with the use of TOPAMAX. Please see full Prescribing Information.

**References: 1.** Herrero AI, Del Olmo N, González-Escalada JR, Solis JM. Two new actions of topiramate: inhibition of depolarizing $GABA_A$-mediated responses and activation of a potassium conductance. *Neuropharmacology*. 2002;42:210-220. **2.** Zhang X-l, Velumian AA, Jones OT, Carlen PL. Modulation of high-voltage–activated calcium channels in dentate granule cells by topiramate. *Epilepsia*. 2000;41(suppl 1):S52-S60. **3.** Internet Mental Health. Carbamazepine. Available at: http://www.mentalhealth.com/drug/p30-t01.html. Accessed March 17, 2004. **4.** Dilantin-125® [prescribing information]. Morris Plains, NJ: Parke-Davis; 1999. **5.** Biton V, Montouris GD, Ritter F, et al, and the Topiramate YTC Study Group. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology*. 1999;52:1330-1337. **6.** Guberman A, Neto W, Gassmann-Mayer C, and the EPAJ-119 Study Group. Low-dose topiramate in adults with treatment-resistant partial-onset seizures. *Acta Neurol Scand*. 2002;106:183-189. **7.** Elterman RD, Glauser TA, Wyllie E, Reife R, Wu S-C, Pledger G, and the Topiramate YP Study Group. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. *Neurology*. 1999;52:1338-1344. **8.** Data on file, Ortho-McNeil Pharmaceutical, Inc. **9.** Nallani SC, Glauser TA, Hariparsad N, et al. Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate. *Epilepsia*. 2003;44:1521-1528. **10.** Doose DR, Wang S-S, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia*. 2003;44:540-549. **11.** Faught E, Wilder BJ, Ramsay RE, et al, and the Topiramate YD Study Group. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology*. 1996;46:1684-1690. **12.** Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G, and the Topiramate YL Study Group. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology*. 1999;52:1882-1887. **13.** Willett WC, Dietz WH, Colditz GA. Primary care: guidelines for healthy weight. *N Engl J Med*. 1999;341:427-434.

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**TOPAMAX Case Study: Fourth in a Series**

*"She's really a smart kid. But she can be out of it for a whole day or more when she's had a couple of spells. Her grandma's always telling me the pills are the problem...but they're not if they stop her spells. Brianna was doing great until this last grading period when the seizures came back big time."*

*—Brianna's mother*

# Brianna T.

## Patient Profile

- 7-year-old 2nd grader who has achieved age-appropriate milestones
- Normal to above normal intelligence, but quickly bored in class and needs extra tasks and projects
- Height/weight: 65th/85th percentiles
- Epilepsy diagnosed at age 3 years (meningitis at age 6 months; febrile seizures until 20 months of age)

## Epilepsy Treatment History

- Phenobarbital controlled seizures, but carbamazepine substituted due to severe irritability and behavior problems (biting, scratching)
- Carbamazepine maintained (blood level, 8 mcg/mL) with only occasional seizures (a day or two with a small flurry of 2 to 3 complex partial seizures every 2 to 3 months) from age 3½ to 5 years; higher blood levels caused too much sedation and slowing
- No seizures for 26 months on carbamazepine (doses adjusted to maintain blood level)

## Concomitant Drug Therapy

- None reported

## Presenting Complaint

After no seizures for more than 2 years, Brianna's seizures reemerged 6 months ago, initially mirroring the earlier pattern. Since then, the pattern has changed; seizures have become longer in duration (up to 2 minutes), with longer recovery, and more frequent. Several episodes in the past 6 weeks suggest the presence of auras ("stinks like tar"). Three weeks ago, Brianna had her first episode in which a seizure generalized to a convulsion.

Since the reemergence of seizures, attempts to increase carbamazepine blood levels have not controlled seizures.

## Clinical Dilemma

- Treatment failure with carbamazepine due to poor seizure control

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This study simulates an actual clinical case.
Individual shown is not a real epilepsy patient.

# TOPAMAX...

## The Next Step for Effective Seizure Control

### Reliable seizure control

- Broad-spectrum efficacy
  - —Partial-onset seizures
  - —Primary generalized tonic-clonic seizures
  - —Seizures of Lennox-Gastaut syndrome
- Clinically significant therapeutic effect[1]
  - —≥50% seizure reduction in 39% of children (2 to 16 years of age) with partial-onset seizures receiving a median average dosage of 6 mg/kg/day of TOPAMAX therapy[1]
- Multiple mechanisms of action may contribute to antiseizure efficacy

### Established safety record

- 3 million patients treated[2]
- Favorable pharmacokinetics
  - —Linear dose-plasma concentration relationship
  - —No autoinduction
- Minimal drug interactions
  - —Low protein binding
  - —Low potential for P450 enzyme induction[3]
- No black box warnings
- Not associated with drug-induced weight gain

Indicated as adjunctive therapy for patients ≥2 years of age with primary generalized tonic-clonic seizures, partial-onset seizures, or seizures associated with Lennox-Gastaut syndrome.

In combination with other traditional antiepileptic drugs (AEDs), the most common side effects of TOPAMAX in adults (200 to 400 mg/day) were somnolence, dizziness, ataxia, speech disorders and related problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, and diplopia; and in children (5 to 9 mg/kg/day), somnolence, anorexia, fatigue, nervousness, difficulty with concentration/attention, weight decrease, aggressive reaction, and memory difficulty.

Serious as well as minor side effects have been reported with the use of TOPAMAX. Please see full Prescribing Information.

**References: 1.** Elterman RD, Glauser TA, Wyllie E, Reife R, Wu S-C, Pledger G, and the Topiramate YP Study Group. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. *Neurology.* 1999;52:1338-1344. **2.** Data on file, Ortho-McNeil Pharmaceutical, Inc. **3.** Nallani SC, Glauser TA, Hariparsad N, et al. Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate. *Epilepsia*. 2003;44:1521-1528.

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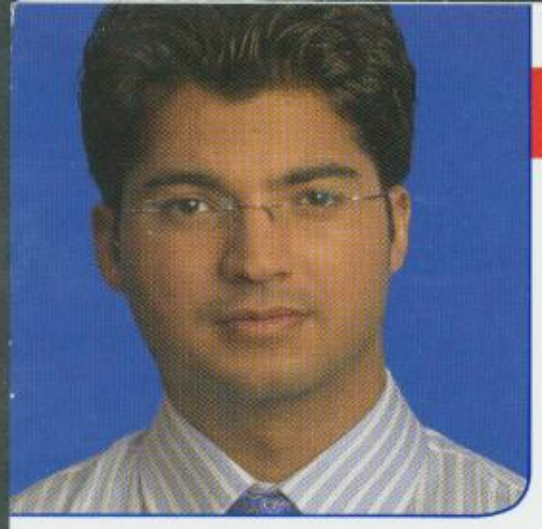

**TOPAMAX Case Study: Third in a Series**

*"I've accepted that I'm going to need pills for the rest of my life if I don't want seizures. And I don't want...can't afford...any more seizures. Especially not when we're on the verge of making a major breakthrough with my robotic leg design."*

# Narish S.

## Patient Profile

- 28-year-old biomedical engineer
- Identified as having borderline elevated LDL
- Epilepsy diagnosed 24 months ago after generalized tonic-clonic seizure without any clear provocative factor (sleep deprivation or alcohol); EEG showed asynchronous epileptiform pattern
- Twin brother recently diagnosed with epilepsy
- Smoker: 1 to 1½ packs per day

## Epilepsy Treatment History

- Phenytoin started by the emergency department physician was continued when likelihood of seizure recurrence was discussed with Narish
- Carbamazepine added 9 months later, after 3 generalized tonic-clonic seizures occurred within an 8-week period (2 seizures possibly related to sleep deprivation)
- Maintained on 400 mg/day phenytoin and 1000 mg/day carbamazepine for the past 9 months
- Attempt at withdrawing phenytoin associated with a breakthrough seizure

## Concomitant Drug Therapy

- None reported although primary care physician may start lipid-lowering drug therapy at next visit if LDL is still elevated

## Presenting Complaint

Until 6 weeks ago, Narish had been seizure-free for 11 months. Narish has had 2 generalized tonic-clonic seizures, which he denies were triggered by lack of sleep or alcohol. Although he understands that sleep deprivation can trigger his seizures, it is occasionally unavoidable because of his job. One seizure occurred at work. His design team was previously unaware of his epilepsy.

He cannot tolerate a higher phenytoin dose (severe ataxia) or a higher carbamazepine dose (dizziness).

## Clinical Dilemma

- Treatment failure with phenytoin-carbamazepine combination due to poor seizure control

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# TOPAMAX...

## The Next Step for Effective Seizure Control

### Reliable seizure control

- Broad-spectrum efficacy
  - —Partial-onset seizures
  - —Primary generalized tonic-clonic seizures
  - —Seizures of Lennox-Gastaut syndrome
- Clinically significant therapeutic effect at doses as low as 200 mg/day[1,2]
  - —≥50% seizure reduction in 45% of adults with partial-onset seizures receiving TOPAMAX 200 mg/day as add-on therapy[1]
  - —≥50% seizure reduction in 56% of adults and children with primary generalized tonic-clonic seizures receiving TOPAMAX as add-on therapy[2]
- Early onset of therapeutic effect[1]
  - —Significant seizure reduction within 2 weeks at 100 mg/day[1]
- Multiple mechanisms of action may contribute to antiseizure efficacy

### Established safety record

- 3 million patients treated[3]
- Favorable pharmacokinetics
  - —Linear dose-plasma concentration relationship
  - —No autoinduction
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