

DRUGDEX-EV 1742

MICROMEDEX

DRUGDEX® Evaluations
Database updated May 2014**TOPIRAMATE**

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0.0] Overview**1] Class**

a) This drug is a member of the following class(es):

Anticonvulsant
Central Nervous System Agent

2] Dosing Information**a) Adult**

1) prior to dosing, a baseline serum bicarbonate level is recommended and in patients at high risk for [renal impairment](#) (older age, or comorbid [diabetes mellitus](#), [hypertension](#), or [autoimmune disease](#)) obtain an estimated GFR [1]

2) (Trokendi XR(TM), [Topamax\(R\)](#)) avoid abrupt withdrawal unless medically necessary [1] [17]

3) ([Topamax\(R\)](#)) [topiramate](#) sprinkle formulation is bioequivalent to [topiramate](#) tablets [17]

a) [Lennox-Gastaut syndrome](#); Adjunct

1) (Topamax(R)) begin at 25 to 50 mg/day ORALLY; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 200 to 400 mg/day in 2 divided doses [17]

2) (Trokendi XR(TM)) initial, 25 to 50 mg ORALLY once daily; may increase by 25 to 50 mg/day at 1-week intervals to usual maintenance dose of 200 to 400 mg/day [1]

b) Migraine; Prophylaxis

1j) (Topamax(R)) 100 mg/day ORALLY administered in 2 divided doses; recommended titration rate is 25 mg in the evening for 1 week, 25 mg twice daily for 1 week, 25 mg in the morning and 50 mg in the evening for 1 week, and then 50 mg twice daily [17]

cj) Partial seizure, Initial monotherapy

1j) (Topamax(R)) first week, 25 mg ORALLY twice daily (morning and evening); second week, 50 mg ORALLY twice daily; third week, 75 mg ORALLY twice daily; fourth week, 100 mg ORALLY twice daily; fifth week, 150 mg ORALLY twice daily; sixth week (MAX dose), 200 mg ORALLY twice daily [17]

2j) (Trokendi XR(TM)) first week, 50 mg ORALLY once daily; second week, 100 mg ORALLY once daily; third week, 150 mg ORALLY once daily; fourth week, 200 mg ORALLY once daily; fifth week, 300 mg ORALLY once daily; sixth week, 400 mg ORALLY once daily [1]

dj) Partial seizure; Adjunct

1j) (Topamax(R)) begin at 25 to 50 mg/day ORALLY; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 200 to 400 mg/day in 2 divided doses [17]

2j) (Trokendi XR(TM)) initial, 25 to 50 mg ORALLY once daily; may increase by 25 to 50 mg/day at 1-week intervals to usual maintenance dose of 200 to 400 mg/day [1]

ej) Tonic-clonic seizure, Primary generalized; Adjunct

1j) (Topamax(R)) begin at 25 to 50 mg/day ORALLY; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 400 mg/day in 2 divided doses [17]

2j) (Trokendi XR(TM)) initial, 25 to 50 mg ORALLY once daily; may increase by 25 to 50 mg/day at 1-week intervals to 400 mg/day [1]

fi) Tonic-clonic seizure, Primary generalized (initial monotherapy)

1j) (Topamax(R)) first week, 25 mg ORALLY twice daily (morning and evening); second week, 50 mg ORALLY twice daily; third week, 75 mg ORALLY twice daily; fourth week, 100 mg ORALLY twice daily; fifth week, 150 mg ORALLY twice daily; sixth week (MAX dose), 200 mg ORALLY twice daily [17]

2j) (Trokendi XR(TM)) first week, 50 mg ORALLY once daily; second week, 100 mg ORALLY once daily; third week, 150 mg ORALLY once daily; fourth week, 200 mg ORALLY once daily; fifth week, 300 mg ORALLY once daily; sixth week, 400 mg ORALLY once daily [1]

bj) Pediatric

1)) prior to dosing, a baseline serum bicarbonate level is recommended, and in patients at high risk for renal impairment (comorbid diabetes mellitus, hypertension, or autoimmune disease), obtain an estimated GFR [1]

2)) (Topamax(R)) safety and efficacy have not been established in children younger than 2 years [17], topiramate extended-release capsule (Trokendi XR(TM)) is not recommended for use in children younger than 6 years [1]

3)) (Trokendi XR(TM), Topamax(R)) avoid abrupt withdrawal unless medically necessary [1] [17]

4)) (Topamax(R)) topiramate sprinkle formulation is bioequivalent to topiramate tablets [17]

a)) Lennox-Gastaut syndrome; Adjunct

1)) (Topamax(R)) (2 to 16 years old) begin at 25 mg or less (range of 1 to 3 mg/kg/day) ORALLY at bedtime for the first week, then increase dosage by 1 to 3 mg/kg/day (in 2 divided doses) at 1- to 2-week intervals to the usual effective dosage of 5 to 9 mg/kg/day [17]

2)) (Topamax(R)) (17 years or older) begin at 25 to 50 mg/day ORALLY; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 200 to 400 mg/day in 2 divided doses [17]

3)) (Trokendi XR(TM)) (6 to 16 years) initial, 25 mg ORALLY (1 to 3 mg/kg/day) once daily at nighttime for 1 week; increase by 1 to 3 mg/kg/day at 1- to 2-week intervals to achieve optimal response; maintenance, 5 to 9 mg/kg/day [1]

4)) (Trokendi XR(TM)) (17 years or older) initial, 25 to 50 mg ORALLY once daily; may increase by 25 to 50 mg/day at 1-week intervals to usual maintenance dose of 200 to 400 mg/day [1]

b)) Partial seizure, Initial monotherapy

1)) (Topamax(R)) (2 to younger than 10 years) first week, 25 mg ORALLY once daily in the evening; second week, 25 mg ORALLY twice daily (morning and evening); may increase dosage by 25 to 50 mg/day at 1-week intervals to a MAX dose based on patient weight (kg) over a total titration period of 5 to 7 weeks [17]

2)) (Topamax(R)) (10 years or older) first week, 25 mg ORALLY twice daily (morning and evening); second week, 50 mg ORALLY twice daily; third week, 75 mg ORALLY twice daily; fourth week, 100 mg ORALLY twice daily; fifth week, 150 mg ORALLY twice daily; sixth week (MAX dose), 200 mg ORALLY twice daily [17]

3)) (Trokendi XR(TM)) (10 years or older) first week, 50 mg ORALLY once daily; second week, 100 mg ORALLY once daily; third week, 150 mg ORALLY once daily; fourth week, 200 mg ORALLY once daily; fifth week, 300 mg ORALLY once daily; sixth week, 400 mg ORALLY once daily [1]

c)) Partial seizure; Adjunct

1j) (Topamax(R)) (2 to 16 years old) begin at 25 mg or less (range of 1 to 3 mg/kg/day) ORALLY at bedtime for the first week, then increase dosage by 1 to 3 mg/kg/day (in 2 divided doses) at 1 to 2 week intervals to the usual effective dosage of 5 to 9 mg/kg/day [17]

2j) (Topamax(R)) (17 years or older) begin at 25 to 50 mg/day ORALLY; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 200 to 400 mg/day in 2 divided doses [17]

3j) (Trokendi XR(TM)) (6 to 16 years) initial, 25 mg ORALLY (1 to 3 mg/kg/day) once daily at nighttime for 1 week; increase by 1 to 3 mg/kg/day at 1- to 2-week intervals to achieve optimal response; maintenance, 5 to 9 mg/kg/day [1]

4j) (Trokendi XR(TM)) (17 years or older) initial, 25 to 50 mg ORALLY once daily; may increase by 25 to 50 mg/day at 1-week intervals to usual maintenance dose of 200 to 400 mg/day [1]

dj) Tonic-clonic seizure, Primary generalized; Adjunct

1j) (Topamax(R)) (2 to 16 years old) begin at 25 mg or less (range of 1 to 3 mg/kg/day) ORALLY at bedtime for the first week, then increase dosage by 1 to 3 mg/kg/day (in 2 divided doses) at 1 to 2 week intervals to the usual effective dosage of 5 to 9 mg/kg/day [17]

2j) (Topamax(R)) (17 years or older) begin at 25 to 50 mg/day ORALLY; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 400 mg/day in 2 divided doses [17]

3j) (Trokendi XR(TM)) (6 to 16 years old) initial, 25 mg ORALLY (1 to 3 mg/kg/day) once daily at nighttime for 1 week; increase by 1 to 3 mg/kg/day at 1- to 2-week intervals to achieve optimal response; maintenance, 5 to 9 mg/kg/day [1]

4j) (Trokendi XR(TM)) (17 years or older) initial, 25 to 50 mg ORALLY once daily; may increase by 25 to 50 mg/day at 1-week intervals to 400 mg/day [1]

ej) Tonic-clonic seizure, Primary generalized (initial monotherapy)

1j) (Topamax(R)) (2 to less than 10 years) first week, 25 mg ORALLY once daily in the evening; second week, 25 mg ORALLY twice daily (morning and evening); may increase dosage by 25 to 50 mg/day at 1-week intervals to a MAX dose based on patient weight (kg) over a total titration period of 5 to 7 weeks [17]

2j) (Topamax(R)) (10 years or older) first week, 25 mg ORALLY twice daily (morning and evening); second week, 50 mg ORALLY twice daily; third week, 75 mg ORALLY twice daily; fourth week, 100 mg ORALLY twice daily; fifth week, 150 mg ORALLY twice daily; sixth week (MAX dose), 200 mg ORALLY twice daily [17]

3j) (Trokendi XR(TM)) (10 years or older) first week, 50 mg ORALLY once daily; second week, 100 mg ORALLY once daily; third week, 150 mg ORALLY once daily;

fourth week, 200 mg ORALLY once daily; fifth week, 300 mg ORALLY once daily;
sixth week, 400 mg ORALLY once daily [1]

3) Contraindications

- a) alcohol use, recent (within 6 hours prior to or 6 hours after [topiramate](#) use) [1]
- b) [metabolic acidosis](#) with concomitant [metformin](#) use [1]

4) Serious Adverse Effects

- a) [Drug-induced encephalopathy](#)
- b) [Erythema multiforme](#)
- c) [Glaucoma](#)
- d) [Hyperammonemia](#), With or without [encephalopathy](#)
- e) [Hypohidrosis](#)
- f) Increased body temperature
- g) [Liver failure](#)
- h) [Metabolic acidosis](#)
- i) [Myopia](#)
- j) [Nephrolithiasis](#)
- k) [Stevens-Johnson syndrome](#)
- l) Suicidal thoughts
- m) [Toxic epidermal necrolysis](#)

5) Clinical Applications

- a) FDA Approved Indications
 - 1) [Lennox-Gastaut syndrome](#); Adjunct
 - 2) Migraine; Prophylaxis
 - 3) Partial seizure, Initial monotherapy
 - 4) Partial seizure; Adjunct
 - 5) Tonic-clonic seizure, Primary generalized; Adjunct
 - 6) Tonic-clonic seizure, Primary generalized (initial monotherapy)

1.0] Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

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1.1] Drug Properties

A)] Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B)] Synonyms

[Topiramate](#)

C)] Physicochemical Properties

1)] Molecular Weight

a)] 339.36 [18]

2)] Solubility

a)] Most soluble in alkaline solutions containing sodium hydroxide or [sodium phosphate](#) (pH 9 to 10). Freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. Soluble in water (9.8 mg/mL) [18].

1.2] Storage and Stability

A)] Preparation

1)] Oral route

a)] [Topamax\(R\)](#)

1)] The topiramate immediate-release sprinkle capsules may be swallowed whole, or opened and sprinkled on a small amount of soft food (about 1 teaspoon). The food and drug mixture should be immediately swallowed whole and not chewed. Do not store opened capsules for future use [17].

2)] Topiramate tablets should not be broken because of the bitter taste [17].

b)] [Trokendi XR\(TM\)](#)

1)] The topiramate extended-release oral capsule may be taken without regard to meals and should be swallowed whole and intact. Do not chew, crush, or sprinkle capsule content onto food [1].

2)] Alcohol use should be completely avoided within 6 hours prior to and 6 hours after topiramate extended-release capsule administration [1].

B)] Oral route

1)] Capsule/Capsule, Extended Release/Tablet

- a) Store extended-release capsules in a well closed container at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture and light [1].
- b) Store sprinkle capsules in a tightly closed container at a controlled room temperature at or below 25 degrees C (77 degrees F); protect from moisture [20].
- c) Store tablets in a tightly closed container at a controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture [20].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Important Note

- j) Prior to dosing, a baseline serum bicarbonate level is recommended and in patients at high risk for renal impairment (older age, or comorbid diabetes mellitus, hypertension, or autoimmune disease) obtain an estimated GFR [1].

1.3.1.B] Oral route

1.3.1.B.1] **Diabetes mellitus type 2 in obese; Adjunct**

- a) **Topiramate** 96 and 192 mg/day, as add-on treatment to diet and lifestyle programs produced greater weight loss than placebo in obese patients with **type 2 diabetes** [4] [3].

1.3.1.B.2] **Lennox-Gastaut syndrome; Adjunct**

- a) **Topamax(R)**

- 1) For adults 17 years or older, the recommended total daily dosage of **topiramate** as adjunctive therapy for seizures associated with **Lennox-Gastaut syndrome** is 200 to 400 mg/day in 2 divided doses. **Topiramate** should be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/week. Doses greater than 1600 mg/day have not been studied [17].

- 2) Monitoring **topiramate** plasma concentrations is not necessary to optimize therapy [20].

- 3) **Topiramate** should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

- b) **Trokendi XR(TM)**

- 1) The recommended adult dose of **topiramate** extended-release oral capsule (Trokendi XR(TM)) for adjunctive treatment of seizures associated with **Lennox-Gastaut syndrome** is 200 to 400 mg orally once daily. Begin therapy at 25 to 50 mg once daily and titrate with weekly increases, to an effective dose, in increments of 25 to 50 mg/week. Doses greater than 1600 mg/day have not been studied [1].

- 2) It is not necessary to monitor **topiramate** plasma concentrations to optimize therapy [1].

3) **Topiramate** should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

a) Coadministration with Other Antiepileptic Drugs

1) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcomes [1].

2) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin and/or carbamazepine may require dose adjustment of topiramate with either addition or withdrawal of phenytoin [1].

1.3.1.B.3] Migraine; Prophylaxis

a) Topamax(R)

1) The recommended total daily dose of **topiramate** immediate-release oral tablet or oral capsule is 100 mg/day given in 2 divided doses. The recommended titration schedule is [17]:

Week	Morning Dose	Evening Dose
1	None	25 mg
2	25 mg	25 mg
3	25 mg	50 mg
4	50 mg	50 mg

2) Dose and titration rate should be guided by clinical outcome [17].

3) It is not necessary to monitor **topiramate** plasma concentrations to optimize therapy [20].

4) **Topiramate** should be gradually withdrawn in patients with or without a history of **epilepsy** or seizures to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

b) Duration of Therapy (Topamax(R))

1) One year of **topiramate** therapy for **migraine prophylaxis** resulted in a significant reduction in monthly migraine days compared with discontinuation of **topiramate** after 6 months; nonetheless, discontinuation of **topiramate** after 6 months was beneficial in reduction of monthly migraine days compared with pretreatment values. Patients should be treated for 6 months with an option to continue treatment to 12 months based on patient efficacy and tolerability [38].

1.3.1.B.4] Obesity

a) **Topiramate** 64, 96, 192, and 384 mg/day produced greater (p less than 0.05 at week 4) weight loss than placebo in obese patients. Patients tolerated 64 and 96 mg/day better than the higher doses and the lower doses were moderately effective in producing weight loss [6].

1.3.1.B.5] Partial seizure, Initial monotherapy**a) Topamax(R)**

1) The recommended dose of [topiramate](#) immediate-release tablet or capsule ([Topamax\(R\)](#)) as monotherapy in the treatment of partial onset seizures is 400 mg/day in 2 divided doses. The dose should be achieved by titrating according to the following schedule [17]:

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

2) In the monotherapy controlled trial, approximately 58% of patients randomized to 400 mg/day achieved this maximal dose; the mean dose achieved was 275 mg/day [17].

3) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].

4) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

b) Trokendi XR(TM)

1) The recommended adult dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) for monotherapy of partial onset seizures is 400 mg orally once daily. Begin therapy at 50 mg once daily and titrate over 6 weeks with weekly increases in 50-mg increments for the first 4 weeks, and then in 100-mg increments for weeks 5 and 6 [1].

2) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

3) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

1.3.1.B.6] Partial seizure; Adjunct**a) Topamax(R)**

1) For adults 17 years or older, the recommended total daily dose of [topiramate](#) as adjunctive therapy for the treatment of partial seizures is 200 to 400 mg/day in 2 divided doses. It is recommended that therapy be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/week. Doses above 1600 mg/day have not been used [17].

2) Doses above 400 mg/day (600 , 800 mg or 1000 mg/day) have not been shown to improve responses in dose-response studies in adults with partial onset seizures [17].

3) Other studies in patients with refractory partial seizures have used [topiramate](#) as add-on therapy with 200 to 800 mg daily in 2 divided doses [45] [50] [46] [44] [27]. The drug has also been given in a 3 times daily schedule [26].

4) Low doses (eg, 50 to 100 mg daily) have been suggested initially to minimize adverse effects, mainly cognitive dysfunction [25] [26]. In one small study, cognitive impairment was not related to the rate of dose increase or absolute dose of [topiramate](#) [27]. However, further studies demonstrating lack of a dose-effect for this complication are needed. As other adverse effects, such as dizziness, somnolence, and paresthesias, have also occurred frequently with rapid dose titration, slow dose increments are advised.

5) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].

6) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

b) Trokendi XR(TM)

1) The recommended adult dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) for adjunctive treatment of partial onset seizures is 200 to 400 mg orally once daily. Begin therapy at 25 to 50 mg once daily and titrate with weekly increases, to an effective dose, in increments of 25 to 50 mg/week. Doses greater than 1600 mg/day have not been studied [1].

2) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

3) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

a) Coadministration with Other Antiepileptic Drugs

1) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcomes [1].

2) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin and/or carbamazepine may require dose adjustment of topiramate with either addition or withdrawal of phenytoin and/or carbamazepine [1].

1.3.1.B.7] Tonic-clonic seizure, Primary generalized; Adjunct

a) [Topamax\(R\)](#)

1) For adults 17 years or older, the recommended total daily dose of [topiramate](#) immediate-release oral capsule or tablet ([Topamax\(R\)](#)) as adjunctive therapy for primary generalized tonic-clonic seizures is 400 mg/day in 2 divided doses. [Topiramate](#) should be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/week. Doses greater than 1600 mg/day have not been studied [17].

2) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].

3) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

4) Low doses (eg, 50 to 100 mg daily) have been suggested initially to minimize adverse effects, mainly cognitive dysfunction [25] [26]. In one small study, cognitive impairment was not related to the rate of dose increase or absolute dose of [topiramate](#) [27]. However, further studies demonstrating lack of a dose-effect for this complication are needed. As other adverse effects, such as dizziness, somnolence, and paresthesias have also occurred frequently with rapid dose titration, slow dose increments are advised.

b) Trokendi XR(TM)

1) The recommended adult dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) as adjunctive therapy for primary generalized tonic-clonic seizures is 400 mg orally once daily. Begin therapy at 25 to 50 mg once daily and titrate with weekly increases, to an effective dose, in increments of 25 to 50 mg/week. In a clinical study, the assigned dose was achieved by the end of week 8. Doses greater than 1600 mg/day have not been studied [1].

2) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

3) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

a) Coadministration with Other Antiepileptic Drugs

1) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcomes [1].

2) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin and/or carbamazepine may require dose adjustment of topiramate with either addition or withdrawal of phenytoin and/or carbamazepine [1].

1.3.1.B.8] Tonic-clonic seizure, Primary generalized (initial monotherapy)

a) [Topamax\(R\)](#)

1) The recommended adult dose of [topiramate](#) immediate-release oral tablet or capsule for monotherapy of primary generalized tonic-clonic seizures is 400 mg per day in 2 divided doses. The dose should be titrated according to the following schedule [17]:

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

2) In the monotherapy controlled trial, approximately 58% of patients randomized to 400 mg/day achieved this maximal dose; the mean dose achieved was 275 mg/day [17].

3J) Monitoring [topiramate](#) plasma concentrations is not necessary to optimize therapy [17].

4J) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

bJ) Trokendi XR(TM)

1J) The recommended adult dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) for monotherapy of primary generalized tonic-clonic seizures is 400 mg orally once daily. Begin therapy at 50 mg once daily and titrate over 6 weeks with weekly increases in 50-mg increments for the first 4 weeks, and then in 100-mg increments for weeks 5 and 6 [1].

2J) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

3J) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

1.3.1.B.9J) The [topiramate](#) sprinkle formulation is bioequivalent to the immediate-release tablet formulation. They may be substituted as therapeutic equivalents [17].

1.3.2] Dosage in Renal Failure

AJ) In renally impaired subjects (CrCl less than 70 mL/min/1.73 m(2)), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose [1] [17].

1.3.3] Dosage in Hepatic Insufficiency

AJ) The clearance of [topiramate](#) may be decreased in patients with [hepatic impairment](#), but no specific dosing guidelines are given [1] [17].

1.3.4] Dosage in Geriatric Patients

AJ) Dosage adjustment may be indicated in the elderly patient to the extent renal function is reduced. When [impaired renal function](#) (CrCl less than 70 mL/min/1.73 m(2)) is evident, one-half the usual dose is recommended [1] [17].

1.3.5] Dosage Adjustment During Dialysis

AJ) [Topiramate](#) is cleared by [hemodialysis](#) at a rate that is 4 to 6 times greater than in normal individuals. During prolonged dialysis periods the concentration may fall to below levels required for maintaining the antiseizure effect. To avoid these drops, a supplemental dose of [topiramate](#) may be required. The actual adjustment should take into account 1) the duration of the dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of [topiramate](#) in the patient [1] [17].

BJ) When a high efficiency, counterflow, single pass-dialysate [hemodialysis procedure](#) was used, [topiramate](#) dialysis clearance was 120 mL/min with blood flow through the [dialyzer](#) at 400 mL/min. This high [topiramate](#) clearance (compared with 20 to 30 mL/min total oral clearance in healthy individuals) will remove a clinically significant amount of [topiramate](#) over the [hemodialysis](#) treatment period. A supplemental dose of [topiramate](#) may be required [1] [17].

1.3.6] Dosage in Other Disease States

A) If [metabolic acidosis](#) develops and persists during [topiramate](#) use, consider dose reduction, discontinuation of use, or addition of alkali treatment [1] [20].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

J) Prior to dosing, a baseline serum bicarbonate level is recommended and in patients at high risk for renal impairment (older age, or comorbid diabetes mellitus, hypertension, or autoimmune disease) obtain an estimated GFR [1].

1.4.1.B] Oral route

1.4.1.B.1] [Lennox-Gastaut syndrome](#); Adjunct

a) [Topamax](#)(R)

1J) For patients 2 to 16 years of age, the recommended total daily dosage of [topiramate](#) as adjunctive therapy for seizures associated with [Lennox Gastaut syndrome](#) is approximately 5 to 9 mg/kg/day. [Topiramate](#) should be initiated at 25 mg or less (1 to 3 mg/kg/day) nightly for 1 week. The dosage should then be increased by increments of 1 to 3 mg/kg/day administered in 2 divided doses at 1- to 2-week intervals. Dose titration should be directed by clinical outcome. [17].

2J) When [topiramate](#) was titrated to clinical effectiveness, the dose range for children exceeded the manufacturer's recommendations of 5 to 9 mg/kg/day. When used as monotherapy in children 5 years or younger, the effective [topiramate](#) dose range was 11 to 35 mg/kg/day (mean 22.5 mg/kg/day). In children 6 to 12 years of age, the effective monotherapy dose range was 5.5 to 16.5 mg/kg/day (mean 9.7 mg/kg/day). Mean serum [topiramate](#) level in the younger children was 14.8 mcg/mL and in the older children 9.8 mcg/mL. For young children receiving [topiramate](#) as a part of polytherapy without an enzyme-inducing antiepileptic drug, the effective dose range was 2 to 13.2 mg/kg/day (mean 8.9 mg/kg/day), and in those receiving an enzyme-inducing antiepileptic drug, 1.9 to 11 mg/kg/day (mean 14.2 mg/kg/day). For older children receiving [topiramate](#) without an enzyme-inducing antiepileptic drug, the effective dose range was 2 to 18 mg/kg/day (mean 9.8 mg/kg/day), and with an enzyme-inducing drug, 1.1 to 11.7 mg/kg/day (mean 7 mg/kg/day) [28].

3J) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].

4J) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

b) [Trokendi XR](#)(TM)

1J) The recommended pediatric dose of [topiramate](#) extended-release oral capsule ([Trokendi XR](#)(TM)) as adjunctive therapy for seizures associated with [Lennox-Gastaut syndrome](#) in children 6 to 16 years of age is 5 to 9 mg/kg orally once daily. The initial recommended dose is 25 mg once daily at nighttime, based on a range of 1 to 3 mg/kg/day, for the first week. Subsequently titrate by increments of 1 to 3 mg/kg/day at 1- to 2-week intervals, to achieve optimal clinical response. In a clinical study, the assigned dose of 6 mg/kg/day was achieved by the end of week 8. If required, longer intervals between dose titration can be used [1].

2)) The recommended dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) for adjunctive treatment of seizures associated with [Lennox-Gastaut syndrome](#) in adolescents 17 years or older is 200 to 400 mg orally once daily. Begin therapy at 25 to 50 mg once daily and titrate with weekly increases, to an effective dose, in increments of 25 to 50 mg/week. Doses greater than 1600 mg/day have not been studied [1].

3)) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

4)) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

a)) Coadministration with Other Antiepileptic Drugs

1)) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcomes [1].

2)) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin and/or carbamazepine may require dose adjustment of topiramate with either addition or withdrawal of phenytoin [1].

1.4.1.B.2) Migraine; Prophylaxis

a)) [Topiramate](#) 25 mg/day to 100 mg/day has shown benefit in [migraine prophylaxis](#) in children and adolescents. Dose and titration rate should be guided by clinical outcome [34] [35] [36] [37].

b)) In adolescents, [topiramate](#) 200 mg/day did not appear to offer greater efficacy than 100 mg/day and adverse events were most frequent in the 200 mg/day group [36].

1.4.1.B.3) Partial seizure, Initial monotherapy

a)) [Topamax\(R\)](#)

1)) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].

2)) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

a)) 2 to Younger Than 10 Years

1)) The recommended dose range of topiramate immediate-release tablet or capsule as monotherapy in the treatment of partial onset seizures in children 2 to younger than 10 years is 150 to 400 mg daily, based on weight, given in 2 equally divided doses. Therapy should be initiated at 25 mg once daily in the evening for the first week, increased to 25 mg twice daily for the second week, with subsequent dose titration of 25 to 50 mg/day per week dependent on patient tolerance, to a maximum dose based on patient weight (kg) over a total titration period of 5 to 7 weeks. Target maintenance dose ranges based on weight are listed in the following table [17]:

Weight (kg)	Total Daily Dose (mg/day) Minimum Maintenance Dose	Total Daily Dose (mg/day) Maximum Maintenance Dose
Up to 11	150 mg	250 mg
12 to 22	200 mg	300 mg
23 to 31	200 mg	350 mg
32 to 38	250 mg	350 mg
Greater than 38	250 mg	400 mg

b) 10 Years or Older

1) The recommended dose of topiramate immediate-release tablet or capsule as monotherapy in the treatment of partial onset seizures in children 10 years or older is 400 mg/day in 2 divided doses. The dose should be achieved by titrating according to the following schedule [17]:

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

2) In the monotherapy controlled trial, approximately 58% of patients randomized to 400 mg/day achieved this maximal dose; the mean dose achieved was 275 mg/day [17].

b) Trokendi XR(TM)

1) The recommended pediatric dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) for monotherapy of partial onset seizures in children 10 years or older is 400 mg orally once daily. Begin therapy at 50 mg once daily and titrate over 6 weeks with weekly increases in 50-mg increments for the first 4 weeks, and then in 100-mg increments for weeks 5 and 6 [1].

2) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

3) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

1.4.1.B.4) Partial seizure; Adjunct

a) [Topamax\(R\)](#)

1) For the adjunct treatment of partial onset seizures in patients ages 2 to 16 years, the initial dose is [topiramate](#) 25 mg or less (1 to 3 mg/kg/day) nightly for 1 week. The dosage should then be increased by increments of 1 to 3 mg/kg/day administered in 2 divided doses at 1- to

2-week intervals. Dose titration should be directed by clinical outcome. Maintenance doses are usually between 5 to 9 mg/kg/day in 2 divided doses [17].

2j) When [topiramate](#) was titrated to clinical effectiveness, the dose range for children exceeded the manufacturer's recommendations of 5 to 9 mg/kg/day. When used as monotherapy in children 5 years or younger, the effective [topiramate](#) dose range was 11 to 35 mg/kg/day (mean 22.5 mg/kg/day). In children 6 to 12 years of age, the effective monotherapy dose range was 5.5 to 16.5 mg/kg/day (mean 9.7 mg/kg/day). Mean serum [topiramate](#) level in the younger children was 14.8 mcg/mL and in the older children 9.8 mcg/mL. For young children receiving [topiramate](#) as a part of polytherapy without an enzyme-inducing antiepileptic drug, the effective dose range was 2 to 13.2 mg/kg/day (mean 8.9 mg/kg/day), and in those receiving an enzyme-inducing antiepileptic drug, 1.9 to 11 mg/kg/day (mean 14.2 mg/kg/day). For older children receiving [topiramate](#) without an enzyme-inducing antiepileptic drug, the effective dose range was 2 to 18 mg/kg/day (mean 9.8 mg/kg/day), and with an enzyme-inducing drug, 1.1 to 11.7 mg/kg/day (mean 7 mg/kg/day) [28].

3j) In children with refractory partial onset seizures, during the double-blind segment of a study, [topiramate](#) was titrated to a dose of 6 mg/kg/day and then maintained for 8 weeks. An open-label segment then began, during which patients receiving placebo were converted to [topiramate](#) and all patients' dosages were titrated to a maximum of 30 mg/kg/day. The mean dose was 9 mg/kg/day. The author's general dosing recommendations were to begin with an initial dose of 0.5 to 1 mg/kg/day titrated with weekly increments of 0.5 to 1 mg/kg; 6 mg/kg/day appears to be the minimal effective dose [31].

4j) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].

5j) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

bj) Trokendi XR(TM)

1j) The recommended pediatric dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) as adjunctive treatment of partial onset seizures in children 6 to 16 years of age is 5 to 9 mg/kg orally once daily. The initial recommended dose is 25 mg once daily at nighttime, based on a range of 1 to 3 mg/kg/day, for the first week. Subsequently titrate by increments of 1 to 3 mg/kg/day at 1- to 2-week intervals, to achieve optimal clinical response. In a clinical study, the assigned dose of 6 mg/kg/day was achieved by the end of week 8. If required, longer intervals between dose titration can be used [1].

2j) The recommended initial dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) as adjunctive treatment of partial onset seizures in adolescents 17 years or older is 25 to 50 mg orally once daily. May increase dose by 25 to 50 mg/day at 1-week intervals to usual maintenance dose of 200 to 400 mg/day. Doses greater than 1600 mg/day have not been studied [1].

3j) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

4j) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

aj) Coadministration with Other Antiepileptic Drugs

1J) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcomes [1].

2J) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin and/or carbamazepine may require dose adjustment of topiramate with either addition or withdrawal of phenytoin and/or carbamazepine [1].

1.4.1.B.5J Tonic-clonic seizure, Primary generalized; Adjunct

aJ) Topamax(R)

1J) For the adjunct treatment of generalized tonic-clonic seizures in patients ages 2 to 16 years, the initial dose is topiramate 25 mg or less (based on a range of 1 to 3 mg/kg/day) orally each night for 1 week. The dosage should then be increased by increments of 1 to 3 mg/kg/day administered in 2 divided doses at 1 to 2-week intervals. Dose titration should be directed by clinical outcome. Maintenance doses are usually between 5 to 9 mg/kg/day in 2 divided doses. Doses above 1600 mg/day have not been studied [17].

2J) When topiramate was titrated to clinical effectiveness, the dose range for children exceeded the manufacturer's recommendations of 5 to 9 mg/kg/day. When used as monotherapy in children 5 years or younger, the effective topiramate dose range was 11 to 35 mg/kg/day (mean 22.5 mg/kg/day). In children 6 to 12 years of age, the effective monotherapy dose range was 5.5 to 16.5 mg/kg/day (mean 9.7 mg/kg/day). Mean serum topiramate level in the younger children was 14.8 mcg/mL and in the older children 9.8 mcg/mL. For young children receiving topiramate as a part of polytherapy without an enzyme-inducing antiepileptic drug, the effective dose range was 2 to 13.2 mg/kg/day (mean 8.9 mg/kg/day), and in those receiving an enzyme-inducing antiepileptic drug, 1.9 to 11 mg/kg/day (mean 14.2 mg/kg/day). For older children receiving topiramate without an enzyme-inducing antiepileptic drug, the effective dose range was 2 to 18 mg/kg/day (mean 9.8 mg/kg/day), and with an enzyme-inducing drug, 1.1 to 11.7 mg/kg/day (mean 7 mg/kg/day) [28].

3J) It is not necessary to monitor topiramate plasma concentrations to optimize therapy [20].

4J) Topiramate should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

bJ) Trokendi XR(TM)

1J) The recommended pediatric dose of topiramate extended-release oral capsule (Trokendi XR(TM)) as adjunctive therapy for primary generalized tonic-clonic seizures in children 6 to 16 years of age is 5 to 9 mg/kg orally once daily. Begin therapy at 25 mg once daily at nighttime, based on a range of 1 to 3 mg/kg/day, for the first week. Subsequently titrate by increments of 1 to 3 mg/kg/day at 1- to 2-week intervals, to achieve optimal clinical response. In a clinical study, the assigned dose of 6 mg/kg/day was achieved by the end of week 8. If required, longer intervals between dose titration can be used. [1].

2J) The recommended initial dose of topiramate extended-release oral capsule (Trokendi XR(TM)) as adjunctive therapy for primary generalized tonic-clonic seizures in adolescents

17 years or older, is 25 to 50 mg orally once daily. May increase the dose by 25 to 50 mg/day at 1-week intervals to 400 mg/day. In a clinical study, the assigned dose was achieved by the end of week 8. Doses greater than 1600 mg/day have not been studied [1].

- 3) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].
- 4) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

a) Coadministration with Other Antiepileptic Drugs

- 1) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcomes [1].
- 2) Patients receiving concurrent topiramate extended-release oral capsule (Trokendi XR(TM)) with phenytoin and/or carbamazepine may require dose adjustment of topiramate with either addition or withdrawal of phenytoin and/or carbamazepine [1].

1.4.1.B.6] Tonic-clonic seizure, Primary generalized (initial monotherapy)

a) [Topamax\(R\)](#)

- 1) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [20].
- 2) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [20].

a) 2 To Younger Than 10 Years

- 1) The recommended dose range of topiramate immediate-release tablet or capsule (Topamax(R)) as monotherapy for primary generalized tonic-clonic seizures in children 2 to younger than 10 years is 150 to 400 mg daily, based on weight, given in 2 equally divided doses. Therapy should be initiated at 25 mg once daily at bedtime for the first week, increased to 25 mg twice daily for the second week, with subsequent dose titration of 25 to 50 mg/day per week dependent on patient tolerance, to a maximum dose based on patient weight (kg) over a total titration period of 5 to 7 weeks. Target maintenance dose ranges based on weight are listed in the following table [17]:

Weight (kg)	Total Daily Dose (mg/day) Minimum Maintenance Dose	Total Daily Dose (mg/day) Maximum Maintenance Dose
Up to 11	150 mg	250 mg
12 to 22	200 mg	300 mg
23 to 31	200 mg	350 mg
32 to 38	250 mg	350 mg

Greater than 38

250 mg

400

b) 10 Years or Older

1) The recommended dose of topiramate immediate-release tablet or capsule (Topamax(R)) as monotherapy for primary generalized tonic-clonic seizures in children 10 years or older is 400 mg per day in 2 divided doses. The dose should be titrated according to the following schedule [17]:

	Morning Dose	Evening
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

2) In the monotherapy controlled trial, approximately 58% of patients randomized to 400 mg/day achieved this maximal dose; the mean dose achieved was 275 mg/day [17].

3) Monitoring topiramate plasma concentrations is not necessary to optimize therapy [17].

b) Trokendi XR(TM)

1) The recommended pediatric dose of [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) for monotherapy of primary generalized tonic-clonic seizures in children 10 years or older is 400 mg orally once daily. Begin therapy at 50 mg once daily and titrate over 6 weeks with weekly increases in 50-mg increments for the first 4 weeks, and then in 100-mg increments for weeks 5 and 6 [1].

2) It is not necessary to monitor [topiramate](#) plasma concentrations to optimize therapy [1].

3) [Topiramate](#) should be gradually withdrawn to minimize potential for seizures or increased seizure frequency upon discontinuation of treatment. Provide appropriate monitoring if rapid withdrawal of therapy is medically necessary [1].

1.4.1.B.7) The safety and efficacy of [topiramate](#) (Topamax(R)) have not been established in children younger than 2 years [17]. Because the [topiramate](#) extended-release oral capsule (Trokendi XR(TM)) must be swallowed whole, and may not be sprinkled on food, chewed, or crushed, Trokendi XR(TM) is not recommended for use in children younger than 6 years [1].

1.4.1.B.8) In patients with or without a history of seizures, [topiramate](#) should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. When rapid withdrawal is medically necessary, appropriate monitoring is recommended (Trokendi XR(TM), Topamax(R)) [1] [17]

1.4.1.B.9) The [topiramate](#) sprinkle formulation is bioequivalent to the immediate-release tablet formulation. They may be substituted as therapeutic equivalents [17].

1.4.2] Dosage in Renal Failure

A) In renally impaired subjects (CrCl less than 70 mL/min/1.73 m²), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose [1] [17].

1.4.3] Dosage in Hepatic Insufficiency

A) The clearance of [topiramate](#) may be decreased in patients with [hepatic impairment](#), but no specific dosing guidelines are given [1] [17].

1.4.4] Dosage Adjustment During Dialysis

A) [Topiramate](#) is cleared by [hemodialysis](#) at a rate that is 4 to 6 times greater than in normal individuals. During prolonged dialysis periods the concentration may fall to below levels required for maintaining the antiseizure effect. To avoid these drops, a supplemental dose of [topiramate](#) may be required. The actual adjustment should take into account 1) the duration of the dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of [topiramate](#) in the patient [1] [17].

B) When a high efficiency, counterflow, single pass-dialysate [hemodialysis procedure](#) was used, [topiramate](#) dialysis clearance was 120 mL/min with blood flow through the [dialyzer](#) at 400 mL/min. This high [topiramate](#) clearance (compared with 20 to 30 mL/min total oral clearance in healthy individuals) will remove a clinically significant amount of [topiramate](#) over the [hemodialysis](#) treatment period. A supplemental dose of [topiramate](#) may be required [1] [17].

1.4.5] Dosage in Other Disease States

A) If [metabolic acidosis](#) develops and persists during [topiramate](#) use, consider dose reduction, discontinuation of use, or addition of alkali treatment [1] [20].

2.0] Pharmacokinetics

Drug Concentration Levels ADME

2.2] Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Seizure control: 10.5 mg/L [155]

a) In the dose range studied from 200 to 800 mg/day of immediate-release [topiramate](#), there was a linear increase in plasma concentration corresponding to increasing doses. Steady-state is reached in approximately 4 days in patients with normal renal function [20].

b) In a double-blinded, randomized, concentration controlled study examining adjunctive [topiramate](#) therapy, patients assigned to a target [topiramate](#) plasma level of 10.5 mg/L obtained better seizure control than those assigned to target levels of 2 mg/L and 19 mg/L. Patients with refractory partial seizures were randomized to 1 of the 3 target plasma levels (n=65). [Topiramate](#) doses were then titrated over 8 weeks to attain these levels. Not all patients obtained their target plasma levels. Median doses were 100 mg for the 2 mg/L group, 450 mg for the 10.5 mg/L group and 677 mg for the 19 mg/L group. Patients randomized to 10.5 mg/L reduced seizure frequency by 85% compared to 39% in the 2 mg/L group (p=0.03) and 39% in the 19 mg/L group (p=0.05). Of note, lower target plasma levels were associated with higher study completion rates (85% compared with 78% and 50% in the 2, 10.5, and 19 mg/L groups, p=0.03). The occurrence of adverse events

also was dose-related. Further studies involving larger numbers of subjects are required to establish target therapeutic levels [155].

B) Peak Concentration

1) Oral

a) Oral, single-dose: 1.7 mcg/mL (100 mg); 3.7 mcg/mL (200 mg); 8 mcg/mL (400 mg) [150] [153] [149]

1) Following oral administration of topiramate 100, 200, and 400 mg to fasting healthy subjects, peak plasma levels of 1.7, 3.7, and 8 mcg/mL, respectively, have been reported. Doses of 800 and 1200 mg produced peak plasma levels of 18 and 29 mcg/mL [150] [153] [149].

2) With multiple doses, accumulation is observed (approximately twofold) [154].

2) Geriatrics

a) Oral, single-dose: 23% higher (immediate-release, 100 mg) [20] to 30% higher (extended-release) [1]

1) In a study of 13 healthy elderly patients and 18 healthy young adults receiving extended-release topiramate, C_{max} was 30% higher in the elderly patients compared with the young adults [1].

2) In a controlled clinical study done in 16 elderly patients (65 to 85 years of age) with impaired renal function (a 20% reduction in CrCl compared with young adults), following a single oral 100 mg dose of topiramate, the C_{max} was 23% higher when compared to young adults due to reduced clearance. Dose adjustments are recommended in all patients with impaired renal function (CrCl 70 mL/min/1.73 m² or less) [20].

3) Rectal

a) Rectal, single-dose: 1.89 mg/L (200 mg) [152]

1) Following rectal administration of a single dose of topiramate 200 mg to healthy subjects, the peak plasma level reached 1.89 mg/L in 2.5 hours [152].

C) Time to Peak Concentration

1) Immediate-Release

a) Oral: 1.5 to 4 hours [20] [150] [153] [149]

1) The T_{max} was 2 hours following a single 400 mg oral dose [20]

2) Following oral administration of topiramate 100, 200, and 400 mg to fasting healthy subjects the time to peak concentration was 1.5 to 4 hours [150] [153] [149].

2)) Extended-Release**a)) Oral: 24 hours [1]**

1)) Following a single 200-mg dose of extended-release topiramate, C_{max} levels were reached at 24 hours [1].

3)) Geriatric, Extended-Release**a)) Oral: 16 hours (extended-release) [1]**

1)) In a study of 13 healthy elderly patients and 18 healthy young adults receiving extended-release topiramate, T_{max} was 16 hours in the elderly patients compared with 24 hours in the young adults [1].

4)) Rectal**a)) Rectal: 2.5 hours [152].**

1)) Following rectal administration of a single dose of topiramate 200 mg to healthy subjects, the peak plasma level reached 1.89 mg/L in 2.5 hours [152].

D)) Area Under the Curve

1)) The [topiramate](#) sprinkle formulation is bioequivalent to the immediate-release tablet formulation. They may be substituted as therapeutic equivalents [20].

2)) The extended-release formulation of [topiramate](#) administered once daily has been shown to be bioequivalent to the immediate-release formulation administered twice daily [1].

a)) Oral

1)) Oral: 60 mcg/hr/mL (100 mg); 300 mcg/hr/mL (400 mg) [149]

a)) The AUC for topiramate is approximately 60 mcg/hr/mL after 100 mg oral doses and 300 mcg/hr/mL after 400 mg [149].

b)) Dose-normalized mean values for AUC increased linearly, but not proportionally, with dose. The mean normalized AUC for the 1200-mg dose was 67% higher than the mean normalized AUC for the 100-mg dose [150].

b)) Geriatrics

1)) Oral, single-dose: 25% higher (immediate-release, 100 mg) [20] to 44% higher (extended-release) [1]

a) In a study of 13 healthy elderly subjects and 18 healthy young adults who received extended-release topiramate, the elderly subjects had a 44% higher AUC compared with the younger adults [1].

b) In a controlled clinical study done in 16 elderly patients (65 to 85 years of age) with impaired renal function (a 20% reduction in CrCl compared to young adults), following a single oral 100-mg dose of topiramate, the AUC was 25% higher when compared to young adults due to reduced clearance. Dose adjustments are recommended in all patients with impaired renal function (CrCl 70 mL/min/1.73 m(2) or less) [20].

c) Renal Impairment

1) Oral, single-dose: 191 mg/L/hr (100 mg) [151]

a) A study of topiramate plasma concentration profiles in healthy volunteers compared to patients with impaired renal function was conducted after a single oral 100-mg dose. Patients with CrCl below 1.8 L/hr/1.73 m(2) exhibited a higher AUC and longer topiramate t(1/2). The mean AUC in the patients with low CrCl levels was 191 mg/L/hr compared with 88 mg/L/hr in subjects with higher CrCl; mean t(1/2) were 59 hours and 32 hours, respectively. Renal topiramate clearance was dramatically reduced, but nonrenal clearance was also decreased [151].

b) Rectal

1) Rectal, single-dose: 0.72 hr/L (200 mg) [152]

a) The AUC for topiramate is approximately 0.72 hr/L after the rectal administration of a 200 mg dose to healthy subjects compared to 0.76 h/L after oral administration [152].

2.3] ADME

2.3.1] Absorption

A) Bioavailability

1) Oral: 80% [20]

a) Absorption of [topiramate](#) is rapid. The relative bioavailability of the immediate-release tablet is about 80% compared to solution [20].

2) Rectal: 80 to 120% [152]

a) The bioavailability of rectal [topiramate](#) ranges between 80% to 120% [152].

B) Effects of Food

1) Immediate-Release**a) none [20]**

1) Bioavailability of immediate-release topiramate is not affected by food [20].

2) When topiramate was administered with food (fatty breakfast), the rate of its absorption was slowed but there was no significant effect on extent of absorption. In these studies, mean C_{max} of topiramate (100 or 400 mg) was approximately 12% lower in nonfasting subjects compared with fasting subjects; T_{max} was delayed by about 2 hours when given with food. AUC values were similar in fasting and nonfasting states. Topiramate can be given with food without a significant effect on bioavailability [150] [149].

2) Extended-Release**a) C_{max} increased by 37%; T_{max} decreased to 8 hours [1]**

1) When extended-release topiramate was administered with a high-fat meal, the C_{max} increased by 37% and the T_{max} was shortened to 8 hours but AUC was not affected. Extended-release topiramate may be given without regard to meals [1].

2.3.2] Distribution**A) Distribution Sites****1) Protein Binding****a) 15% to 41% [1] [20]**

1) Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 mcg/mL. The fraction bound decreased as blood concentration increased [1] [20].

2) Topiramate is only minimally bound to plasma proteins (9% to 17%); however, the drug exhibits significant binding to erythrocytes. Until the red cell binding sites are saturated, drug concentrations in whole blood may be nonlinear and vary from values calculated for plasma. When steady-state is reached, the significance of this binding becomes negligible [156].

2) Tissues and Fluids

a) Topiramate distributes into all tissue sites and crosses the blood-brain and placental barriers [157].

1) CSF**a) 85% [158]**

1) The topiramate concentration in cerebrospinal fluid of adult epileptics (n=14) was 85% of the concentration in serum, regardless of the dose (correlation coefficient=0.9993) [158].

2) Saliva

a) 89.8% [159]

1) The mean fraction of saliva to serum concentration of topiramate was 89.8% (range 62.9% to 112.7%). There is a strong correlation between serum and saliva concentrations (adjusted $r(2)=0.97$) making saliva monitoring of topiramate levels a potential option [159].

B) Distribution Kinetics

1) Volume of Distribution

a) 0.6 to 0.8 L/kg [153].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) not extensively metabolized [1] [20]

a) **Topiramate** is not extensively metabolized. Six metabolites, each constituting 5% or less of an administered dose, are formed by hydroxylation, hydrolysis, and glucuronidation [1] [20].

B) Other

1) Metabolic Enzymes and Transporters

a) Inducer of CYP3A4

1) Topiramate is a mild inducer of CYP3A4 [20].

b) Inhibitor of CYP2C19

1) Topiramate is a mild inhibitor of CYP2C19 [20].

2.3.4] Excretion

A) Kidney

1) Renal Clearance (rate)

a) 13.9 mL/min [150]

1)) The renal clearance rate is 13.9 mL/min [150].

2)) Renal impairment

a)) clearance reduced 42% to 54% [1] [20]

1)) In moderate renal impairment (CrCl 30 to 69 mL/min/1.73 m(2)) and severe impairment (CrCl less than 30 mL/min/1.73 m(2)), clearance was reduced by 42% and 54%, respectively. Topiramate undergoes significant renal tubular reabsorption, but it is unclear whether CrCl is a predictor of topiramate clearance in all forms of renal disease. Some forms of renal disease could differentially affect GFR and tubular reabsorption resulting in a clearance that is not predicted by CrCl. Dose adjustments are recommended in all patients with moderate and severe renal impairment [1] [20].

2)) A study of topiramate plasma concentration profiles in healthy volunteers compared to patients with impaired renal function was conducted after a single oral 100-mg dose. Patients with CrCl below 1.8 L/hr/1.73 m(2) exhibited a higher AUC and longer topiramate t(1/2). The mean AUC in the patients with low CrCl was 191 mg/L/hr compared with 88 mg/L/hr in subjects with higher CrCl; mean t(1/2) was 59 hours and 32 hours, respectively. Renal topiramate clearance was dramatically reduced, but nonrenal clearance was also decreased [151].

3)) Geriatrics

a)) clearance reduced 19% [1] [20]

1)) In a controlled clinical study done in 16 elderly patients (65 to 85 years of age) with impaired renal function (a 20% reduction in CrCl compared with young adults), following a single oral 100 mg dose of topiramate, the renal clearance was decreased by 19% as a result of impaired renal function. Dose adjustments are recommended in all patients with impaired renal function (CrCl 70 mL/min/1.73 m(2) or less) [1] [20].

2)) Renal Excretion (%)

a)) 70% unchanged in urine [1] [20]

1)) Approximately 70% of an administered dose is eliminated unchanged in the urine with evidence of renal tubular reabsorption [1] [20].

2)) Between 55% and 97% of an oral dose of topiramate is excreted unchanged in the urine [153] [160] [154] [156]. Following a single oral dose, approximately 23% and 35%

of the topiramate dose was recovered in the urine within 16 and 32 hours, respectively [150].

B) Total Body Clearance

1) 20 to 30 mL/min [1] [20]

a) The plasma clearance rate following oral dosing is approximately 20 to 30 mL/min [1] [20].

b) The mean plasma clearance of **topiramate** after a single dose is 27.2 mL/min. However, the total clearance is inversely related to the dose with values of approximately 22 and 36 mL/minute for 1200- and 100-mg doses, respectively. The mean renal clearance was 13.9 mL/min and was not dependent upon dose. The renal clearance makes up approximately 51% of the total clearance [150].

c) During multiple-dose administration of 50 to 200 mg once daily or 50 to 100 mg twice daily, mean total clearance and renal clearance values were constant across dosages (21 mL/minute and 13 mL/minute, respectively) [153].

d) Pediatrics

1) increased compared with adults [1] [20]

a) In a study of 250 pediatric patients 2 to less than 16 years old (younger than 10 years, n=95), oral clearance of topiramate was higher with adjunctive therapy compared with monotherapy. Topiramate clearance per kg was higher in pediatric patients compared with adults, and in younger pediatric patients compared with older pediatric patients [1] [20].

b) Topiramate elimination occurs more quickly in children than in adults resulting in plasma concentrations that are approximately 30% lower for the same mg/kg dose [151].

e) Geriatrics

1) clearance reduced by 21% [1] [20]

a) In a controlled clinical study done in 16 elderly patients (65 to 85 years of age) with impaired renal function (a 20% reduction in CrCl compared with younger adults), following a single oral 100 mg dose of topiramate, the plasma clearance is decreased by 21% as a result of impaired renal function. Dose adjustments are recommended in all patients with impaired renal function (CrCl 70 mL/min/1.73 m² or less) [1] [20].

2.3.5] Elimination Half-life

A) Parent Compound

1) Immediate-Release

a) 21 hours [20]

1) The $t(1/2)$ was 21 hours following single or multiple doses [20].

2) Geriatrics

a) 13% longer [1] [20]

1) In a controlled clinical study done in 16 elderly patients (65 to 85 years of age) with impaired renal function (a 20% reduction in CrCl compared with young adults), following a single oral 100 mg dose of topiramate, the $t(1/2)$ was 13% longer when compared to young adults. Dose adjustments are recommended in all patients with impaired renal function (CrCl 70 mL/min/1.73 m²) or less) [1] [20].

3) Renal Impairment

a) 59 hours [151]

1) A study of topiramate plasma concentration profiles in healthy volunteers compared to patients with impaired renal function was conducted after a single oral 100-mg dose. Patients with CrCl below 1.8 L/hr/1.73 m²) exhibited a higher AUC and longer topiramate $t(1/2)$. The mean AUC in the patients with low CrCl levels was 191 mg/L/hr compared with 88 mg/L/hr in subjects with higher CrCl; mean $t(1/2)$ was 59 hours and 32 hours, respectively. Renal topiramate clearance was dramatically reduced, but nonrenal clearance was also decreased [151].

4) Extended-Release

a) 31 hours [1]

1) Following repeat administration of extended-release topiramate, $t(1/2)$ was 31 hours [1].

2.3.6] Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: yes, 120 mL/min [1] [20]

a) **Topiramate** is cleared by **hemodialysis** at a rate that is 4 to 6 times greater than in normal individuals. During prolonged dialysis periods the concentration may fall to below levels required for maintaining the antiseizure effect. To avoid these drops, a supplemental dose of **topiramate** may be required. The actual adjustment should take into account 1) the duration of the dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of **topiramate** in the patient [1] [20].

b)) When a high efficiency, counterflow, single pass-dialysate [hemodialysis procedure](#) was used, [topiramate](#) dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high [topiramate](#) clearance (compared to 20 to 30 mL/min total oral clearance in healthy individuals) will remove a clinically significant amount of [topiramate](#) over the [hemodialysis](#) treatment period. A supplemental dose of [topiramate](#) may be required [1] [20].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.1] Contraindications

A)) alcohol use, recent (within 6 hours prior to or 6 hours after [topiramate](#) use) [1]

B)) [metabolic acidosis](#) with concomitant [metformin](#) use [1]

3.2] Precautions

A)) abrupt withdrawal may increase seizure frequency in patients with or without history of seizures or [epilepsy](#); withdraw gradually; if sudden discontinuation is required, monitoring is recommended [1] [17]

B)) CNS depression may occur, especially with concomitant use of other CNS depressants [1] [17]

C)) cognitive-related dysfunction may occur; increased risk with rapid titration rate and higher initial doses [1]

D)) concomitant use of drugs that induce [metabolic acidosis](#), including other carbonic anhydrase inhibitors (eg, [zonisamide](#), [acetazolamide](#), [dichlorphenamide](#)) should be avoided [1] [17]; increased risk of [kidney stone](#) formation [1]

E)) [hepatic impairment](#); use cautiously due to reduced [topiramate](#) clearance [17]

F)) [hyperammonemia](#) with or without [encephalopathy](#) has been reported in patients with and without concomitant [valproic acid](#) administration [1]; increased risk in patients with inborn errors of metabolism or reduced hepatic mitochondrial activity [1] [17]; monitoring recommended [17]

G)) [hypothermia](#) (body core temperature less than 95 degrees F [35 degrees C]) with or without [hyperammonemia](#) has been reported with concomitant [valproate](#) use [1] [17]; discontinuation of [topiramate](#) or [valproate](#) may be required [1]

H)) [metabolic acidosis](#) has been reported; increased risk in patients with conditions or therapies that predispose to [acidosis](#) (eg, [renal disease](#), severe respiratory disorders, [status epilepticus](#), diarrhea, surgery, ketogenic diet, or drugs); monitoring recommended; dose reduction [1] [17] or discontinuation may be necessary [1]

I)) [myopia](#), acute, associated with [secondary angle closure glaucoma](#), has been reported; drug discontinuation recommended [1] [17]

J)) [oligohidrosis](#) and body temperature above normal have been reported; increased risk in pediatric patients; monitoring recommended [1] [17]

K)) pregnancy; may cause fetal harm [1]

L)) psychiatric or behavioral disturbances, including depression or mood changes, may occur; typically dose related [1]

M)) [renal impairment](#), moderate to severe; dose reduction recommended [1] [17]

N)) suicidal thoughts or behavior may occur; monitoring recommended [1] [17]

O)) report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or [www.fda.gov/medwatch](#) [1] [17]

3.3] Adverse Reactions

3.3.2] Dermatologic Effects

3.3.2.A] Alopecia

1) Incidence: 2% to 5% [1] [17]

2) Adults

a) Alopecia was reported in 4% of adult patients who received topiramate 400 mg/day (n=159) compared with 3% of patients who received topiramate 50 mg/day (n=160), in a monotherapy epilepsy trial [20].

3) Pediatrics

a) Alopecia was reported in 5% of pediatric patients (ages 10 to 16 years) who received immediate-release topiramate 400 mg/day (n=57) compared with 2% on immediate-release topiramate 50 mg/day (n=57) in a monotherapy epilepsy trial [1].

b) The incidence of alopecia was 4% in pediatric patients (age 6 to less than 16 years) who received monotherapy with topiramate 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of epilepsy [20].

c) Alopecia was reported in 2% of pediatric patients 2 to 16 years of age on topiramate (n=98) compared with 1% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.2.B] Erythema multiforme

1) Erythema multiforme was reported during postmarketing experience with topiramate [1] [20]

3.3.2.C] Flushing

1) Incidence: pediatrics, 5% [20]

2) Pediatrics

a) The incidence of flushing was 5% in pediatric patients (age 6 to less than 16 years) who received monotherapy with topiramate 400 mg/day (n=77) and 0% in those who received 50 mg/day (n=74) for the treatment of epilepsy. Flushing was one of the most common adverse reactions leading to therapy discontinuation [20].

3.3.2.D] Pemphigus

1) Pemphigus has been reported with postmarketing use of topiramate [1] [20].

3.3.2.E] Pruritus

1) Incidence: adults, 2% to 4% [1] [20]

2) Adults

a) Pruritus was reported in 4% of adult patients on topiramate 400 mg/day (n=159) compared with 1% of patients on 50 mg/day (n=160), in a monotherapy epilepsy trial [1] [20].

b) **Pruritus** was reported in 2% of patients on **topiramate** 100 mg/day (n=386) and 2% on placebo (n=445), in placebo-controlled, migraine trials [20].

c) **Topiramate** associated **pruritus** was reported in a 5-patient case series. **Pruritus** generally appeared after a dose increase and at doses ranging from 50 to 700 mg. Symptoms were described as diffuse body itching without the presence of a visible rash. As a result, **topiramate** therapy was discontinued in 2 patients, and doses were reduced in 2 patients. Slower dose titration led to better tolerance in the remaining patient (Ochoa et al, 2003).

3.3.2.F] Rash

1) Incidence: 4% [1] [20]

2) Adults

a) Rash was reported in 4% of adult patients on **topiramate** 400 mg/day (n=159) compared with 1% of patients on 50 mg/day (n=160), in a monotherapy **epilepsy** trial [1] [20].

b) Rash developed in a 17-year-old man taking the sprinkle-capsule formulation of **topiramate** for seizure disorder. When rechallenged with the tablet formulation, no reaction occurred. The original reaction occurred 3 months after the initiation of therapy and involved discrete red areas with papules covering the entire body. **Topiramate** was gradually withdrawn and the rash disappeared 3 weeks later. Due to inadequate seizure control, **topiramate** was restarted under strict observation (as an inpatient) in the tablet form. No reaction reappeared in the following months. Authors speculate that the reaction may be a result of sensitivity to the components of the sprinkle-capsule formulation [80].

3) Pediatrics

a) The incidence of rash was 4% in pediatric patients (age 6 to less than 16 years) who received monotherapy with **topiramate** 400 mg/day (n=77) and 3% in those who received 50 mg/day (n=74) for the treatment of **epilepsy** [20].

3.3.2.G] Stevens-Johnson syndrome

1) **Stevens-Johnson syndrome** was reported during postmarketing experience with **topiramate** [1] [20]

3.3.2.H] Toxic epidermal necrolysis

1) **Toxic epidermal necrolysis** was reported during postmarketing experience with **topiramate** [1] [20]

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Hyperammonemia, With or without encephalopathy

1) **Hyperammonemia** with or without **encephalopathy** has been reported in patients administered **topiramate** with and without concomitant **valproic acid** therapy [1] [20]. Signs and symptoms resolved upon discontinuation of either drug [20].

2) Clinicians reported 2 adult cases of valproate-induced **hyperammonemic encephalopathy** that occurred during combination therapy including **valproate** and **topiramate**. The patients were a 32-year-old man who had left centro-temporal **epilepsy** with complex partial and secondarily generalized seizures and a 37-year-old woman with **focal epilepsy** caused by right parietal **angioma**. Among the patients' symptoms were sudden somnolence, slurred speech, ataxia, **dysarthria**, **horizontal nystagmus**, and nausea. One day after admission, the man was reacting only to strong stimuli; both patients experienced 2 secondarily

generalized tonic-clonic seizures (the first time in 10 years for the woman). EEG revealed continuous generalized slowing for both. The patients had previously tolerated [valproate](#) in combination with other medications ([phenobarbital](#), [carbamazepine](#), [lamotrigine](#)). The [encephalopathy](#) occurred in both instances when [valproate](#) and [topiramate](#) were given concurrently in a combination regimen. Both had serum levels of [valproate](#) below the therapeutic range (38 and 47 mcg/mL, respectively; therapeutic range, 50 to 100 mcg/mL) and elevated serum ammonia concentrations (116 and 88 micromol/L, respectively; normal range 11 to 60 micromol/L). One patient was normalized by discontinuation of [valproate](#) and the other by withdrawal of [topiramate](#). The authors suggested that [topiramate](#) may increase ammonia levels by its inhibition of carbonic anhydrase and cerebral glutamine synthetase [59].

3.3.3.B] Hypohidrosis

1) [Hyperthermia](#) and [oligohidrosis](#) have been associated with the administration of [topiramate](#), especially in pediatric patients. Some cases have resulted in hospitalization. Monitor patients for evidence of increased body temperature and decreased sweating, especially in hot weather and when patients are treated concomitantly with other drugs that predispose them to heat-related disorders (eg, anticholinergics, carbonic anhydrase inhibitors) [1] [20].

2) A case report described development of severe, topiramate-induced [hypohidrosis](#) in a 4-year-old girl with complex partial seizures. Initially, treatment with [topiramate](#) was well-tolerated, where [topiramate](#) was initiated at a dose of 0.5 mg/kg/day and slowly titrated to a dose of 3.3 mg/kg/day (25 mg twice daily). However, 5 months into the treatment, the patient became irritable, had reduced appetite, and experienced multiple awakenings per night, which were found to be unrelated to [epilepsy](#). Over the next 2 weeks, she developed intermittent daily [hyperthermia](#), with temperature ranging between 38.3 and 38.8 degrees C, headache, inability to secrete sweat, and dryness of the skin. Results of a sweat test, using the Wescor Macroduct collection procedure, showed a higher than normal conductivity value (95 mmol/L) and sodium concentration in sweat (108 mEq/L). Subsequently, [topiramate](#) was gradually discontinued, which prompted restoration of normal sweating and skin appearance within 2 weeks. A repeat sweat test, performed 3 weeks after drug discontinuation, demonstrated increased sweat quantity with normal electrolyte composition. Additionally, [hyperthermia](#) and sleep disturbances disappeared and the patient's appetite returned to normal. While the exact mechanism for the [hypohidrosis](#) has not been elucidated, it is proposed that it may be a result of an autonomic dysfunction due to inhibition of carbonic anhydrase localized in human eccrine sweat glands [67].

3.3.3.C] Hypophosphatemia

1) Incidence: adults, 6% [1] [20]

2) Adults

a) Markedly decreased serum phosphorus was reported in 6% of adult patients with partial onset seizures who received adjunctive treatment with immediate-release [topiramate](#) compared with 2% of patients who received placebo [1] [20].

3.3.3.D] Increased body temperature

1) [Hyperthermia](#) and [oligohidrosis](#) have been associated with the administration of [topiramate](#), especially in pediatric patients. Some cases have resulted in hospitalization. Monitor patients for evidence of increased body temperature and decreased sweating, especially in hot weather and when patients are treated concomitantly with other drugs that predispose them to heat-related disorders (eg, anticholinergics, carbonic anhydrase inhibitors) [1] [20].

3.3.3.E] Lipids abnormal

1J) Fasting total cholesterol at 3 months were significantly reduced in 38 patients who received adjunctive [topiramate](#) therapy. After 3 months of [topiramate](#) therapy (mean dose 81 mg/day), total cholesterol levels had decreased 0.28 mmol (p less than 0.01). This effect was maintained 9 months later [68].

3.3.3.FJ Metabolic acidosis

1J) Summary

aJ) [Topiramate](#) has been associated with hyperchloremic, non-anion gap, [metabolic acidosis](#) (ie, decreased serum bicarbonate below the normal reference range in the absence of [chronic respiratory alkalosis](#)). [Topiramate](#) inhibits carbonic anhydrase leading to renal bicarbonate excretion. Most cases of [metabolic acidosis](#) occur early in the course of treatment. The average decrease in bicarbonate is 4 mEq/L at daily doses of 400 mg in adults and approximately 6 mg/kg/day in pediatric patients. [Metabolic acidosis](#) has been occurred with doses as low as 50 mg/day. There have been rare occurrences of severe bicarbonate loss to less than 10 mEq/L. Risk factors include [renal disease](#), severe respiratory disorders, [status epilepticus](#), diarrhea, surgery, ketogenic diet, or drugs. Signs and symptoms may include hyperventilation, nonspecific symptoms (eg, fatigue, anorexia), or more severe [sequelae](#) including [cardiac arrhythmias](#) or stupor. Chronic untreated [metabolic acidosis](#) may increase the risk for [nephrolithiasis](#) or [nephrocalcinosis](#), and may also result in [osteomalacia](#) or [osteoporosis](#). Growth rates may be reduced in children resulting in a decreased maximal height. Serum bicarbonate should be measured at baseline and periodically throughout treatment. Reduce dose or discontinue (by tapering) [topiramate](#) if [metabolic acidosis](#) occurs and persists. Consider alkali treatment if the decision is to continue [topiramate](#) in the presence of [metabolic acidosis](#) [1] [20].

2J) Adults

aJ) [Metabolic acidosis](#) developed in a 22-year-old mentally retarded man with [Lennox-Gastaut syndrome](#) after 4 months of treatment with [topiramate](#) 800 mg/day. The patient developed severe fatigue, lethargy, hypotonia and hyperventilation, associated with an arterial blood pH of 7.3, and a serum bicarbonate level of 19.2 mEq/L. The condition resolved after withdrawal from the [topiramate](#). The patient received the [topiramate](#) in addition to his normal antiseizure medication, but the specific medication was not named. A 20-year-old man developed hyperchloremic [metabolic acidosis](#) and associated mental status changes while receiving [topiramate](#) therapy of 400 mg/day for 9 months. Admission laboratory tests revealed a [serum chloride](#) level of 120 mEq/L, bicarbonate of 12 mEq/L, and an anion gap of 13. In addition to supportive therapy, [topiramate](#) was discontinued over 6 days, with normalization of [metabolic acidosis](#) and mental status changes [63] [64].

3J) Pediatrics

aJ) The results of 1 study indicate that [metabolic acidosis](#) developed in 8 of 9 young children (ages 5 months to 2.3 years) while receiving [topiramate](#) for the treatment of [epilepsy](#). Blood gases revealed [metabolic acidosis](#) (median pH, 7.35) following 8 to 26 days of therapy at maximum doses of 8.2 to 26 mg/kg/day. This data suggests that [metabolic acidosis](#) may be a frequent adverse event of [topiramate](#) therapy in young children. The authors suggest evaluation of the acid-base balance prior to initiating [topiramate](#) treatment and after the addition of any other antiepileptic drug. They recommend regular monitoring of infants and toddlers receiving [topiramate](#) [65].

bJ) Two children developed [metabolic acidosis](#) while being treated with [topiramate](#) as adjunct therapy for [epilepsy](#). [Acidosis](#) resolved with discontinuation of [topiramate](#) or dose reduction. Seizures in an 11-year-old boy with intractable [complex partial epilepsy](#) were controlled with [topiramate](#) 100 mg twice daily (about 3.5 mg/kg/day) and sodium [valproate](#) 1 g daily. Thirteen

months after the initiation of [topiramate](#) therapy, the boy had a [relapse](#) of seizures. [Topiramate](#) was increased to 150 mg twice daily (about 5 mg/kg/day). A week later, he was admitted to the emergency department with shortness of breath. Arterial blood gas analysis revealed [metabolic acidosis](#) (pH 7.36) with partial respiratory compensation. He was given 50 mL of 8.4% [sodium bicarbonate](#) by slow infusion. Gradually, the hyperventilation was alleviated and venous blood gas analysis showed resolution of [acidosis](#). [Topiramate](#) was reduced to 100 mg twice daily. Subsequent blood gas analyses showed persistent subclinical [metabolic acidosis](#). [Topiramate](#) was further reduced to 150 mg/day, yielding resolution of [acidosis](#). After 7 months, the boy remained seizure-free and without [acidosis](#). A 16-month-old girl was given [topiramate](#) 6.25 mg/day and developed marked irritability 4 days later, which resolved with stopping [topiramate](#). At 21 months of age, [topiramate](#) was again given, with sodium [valproate](#) and [lamotrigine](#). The [topiramate](#) dose was increased to 50 mg/day (about 5 mg/kg/day) after 4 weeks. She had no seizures for 12 days after the initiation of [topiramate](#) therapy, but she became irritable and had a poor appetite. Blood gases showed [metabolic acidosis](#) (pH 7.34). The irritability and poor appetite disappeared shortly after withdrawal of [topiramate](#) [66].

3.3.3.G] Serum bicarbonate level abnormal

1) Incidence: 25% to 67% [1] [20]

2) Adults

a) In adults with [epilepsy](#) who received immediate-release [topiramate](#) monotherapy, the incidence of a persistent decrease in serum bicarbonate was 15% for 50 mg/day and 25% for 400 mg/day. An abnormally low serum bicarbonate level (absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from baseline) occurred in 1% of patients who received [topiramate](#) 50 mg/day and in 7% of those who received [topiramate](#) 400 mg/day [1] [20].

b) Persistent treatment-emergent decreases in serum bicarbonate (less than 20 mEq/L) were reported in 32% of adult patients on immediate-release [topiramate](#) 400 mg/day compared with 1% of patients on placebo, in controlled clinical trials for adjunctive treatment of [epilepsy](#). An abnormally low serum bicarbonate level (absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from baseline) occurred in 3% of patients who received [topiramate](#) compared with 0% in placebo [1] [20].

c) Persistent treatment-emergent decreases in serum bicarbonate were reported in 39% of adult patients who received [topiramate](#) 100 mg/day compared with 7% for placebo, in controlled trials for [prophylaxis of migraine](#). An abnormally low serum bicarbonate level (absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from baseline) occurred in 9% of patients who received [topiramate](#) 100 mg/day compared with less than 1% for placebo [20].

3) Pediatrics

a) In monotherapy controlled trials, persistent treatment-emergent decreases in serum bicarbonate were reported in 9% of pediatric patients, 6 to 15 years of age, who received immediate-release [topiramate](#) 50 mg/day and 25% for those who received 400 mg/day in the epilepsy-controlled clinical trial for monotherapy. An abnormally low serum bicarbonate level (absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from baseline) occurred in 1% of patients who received [topiramate](#) 50 mg/day and in 6% who received 400 mg/day [1] [20].

b) Persistent treatment-emergent decreases in serum bicarbonate were reported in 67% of pediatric patients 2 to 16 years of age who received immediate-release [topiramate](#) 6 mg/kg/day compared with 10% for placebo, in controlled trials for adjunctive treatment of [Lennox-Gastaut syndrome](#)

or refractory partial onset seizures. An abnormally low serum bicarbonate level (absolute value less than 17 mEq/L and greater than 5 mEq/L decrease from baseline) occurred in 11% of patients who received [topiramate](#) compared with 0% in placebo [1] [20].

3.3.4] Gastrointestinal Effects

3.3.4.A] Abdominal pain

1) Incidence: adults, 6% [1] [20]

2) Adults

a) Abdominal pain was reported in 6% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 4% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

b) Abdominal pain was reported in 6% of patients on [topiramate](#) 100 mg/day (n=386) compared with 5% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3.3.4.B] Constipation

1) Incidence: 4% to 5% [1] [20]

2) Adults

a) Constipation was reported in 4% of adult patients on [topiramate](#) 400 mg/day (n=159) compared with 1% of patients on [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b) Constipation was reported in 4% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

3) Pediatrics

a) Constipation was reported in 5% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 4% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.4.C] Diarrhea

1) Incidence: 6% to 11% [1] [20]

2) Adults

a) Diarrhea was reported in 6% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 5% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1].

b) Diarrhea was reported in 11% of patients on [topiramate](#) 100 mg/day (n=386) compared with 4% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a)) Diarrhea was reported in 11% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 5% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b)) The incidence of diarrhea was 9% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 8% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

3.3.4.D) Excessive salivation

1)) Incidence: pediatrics, 6% [1] [20]

2)) Pediatrics

a)) Increased saliva was reported in 6% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 4% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.4.E) Indigestion

1)) Incidence: adults, 5% to 7% [1] [20]

2)) Adults

a)) [Dyspepsia](#) was reported in 7% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 6% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

b)) [Dyspepsia](#) was reported in 5% of patients on [topiramate](#) 100 mg/day (n=386) compared with 3% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3.3.4.F) Loss of appetite

1)) Incidence: 10% to 24% [1] [20]

2)) Adults

a)) Anorexia was reported in 14% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 4% on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b)) Anorexia was reported in 10% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 4% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [20].

c)) Anorexia was reported in 15% of patients on [topiramate](#) 100 mg/day (n=386) compared with 6% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3)) Pediatrics

a)) Anorexia was one of the most frequently reported neuropsychiatric events reported in pediatric patients on [topiramate](#) 50 mg/day and 400 mg/day during a monotherapy double-blind study [1] [20].

b) Anorexia was reported in 14% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 11% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

c) Anorexia was reported in 24% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 15% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.4.G] Nausea

1) Incidence: 6% to 13% [1] [20]

2) Adults

a) Nausea was reported in 10% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 8% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

b) Nausea was reported in 13% of patients on [topiramate](#) 100 mg/day (n=386) compared with 8% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Nausea was reported in 6% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 5% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.4.H] [Pancreatitis](#)

1) [Pancreatitis](#) has been reported with postmarketing use of [topiramate](#) [1] [20].

3.3.4.I] Taste sense altered

1) Incidence: adults, 2% to 8% [1] [20]

2) Adults

a) Taste perversion was reported in 5% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 3% of patients on immediate-release [topiramate](#) 50 mg/day in a monotherapy [epilepsy](#) trial [1] [20].

b) Taste perversion was reported in 2% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 0% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Taste perversion was reported in 8% of patients on [topiramate](#) 100 mg/day (n=386) compared with 1% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3.3.4.J] Weight decreased

1) Incidence: 9% to 21% [1] [20]

2) Adults

a) Weight decrease was reported in 17% of adult patients on [topiramate](#) immediate-release 400 mg/day (n=159) compared with 6% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [20].

b) Weight decrease was reported in 9% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 3% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [20]. Weight decrease was dose-related in the patient population with partial onset seizures in these studies, occurring at an incidence of 4% for [topiramate](#) 200 mg/day (n=45) and 9% for 400 mg/day (n=68) compared with 3% for placebo (n=216) [1] [20].

c) Weight decrease was reported in 9% of patients on [topiramate](#) 100 mg/day (n=386) compared with 1% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

d) In a prospective, open-label study aimed at identifying factors associated with topiramate-related weight loss, patients lost an average of 5.9 kg (7.3% of baseline body weight) after 1 year. The mean [topiramate](#) dose after 1 year was 129 mg/day (range 45 to 262 mg/day). Of 38 patients, 58% lost at least 5% of their baseline body weight and 32% lost 10% or more after 1 year. Mean weight loss was greatest in patients with a baseline BMI of 30 kg/m² or greater. By 3 months, 88% of these patients had lost weight and by 1 year, 100% had lost a mean of 10.9 kg (11% of baseline body weight). Patients were found to have lost more body fat than lean mass. Although patients were instructed not to change their diet or exercise regimen, mean caloric intake at 3 months was reduced from 2009 kcal/day to 1823 kcal/d. However, by 1 year caloric intake had returned to baseline (1964 kcal/day). The authors concluded that mechanisms other than loss of appetite are involved in the long-term weight loss effects of [topiramate](#) [68].

3) Pediatrics

a) Weight decrease was reported in 21% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 7% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b) The incidence of a weight decrease was 17% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 7% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

c) Weight decrease was reported in 9% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 1% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.5] Hematologic Effects

3.3.5.A] [Purpura](#)

1) Incidence: pediatrics, 8% [1] [20]

2) Pediatrics

a) [Purpura](#) was reported in 8% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 4% of patients on placebo (n=101) in a randomized, double-

blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.6] Hepatic Effects

3.3.6.A] Hepatitis

1) Hepatitis was reported during postmarketing experience with [topiramate](#) [1] [20]

3.3.6.B] Liver failure

1) [Hepatic failure](#), in some cases fatal, was reported during postmarketing experience with [topiramate](#) [1] [20].

2) A 39-year-old woman maintained on [carbamazepine](#) for 2 years with evidence of liver disease began taking [topiramate](#) with the dose increased gradually to 300 mg/day over 4 months. A few days after the last dose increase she developed CNS depression and was admitted to the hospital 1 week later with [hypoglycemia](#), elevated liver enzymes, and [metabolic acidosis](#). This progressed to [fulminant liver failure](#) with [encephalopathy](#), [renal failure](#), and [coagulopathy](#). She received a liver [allograft](#) 4 days after admission. The explanted liver showed massive centrilobular necrosis. [Viral hepatitis](#), [autoimmune liver diseases](#), metabolic and [vascular diseases](#) were excluded [69].

3.3.7] Immunologic Effects

3.3.7.A] Infectious disease

1) Incidence: 2% to 8% [1] [20]

2) Adults

a) Infection was reported in 3% of adult patients on [topiramate](#) 400 mg/day (n=159) compared with 2% of patients on [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b) Infection was reported in 2% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

3) Pediatrics

a) Infection was reported in 7% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 2% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b) The incidence of infection was 8% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 3% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

3.3.7.B] Viral disease

1) Incidence: 2% to 9% [1] [20]

2) Adults

a) Viral infection was reported in 8% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 6% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1]. [20].

b) Viral infection was reported 2% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Viral infection was reported in 4% of patients on [topiramate](#) 100 mg/day (n=386) compared with 3% on of patients on placebo (n=445), in placebo-controlled migraine trials [20].

3) Pediatrics

a) Viral infection was reported in 9% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 4% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b) The incidence of viral infection was 6% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 3% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

c) Viral infection was reported in 7% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 3% on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.8] Musculoskeletal Effects

3.3.8.A] Backache

1) Incidence: 1% to 5% [1] [20]

2) Adults

a) Back pain was reported in 5% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 4% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

3) Pediatrics

a) Back pain was reported in 1% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 0% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9] Neurologic Effects

3.3.9.A] Abnormal gait

1) Incidence: 3% to 8% [1] [20]

2) Adults

a) Abnormal gait was reported in 3% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [20].

3) Pediatrics

a)) Abnormal gait was reported in 8% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 5% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.B) Asthenia

1)) Incidence: 2% to 6% [1] [20]

2)) Adults

a)) Asthenia was reported in 6% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 4% of patients on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial. Asthenia was one of the most common adverse reactions causing [topiramate](#) discontinuation [1] [20].

b)) Asthenia was reported in 6% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c)) Asthenia was reported in 2% of patients on [topiramate](#) 100 mg/day (n=386) compared with 1% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3)) Pediatrics

a)) The incidence of asthenia was 3% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 0% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

3.3.9.C) Ataxia

1)) Incidence: 2% to 16% [1] [20]

2)) Adults

a)) Ataxia was reported in 4% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 3% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b)) Ataxia was reported in 16% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 7% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c)) Ataxia was reported in 2% of adult patients on [topiramate](#) 100 mg/day (n=386) compared with less than 1% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3)) Pediatrics

a)) Ataxia was reported in 6% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 2% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.D] Confusion

1) Incidence: 3% to 11% [1] [20]

2) Adults

a) Confusion was reported in 4% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 3% on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial [1].

b) Confusion was reported in 11% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 5% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20]. Confusion was dose-related in the patient population with partial onset seizures in these studies, occurring at an incidence of 9% for [topiramate](#) 200 mg/day (n=45) and 10% for 400 mg/day (n=68) compared with 4% for placebo (n=216) [1] [20].

c) Confusion was reported in 3% of adult patients on [topiramate](#) 100 mg/day (n=386) compared with 2% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) The incidence of confusion was 3% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 0% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#). Confusion was one of the most common adverse reactions leading to therapy discontinuation [20].

b) Confusion was reported in 4% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 3% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.E] Disorder of language

1) Incidence: adults, 6% [1] [20]

2) Adults

a) Language problems were reported in 6% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [20]. Language problems were dose-related in the patient population with partial onset seizures in these studies, occurring at an incidence of 2% for [topiramate](#) 200 mg/day (n=45) and 9% for 400 mg/day (n=68) compared with less than 1% for placebo (n=216) [1] [20].

b) Language problems were reported in 6% of patients on [topiramate](#) 100 mg/day (n=386) compared with 2% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Language regression was reported in 3 pediatric patients between the ages of 5 to 17 years taking [topiramate](#) for [epilepsy](#). Adjunctive [topiramate](#) was administered at doses ranging from 2.5 to 6 mg/kg/day. [Topiramate](#) was added to vigabatrin in 1 case, [valproic acid](#) in another, and [carbamazepine](#) in the third case. Language regression developed 4 to 28 weeks after drug

initiation. Cases were marked with regression to single-word utterances, communication via gestures or use of repetitive syllables, [stuttering](#) or a decline in language output. Comprehension seemed to be maintained. In 1 case, language regression was accompanied with deterioration in motor skills without concomitant alteration in metabolic status. Symptoms slowly resolved upon discontinuation or with decreased doses of [topiramate](#) (Tsur et al, 2004).

3.3.9.F] Dizziness

1) Incidence: 4% to 25% [1] [20]

2) Adults

a) Dizziness was reported in 14% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 13% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b) Dizziness was reported in 25% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 15% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Dizziness was reported in 9% of patients on [topiramate](#) 100 mg/day (n=386) compared with 10% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Dizziness was one of the most frequently reported neuropsychiatric events in pediatric patients on immediate-release [topiramate](#) 50 mg/day and 400 mg/day during a monotherapy double-blind study [1] [20].

b) Dizziness was reported in 4% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 2% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.G] Drug-induced encephalopathy

1) [Hyperammonemia](#), with or without [encephalopathy](#), has been reported in patients administered [topiramate](#) with and without concomitant [valproic acid](#) therapy [1]. Signs and symptoms resolved upon discontinuation of either drug [20].

2) Clinicians reported two adult cases of valproate-induced [hyperammonemic encephalopathy](#), which occurred during combination therapy including [valproate](#) and [topiramate](#). the patients were a 32-year-old man who had left centro-temporal [epilepsy](#) with complex partial and secondarily generalized seizures and a 37-year-old woman with [focal epilepsy](#) caused by right parietal [angioma](#). Among the patients' symptoms were sudden somnolence, slurred speech, ataxia, [dysarthria](#), [horizontal nystagmus](#), and nausea. One day after admission, the man was reacting only to strong stimuli; both patients experienced 2 secondarily generalized tonic-clonic seizures (the first time in 10 years for the woman). EEG examinations revealed continuous generalized slowing for both. The patients had previously tolerated [valproate](#) in combination with other medications ([phenobarbital](#), [carbamazepine](#), [lamotrigine](#)). The [encephalopathy](#) occurred in both instances when [valproate](#) and [topiramate](#) were given concurrently in a combination regimen. Both had serum levels of [valproate](#) below the therapeutic range (ie, 38 and 47 mcg/mL, respectively; therapeutic range, 50 to 100 mcg/mL) and elevated serum ammonia concentrations (116 and 88 micromol/L, respectively; normal range 11 to 60 micromol/L). One patient was normalized by discontinuation of

valproate and the other by withdrawal of topiramate. The authors suggested that topiramate may increase ammonia levels by its inhibition of carbonic anhydrase and cerebral glutamine synthetase [59].

3.3.9.H] Headache

1) Headache was one of the most frequently reported neuropsychiatric events reported in pediatric patients on topiramate 50 mg/day and 400 mg/day during a monotherapy double-blind study [1] [20].

3.3.9.I] Hemiparesis

1) Two cases of hemiparesis associated with topiramate have been reported in patients with already compromised neurological function. The first was a 41-year-old man with cerebral palsy who received topiramate (up to 25 mg twice daily) for 1 month for complex partial seizures. He developed fatigue, left-sided weakness, and slurred speech. Weakness resolved over 8 weeks after topiramate was withdrawn. The second was a 59-year-old woman with generalized seizures secondary to herpes simplex encephalitis. Over the first 2 months of topiramate therapy (up to 100 mg twice daily), she developed reduced tone and power in her right arm and leg. Normal strength returned 2 weeks after topiramate discontinuance [60].

3.3.9.J] Hypesthesia

1) Incidence: adults, 2% to 7% [1] [20]

2) Adults

a) Hypoesthesia was reported in 5% of adult patients on immediate-release topiramate 400 mg/day (n=159) compared with 4% of patients on immediate-release topiramate 50 mg/day (n=160), in a monotherapy epilepsy trial [1] [20].

b) Hypoesthesia was reported in 2% of adult patients on immediate-release topiramate 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for epilepsy (partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome) [1] [20].

c) Hypoesthesia was reported in 7% of patients on topiramate 100 mg/day (n=386) compared with 2% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3.3.9.K] Impaired cognition

1) Incidence: 2% to 7% [1] [20]

2) Adults

a) Cognitive problems were reported in 4% of adult patients on immediate-release topiramate 400 mg/day (n=159) compared with 1% of patients on 50 mg/day (n=160), in a monotherapy epilepsy trial [1] [20].

b) Cognitive problems were reported in 3% of adult patients on topiramate 200 to 400 mg/day (n=183) compared with 1% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for epilepsy (partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome) [1] [20].

c) Cognitive problems were reported in 2% of patients on topiramate 100 mg/day (n=386) compared with 1% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

d)) In one study (n=65), signs of cognitive dysfunction occurred in 83% of healthy subjects given doses of 400 mg daily but in only 14% administered initial doses of 100 mg. In epileptic patients beginning titration with 100 mg daily (combined with [carbamazepine](#) or [phenytoin](#)), 18% developed declines in cognitive function; however, all patients tolerated the dose titration with improvement or resolution of cognitive dysfunction. Impairments in cognition were not observed again in these patients until high chronic therapy doses were achieved [25]. This study suggests that beginning therapy with low doses can reduce cognitive impairment and enable continued therapy.

e)) Evidence of cognitive dysfunction (slower than expected information retrieval) was observed in 4 of 11 partial seizure patients during a mean of 10 weeks of [topiramate](#) administration (mean, 500 mg daily) as add-on therapy. Cognitive impairment persisted for 5 weeks in one patient and continued in the others (up to 9 weeks), although it was considered mild-to-moderate, not dose-limiting, and did not require discontinuation of therapy. Cognitive dysfunction in this study was not related to the rate of dose increases of [topiramate](#), absolute doses, concurrent antiepileptic therapy, or seizure frequency. It was, however, more likely to occur in patients over 38 years of age who were male and had partial seizures for longer than 16 years [55].

f)) A 30-year-old woman developed decreased cognition, dulled thinking, blunted mental reactions, blurred vision, paresthesias and moderate sleepiness after rapidly escalating her [topiramate](#) dose to 450 mg per day over 2 weeks in an attempt to lose weight [56].

g)) A study of 17 healthy volunteers randomized to receive [topiramate](#), [gabapentin](#), or [lamotrigine](#) showed that subjects who received [topiramate](#) were more likely to experience [cognitive deficits](#) compared with the other groups. [Topiramate](#) subjects scored significantly worse on tests of letter and category word fluency and visual attention during the acute dosing phase (within 5 days of drug initiation). Cognitive functioning was also statistically worse compared with the other groups in the chronic phase of dosing (4 weeks of medication) [57].

h)) In a retrospective study of 87 patients with [epilepsy](#), adverse effects from [topiramate](#) resulted in discontinuation of the drug in 41%, with 31% of patient's families reporting unacceptable cognitive dulling as a major cause for discontinuation [58].

3)) Pediatrics

a)) Cognitive problems were reported in 7% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 0% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b)) The incidence of problems with cognition was 6% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

3.3.9.L) Impaired psychomotor performance

1)) Incidence: 2% to 13% [1] [18]

2)) Adults

a)) Psychomotor slowing was reported in 5% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 3% on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial [1] [20].

b) Psychomotor slowing was reported in 13% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Psychomotor slowing was reported in 2% of patients on [topiramate](#) 100 mg/day (n=386) compared with 1% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Psychomotor slowing was reported in 3% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 2% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.M) Insomnia

1) Incidence: 7% to 9% [1] [20]

2) Adults

a) Insomnia was reported in 9% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 8% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial. Insomnia was one of the most common adverse reactions causing [topiramate](#) discontinuation [1] [20].

b) Insomnia was reported in 7% of patients on [topiramate](#) 100 mg/day (n=386) compared with 5% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Insomnia was reported in 8% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 7% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.N) Memory impairment

1) Incidence: 3% to 12% [1] [18]

2) Adults

a) Difficulty with memory was reported in 11% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 6% of patients on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial [20]. Difficulty with memory was one of the most common adverse reactions causing [topiramate](#) discontinuation [1] [20].

b) Difficulty with memory was reported in 12% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 3% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Difficulty with memory was reported in 7% of patients on [topiramate](#) 100 mg/day (n=386) compared with 2% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) The incidence of difficulty with memory was 3% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

b) Difficulty with memory was reported in 5% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 0% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.O] Paresthesia

1) Incidence: 1% to 51% [1] [20]

2) Adults

a) Paresthesia was reported in 40% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 21% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial. Paresthesia was one of the most common adverse reactions causing [topiramate](#) discontinuation [1] [20].

b) Paresthesia was reported in 11% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 4% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Paresthesia was reported in 51% of patients on [topiramate](#) 100 mg/day (n=386) compared with 6% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Paresthesia was reported in 16% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 2% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b) The incidence of paresthesia was 12% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 3% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

c) Paresthesia was reported in 1% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 0% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.P] Reduced concentration span

1) Incidence: 6% to 10% [1] [20]

2) Adults

a) Difficulty with concentration/attention was reported in 8% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 7% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b) Difficulty with concentration/attention was reported in 6% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo

(n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20]. Difficulty with concentration or attention was dose-related in the patient population with partial onset seizures in these studies, occurring at an incidence of 7% for [topiramate](#) 200 mg/day (n=45) and 9% for 400 mg/day (n=68) compared with 1% for placebo (n=216) [1] [20].

c) Difficulty with concentration/attention was reported in 6% of patients on [topiramate](#) 100 mg/day (n=386) compared with 2% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Difficulty with concentration or attention was reported in 9% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 4% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial. Difficulty with concentration/attention was the most common adverse reaction causing [topiramate](#) discontinuation [1].

b) The incidence of difficulty with concentration or attention was 10% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 7% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

c) Difficulty with concentration/attention was reported in 10% of pediatric patients ages 2 to 16 on immediate-release [topiramate](#) (n=98) compared with 2% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.Q] Seizure, Worsening

1) [Topiramate](#) was associated with seizure worsening in 19% of patients enrolled in a prospective open-label add-on study, based in India, for patients with refractory [epilepsy](#). Patients (n=95) had been diagnosed with refractory [epilepsy](#) for greater than 1 year and were started on [topiramate](#) 25 mg daily. Doses were titrated biweekly by 25 to 50 mg up to a maximum dose of 10 mg/kg/day or to a tolerated effective dose. Children were initiated at 0.5 mg/kg/day and titrated in a similar fashion. Patients between 20 and 30 years of age (p=0.02), patients with a history of [status epilepticus](#) (p=0.031), and those who were on three other conventional anti-epileptic agents (p=0.027) were more likely to have seizure worsening. Seizure worsening occurred between 4 and 6 months after initiation of [topiramate](#) [61].

3.3.9.R] Sleep walking disorder

1) A 27-year-old man developed episodes of [somnambulism](#) and automatic behavior 2 weeks after initiating [migraine prophylaxis](#) with [topiramate](#). [Topiramate](#) was dosed at 100 milligrams/day. The patient had 2 episodes of [somnambulism](#) during which he was amnesic. In addition, when waking from sleep, he was only partially aware of his actions and performed the same acts repeatedly. Each episode would last for 1 hour. After 4 weeks of therapy, the patient discontinued [topiramate](#). No further episodes were reported during the 6 months of follow-up [62].

3.3.9.S] Somnolence

1) Summary

a) Somnolence and fatigue were the most common adverse reactions in clinical trials of [topiramate](#) for adjunctive [epilepsy](#). Headache, dizziness, anorexia, and somnolence were the most frequently

reported neuropsychiatric events reported in pediatric patients on immediate-release [topiramate](#) 50 mg/day and 400 mg/day during a monotherapy double-blind study [1] [20].

2) Incidence: 7% to 29% [1] [20]

3) Adults

a) Somnolence was reported in 15% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 10% on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial [20]. Somnolence was one of the most common adverse reactions causing [topiramate](#) discontinuation [1] [20].

b) Somnolence was reported in 29% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 12% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c) Somnolence was reported in 7% of patients on [topiramate](#) 100 mg/day (n=386) compared with 5% on placebo (n=445), in placebo-controlled, migraine trials [20].

4) Pediatrics

a) Somnolence was reported in 26% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 16% on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.T] Speech problem

1) Incidence: less than 1% to 13% [1] [20]

2) Adults

a) Speech disorders or speech-related problems were reported in 13% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

b) Speech disorders or speech related problems were reported in less than 1% of patients on [topiramate](#) 100 mg/day (n=386) and less than 1% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Speech disorders or speech-related problems were reported in 4% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 2% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.9.U] Summary

1) One of the most common adverse events related to [topiramate](#) was cognitive-related dysfunctions (eg, confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, especially word-finding problems), which were typically mild to moderate and occurred in isolation. In adults, the most common cognitive adverse events that occurred together included (1) difficulty with memory occurring with difficulty with concentration/attention, (2) difficulty with

memory occurring with language problems, and (3) difficulty with concentration/attention occurring with language problems. The occurrence of 3 concurrent cognitive events occurred rarely. Higher incidences were associated with rapid dose titration and higher initial dose. Cognitive events were dose-related, and many of the events contributed to withdrawal from treatment [20].

a) In an adult monotherapy [epilepsy](#) trial, 1 or more cognitive-related dysfunctions were reported in 26% of patients on [topiramate](#) 400 mg/day and 19% on 50 mg/day [20].

b) In an adult add-on [epilepsy](#) controlled trial using rapid titration, 1 or more cognitive-related dysfunctions were reported in 42% of adult patients on immediate-release [topiramate](#) 200 mg/day and 41% on 400 mg/day compared with 14% of patients on placebo [20].

c) In an adult 6-month [migraine prophylaxis](#) controlled trial using a slow titration regimen, 1 or more cognitive-related dysfunctions were reported in 22% of adult patients on [topiramate](#) 100 mg/day compared with 10% of patients on placebo [20].

d) Cognitive-related dysfunctions (eg, psychomotor slowing, difficulty with concentration/attention, and speech or language problems) have been reported in pediatric patients in double-blind adjunctive therapy and monotherapy [epilepsy](#) clinical studies [20]

3.3.9.V] Tremor

1) Incidence: adults, 9% [1] [20]

2) Adults

a) Tremor was reported in 9% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 6% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

3.3.10] Ophthalmic Effects

3.3.10.A] Abnormal vision

1) Incidence: 2% to 13% [1] [20]

2) Adults

a) Abnormal vision was reported in 13% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

b) Abnormal vision was reported in 2% of patients on [topiramate](#) 100 mg/day (n=386) compared with less than 1% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Abnormal vision was reported in 2% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 1% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.10.B] Diplopia

1) Incidence: 1% to 10% [1] [20]

2) Adults

a) **Diplopia** was reported in 10% of adult patients on immediate-release **topiramate** 200 to 400 mg/day (n=183) compared with 5% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for **epilepsy** (partial onset seizures, primary generalized tonic-clonic seizures, or **Lennox-Gastaut syndrome**) [1] [20].

3) Pediatrics

a) **Diplopia** was reported in 1% of pediatric patients 2 to 16 years of age on immediate-release **topiramate** (n=98) compared with 0% of patients on placebo (n=101), in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.10.C) **Disorder of macula of retina**

1) **Maculopathy** was reported during postmarketing experience with **topiramate** [1] [20].

3.3.10.D) **Glaucoma**

1) Summary

a) Acute **myopia** associated with **secondary angle closure glaucoma** has been reported in patients taking **topiramate**. Acute onset of decreased visual acuity and ocular pain have been symptoms. Ophthalmologic findings of **myopia**, anterior chamber shallowing, **ocular hyperemia**, and increased intraocular pressure have been noted. Mydriasis may or may not be present. In general, symptoms present within 1 month of starting **topiramate**. Secondary angle closure associated with **topiramate** may occur in pediatrics. Discontinue **topiramate** immediately, according to the judgement of physician, to reverse symptoms. Serious consequences including permanent vision loss may result from untreated elevated intraocular pressure [1] [20].

2) **Acute angle-closure glaucoma**, with eye pain, headache, and blurred vision, abnormal vision, **conjunctivitis** and **diplopia** are described with the administration of **topiramate** [73] [74]. In a report of 83 cases of acute, **secondary angle-closure glaucoma**, 85% of cases occurred within the first 2 weeks of **topiramate** therapy. In this group of patients, doses ranged from less than 50 mg/day (47%), 50 to 75 mg/day (33%), 100 mg/day (13%) to doses greater than 100 mg/day (7%). Onset was acute and occurred a mean of 7 days from treatment initiation (range 1 to 49 days). In most cases, intraocular pressure decreases rapidly after the drug is stopped [75].

3) Acute **myopia** and **angle closure glaucoma** was reported in 23 patients taking **topiramate** (22 adults, 1 child) according to August 2001 postmarketing surveillance data. Symptoms typically develop during the first month of therapy and include acute onset of decreased visual acuity and/or eye pain. Physical exam may reveal **myopia**, redness, elevated intraocular pressure, shallow anterior chamber, and mydriasis (Pers com, 2001).

4) Case Reports

a) A 34-year-old man developed acute **myopia** and acute **glaucoma** following treatment with **topiramate** for migraine with and without aura while taking **citalopram** (20 mg daily for 2 months) for anxious-depressive syndrome. He was prescribed **topiramate** 25 mg/day, with a dose increase of 25 mg/day every 15 days up to a dose of 100 mg/day. Within 7 days following the initiation of **topiramate**, the patient experienced blurred vision, ocular pain, confirmed ocular pressure of 40 mmHg in both eyes, anterior chamber shallowing, **hyperaemia** of the sclera, and light **corneal edema**. Severe acute **glaucoma** and **myopia** (right eye = -5.5 diopters, left eye = -5 diopters)

were confirmed. Plasma [topiramate](#) concentration of 1.7 mcg/mL was below the therapeutic range of 2 to 25 mcg/mL. [Topiramate](#) was immediately discontinued and antiglaucoma therapy ([acetazolamide](#), [latanoprost](#), [timolol](#) and [pilocarpine](#)) was initiated. Within 2 days, the patient's ocular pressure had decreased to 14 mmHg in his right eye and 17 mmHg in his left eye. Four days later, his anterior chamber depth returned to normal, and ocular tone decreased to 10 mmHg in both eyes. Full resolution was achieved 8 days after discontinuation of [topiramate](#), during which the patient had a visus of 10/10 bilaterally, normalized fundus oculi and ocular pressure. Although the exact mechanism of this side effect is unknown, it has been hypothesized that SSRI can strengthen the uveal effusion of [topiramate](#), thereby increasing the risk of developing of [glaucoma](#). In this patient, both [topiramate](#) and [citalopram](#) may attribute to the increase in intraocular pressure and subsequently [glaucoma](#) [76].

b)) A 5-year-old girl developed bilateral [angle closure glaucoma](#) with ciliary block 10 days after initiating oral [topiramate](#) therapy for breakthrough seizures. Her only other concomitant medication was [carbamazepine](#), which was initiated one year prior. Patient history revealed mild [anisometropic amblyopia](#) in the right eye. Tests administered 2 months previously showed a visual acuity 20/50 of in the right eye and 20/20 in the left eye, and normal [slit-lamp and fundus examinations](#). The patient presented with headache, nausea and fatigue. Ophthalmic examination revealed a visual acuity of 20/200 in the left eye and finger counting in the right eye. Both eyes exhibited conjunctival [hyperemia](#) and microcystic [corneal edema](#) through [slit-lamp examination](#). Anterior chambers were described as extremely shallow but without [iris bombe](#) or iridocorneal touch. Intraocular pressures (IOPs) were elevated in both the right (50 mm Hg) and left eye (46 mm Hg). [Topiramate](#) was then discontinued. [Pilocarpine](#), [timolol](#) and [dorzolamide](#) were used to decrease the intraocular pressures. Three days later, the patient had discontinued all eye drops and the IOP in both eyes was 10 mmHg. Further examination resulted in a diagnosis of [secondary angle closure glaucoma](#) with ciliochoroidal effusions. The patient was then prescribed [cyclopentolate](#) and [prednisolone](#) acetate. Final examination revealed a change in the visual acuity of both eyes (20/60 in the right eye and 20/40 in the left) [77].

c)) Bilateral [acute angle-closure glaucoma](#) occurred in a 51- year-old man 2 weeks after he began oral [topiramate](#) (50 mg in the morning and 100 mg in the evening) for [bipolar affective disorder](#). His other medications were [glimepiride](#) and [metformin](#) for [type 2 diabetes mellitus](#). Symptoms included eye pain, headache and blurred vision. The patient was treated with IV [acetazolamide](#) 1500 mg, topical [pilocarpine](#) 1% and [prednisolone](#) 1%, and 2 doses of IV [mannitol](#) 1.5 mg/kg without success. After referral to a hospital, his visual acuity was 20/200 in both eyes and intraocular pressure was 32 and 38 in the right and left eyes, respectively. [Slit-lamp examination](#) revealed conjunctival [chemosis](#) and injection, [corneal edema](#), and a very shallow anterior chamber with irido-corneal apposition peripherally. [Gonioscopy](#) showed closed angles and a flat iris configuration in both eyes. Topical [brimonidine](#) tartrate 0.2%, [timolol](#) maleate 0.5%, [prednisolone](#) acetate 1% were initiated. A [laser peripheral iridotomy](#) to the right eye brought no change in intraocular pressure or anterior chamber depth. [Ultrasonography](#) showed lens thickening and ciliochoroidal detachment (360 degrees) in both eyes. A diagnosis of presumed topiramate-induced [glaucoma](#) was made. [Topiramate](#) was withdrawn, and the topical therapy continued. Signs and symptoms, including ciliochoroidal detachment, gradually resolved over 2 weeks. Visual acuity returned to 20/25 in both eyes [73].

d)) A 43-year-old woman developed blurred distance vision in both eyes and a mild frontal headache within 24 hours of starting [topiramate](#). She stopped taking [topiramate](#) after 3 doses, with the onset of symptoms. Four days later, ophthalmic examinations showed [myopia](#), narrow angles with increased intraocular pressure in both eyes (bilateral [angle-closure glaucoma](#)). Forward

displacement of the lens and swollen ciliary processes were evident in both eyes. Topical timolol maleate was applied twice daily in both eyes for 5 days. Twelve days after stopping topiramate, visual acuity was 20/15 without correction, angles were open, and the lenses of both eyes were more posteriorly positioned [78].

3.3.10.E] Myopia

1) Summary

a) Acute myopia associated with secondary angle closure glaucoma has been reported in patients taking topiramate. Acute onset of decreased visual acuity and ocular pain have been symptoms. Ophthalmologic findings of myopia, anterior chamber shallowing, ocular hyperemia, and increased intraocular pressure have been noted. Mydriasis may or may not be present. In general, symptoms present within 1 month of starting topiramate. Secondary angle closure associated with topiramate may occur in pediatrics. Discontinue topiramate immediately, according to the judgement of physician, to reverse symptoms. Serious consequences including permanent vision loss may result from untreated elevated intraocular pressure [1] [20].

2) Case Reports

a) A 34-year-old man developed acute myopia and acute glaucoma following treatment with topiramate for migraine with and without aura while taking citalopram (20 mg daily for 2 months) for anxious-depressive syndrome. He was prescribed topiramate 25 mg/day, with a dose increase of 25 mg/day every 15 days up to a dose of 100 mg/day. Within 7 days following the initiation of topiramate, the patient experienced blurred vision, ocular pain, confirmed ocular pressure of 40 mmHg in both eyes, anterior chamber shallowing, hyperaemia of the sclera, and light corneal edema. Severe acute glaucoma and myopia (right eye = -5.5 diopters, left eye = -5 diopters) were confirmed. Plasma topiramate concentration of 1.7 mcg/mL was below the therapeutic range of 2 to 25 mcg/mL. Topiramate was immediately discontinued and antiglaucoma therapy (acetazolamide, latanoprost, timolol and pilocarpine) was initiated. Within 2 days, the patient's ocular pressure had decreased to 14 mmHg in his right eye and 17 mmHg in his left eye. Four days later, his anterior chamber depth returned to normal, and ocular tone decreased to 10 mmHg in both eyes. Full resolution was achieved 8 days after discontinuation of topiramate, during which the patient had a visus of 10/10 bilaterally, normalized fundus oculi and ocular pressure. Although the exact mechanism of this side effect is unknown, it has been hypothesized that SSRI can strengthen the uveal effusion of topiramate, thereby increasing the risk of developing of glaucoma. In this patient, both topiramate and citalopram may attribute to the increase in intraocular pressure and subsequently glaucoma [76].

b) A 35-year-old woman developed acute myopia 11 days after beginning oral topiramate therapy for prophylaxis of episodic headache. She was started on 25 mg twice a day for 7 days and then increased to 50 mg twice a day. Four days following the increased dose she developed severe "blurry" vision and bilateral retrobulbar pain. Two days later topiramate was discontinued and within 3 days the patient's vision improved and in 6 days her vision returned to baseline [79].

c) Transient myopia was reported in a 40-year-old woman 9 days after receiving topiramate 25 mg/day for 2 days followed by 25 mg twice daily. Two hours after awaking to severe visual impairment, measured visual acuity was 4/60 bilaterally, improving to 6/12 bilaterally through a pin hole, with close vision tests normal. After discontinuation of topiramate, visual abnormalities ceased within 48 hours; the patient later took topiramate 25 mg every other day without recurrence of visual problems [74].

3.3.10.F] Nystagmus

1) Incidence: adults, 10% [1] [20]

2) Adults

a) **Nystagmus** was reported in 10% of adult patients on immediate-release **topiramate** 200 to 400 mg/day (n=183) compared with 7% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for **epilepsy** (partial onset seizures, primary generalized tonic-clonic seizures, or **Lennox-Gastaut syndrome**) [1] [20].

3.3.10.G] Palinopsia

1) A 35-year-old woman reported visual disturbances of "afterimages" soon after the gradual dose titration of **topiramate** to 100 mg/day. The patient had a history of **obesity**, alcohol abuse and several psychiatric conditions, such as **bulimia nervosa** and **bipolar disorder**. At the time the symptoms were reported, she had normal findings upon neurological examination and she was not taking any concomitant medications. She had no history of seizures or substance abuse, other than alcohol abuse. Soon after the **topiramate** dose was increased to 100 mg/day, the patient reported seeing "picture in picture" images. She described the images to be like "she was in a place with stroboscopic lights." The patient reported that the persistent "frozen pictures" would fade away after a few seconds. A temporal relationship appeared to exist between the occurrence of **palinopsia** and the administration of the **topiramate** [72].

3.3.10.H] Summary

1) By October 2002, 115 spontaneous reports of 1 or more possible ocular adverse events associated with **topiramate** use were sent to Ortho McNeil Pharmaceuticals, Inc, the Food and Drug Administration, the World Health Organization or the National Registry of Drug-Induced Ocular Side Effects at the Casey Eye Institute in Oregon. Of these cases, 83 cases of bilateral and 3 cases of unilateral acute, **secondary angle-closure glaucoma** were reported. Bilateral **myopia** up to 8.75 diopters (n=17), bilateral suprachoroidal effusions (n=9), **blepharospasm** (n=2), myokymia (n=1), **oculogyric crisis** (n=2), and **scleritis** (n=4) were included in the reports. Occasional reports of bilateral periocular edema, paresthesias and periocular pain have also occurred. A literature review also have reported **nystagmus** in 15% of patients and **diplopia** in 14% of patients on doses of at least 200 to 400 mg/day [75].

3.3.10.I] Uveitis

1) A case report described a 40-year-old woman with bilateral **anterior uveitis** and acute, **angle-closure glaucoma** following 7 days of treatment with **topiramate** 25 mg every 8 hours for migraine headache. The patient presented with bilateral ocular redness, pain, and blurred vision with an acuity of 5/200 in both eyes. Examination revealed bilateral conjunctival injection, microcystic **corneal edema**, shallow anterior chamber with 1+ cells and flare in both eyes, bilateral **choroidal effusion**, and intraocular pressure of 60 mmHg. Upon discontinuation of **topiramate** and medical management, the IOP was reduced to 13 mmHg with significant clearing of the **corneal edema**; however, visual acuity did not improve. On day 3 of admission, the visual acuity suddenly decreased with the development of severe bilateral **anterior uveitis** with posterior synechiae and **hypopyon**. **Uveitis** was controlled following 3 weeks of steroid treatment. Visual acuity improved to 20/25 six months later following **phacoemulsification** with **posterior chamber intraocular lens** implantation for severe cataract and posterior synechiae formation [70].

2) A case of severe bilateral **uveitis** with **angle-closure glaucoma** was reported in a 49-year-old man treated for 2 weeks with **topiramate** for **alcohol addiction**. The patient presented with 1-day duration of severe bilateral headache, and redness and watering eyes. Examination revealed bilateral circum-corneal congestion, severe **corneal edema**, and visual acuity less than 20/1200 in both eyes. Intraocular pressure

(IOP) was 37 mmHg. Ultrasound of the right eye revealed increased central corneal thickness and anterior chamber reaction, with angles closed over 360 degrees. There was also [choroidal effusion](#) and peripheral [choroidal detachment](#). The left eye had less severe, but similar findings. Corneal clarity improved 1 day after discontinuing [topiramate](#), revealing severe nongranulomatous [anterior uveitis](#) with graded 4 cells and flare in both eyes. Following discontinuation of all medical management of [uveitis](#) and [glaucoma](#) over 6 weeks, visual acuity returned to 20/40 and 20/20 in the right and left eye with normal IOP. The patient was not rechallenged. The Naranjo probability score of causality assessment rated this adverse event as probable [71].

3.3.12] Psychiatric Effects

3.3.12.A] Aggressive behavior

1) Incidence: 3% to 9% [1] [20]

2) Adults

a) Aggressive reactions were reported in 3% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

3) Pediatrics

a) Aggressive reactions were reported in 9% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 4% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.12.B] Anxiety

1) Incidence: adults, 5% to 6% [1] [20]

2) Adults

a) Anxiety was reported in 6% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 4% of patients on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial [1] [20].

b) Anxiety was reported in 5% of patients on [topiramate](#) 100 mg/day (n=386) compared with 3% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3.3.12.C] Depression

1) Summary

a) Psychiatric and behavioral disturbances such as depression and mood problems have been reported in adult patients taking [topiramate](#). Incidences were dose-related for both the [epilepsy](#) [1] [20] and migraine populations [20].

2) Incidence: 3% to 9% [1] [20]

3) Adults

a) Depression was reported in 9% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 7% of patients on immediate-release [topiramate](#) 50 mg/day (n=160), in a monotherapy [epilepsy](#) trial [1] [20].

b)) Depression was reported in 5% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) and 5% of patients on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [1] [20].

c)) Depression was reported in 4% of patients on [topiramate](#) 100 mg/day (n=386) and 4% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

4)) Pediatrics

a)) The incidence of depression was 3% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 0% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

3.3.12.D) Feeling nervous

1)) Incidence: 4% to 16% [1] [20]

2)) Adults

a)) Nervousness was reported in 16% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 6% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)). Nervousness was dose-related in the patient population with partial onset seizures in these studies, occurring at an incidence of 13% for [topiramate](#) 200 mg/day (n=45) and 18% for 400 mg/day (n=68) compared with 7% for placebo (n=216) [1] [20].

b)) Nervousness was reported in 4% of patients on [topiramate](#) 100 mg/day (n=386) compared with 2% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3)) Pediatrics

a)) Nervousness was reported in 5% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 4% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b)) Nervousness was reported in 14% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 7% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.12.E) Hallucinations

1)) Auditory hallucinations were associated with use of [topiramate](#) in a 28-year-old woman. The patient had a history of [schizoaffective disorder](#), bipolar type (DSM-IV), and during psychotic episodes, had experienced delusions and auditory hallucinations. She had been treated with [quetiapine](#) therapy (up to 500 mg at bedtime), and for several months had been free of psychotic symptoms. She also suffered from migraine headaches without aura. [Topiramate](#) 25 mg twice daily was introduced as prophylaxis for headache. After 2 days of [topiramate](#) therapy, she began to hear voices (voices from the center of the earth and the voice of Charles Manson). [Topiramate](#) was withdrawn. Two days later, she had returned to her baseline mental status [81].

3.3.12.F) Hyperactive behavior

1) Incidence: pediatrics, 5% [1] [20]

2) Pediatrics

a) Hyperkinesia was reported in 5% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 4% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.12.G] Mania

1) Severe manic symptoms developed in a 57-year-old woman with no previous history of psychiatric symptoms while receiving adjunctive [topiramate](#) (200 mg/day) therapy for the treatment of [epilepsy](#). Following discontinuation of [topiramate](#), the patient was treated with [haloperidol](#) (up to 40 mg/day) and intravenous [diazepam](#) (20 mg/day) and her extreme manic symptoms resolved within one day [82].

3.3.12.H] Mood disorder

1) Summary

a) Psychiatric and behavioral disturbances such as depression and mood problems have been reported in adult patients taking [topiramate](#). Incidences were dose-related for both the [epilepsy](#) [1] [20] and migraine populations [20].

2) Incidence: 4% to 11% [1] [20]

3) Adults

a) Mood problems were reported in 5% of adult patients on immediate-release [topiramate](#) 400 mg/day (n=159) compared with 2% on immediate-release [topiramate](#) 50 mg/day (n=160) in a monotherapy [epilepsy](#) trial [1] [20].

b) Mood problems were reported in 4% of adult patients on immediate-release [topiramate](#) 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for [epilepsy](#) (partial onset seizures, primary generalized tonic-clonic seizures, or [Lennox-Gastaut syndrome](#)) [20].

c) Mood problems have been reported in 6% of patients on [topiramate](#) 100 mg/day (n=386) compared with 2% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

4) Pediatrics

a) Mood problems were reported in 11% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 2% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

b) The incidence of problems with mood was 8% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

3.3.12.I] Panic attack

1) Panic attacks occurred in a 24-year-old woman with [bipolar disorder](#) when [topiramate](#) was added to her [lamotrigine](#) therapy. Initially she had been treated with [lithium](#) 1200 mg/day, but was switched to [lamotrigine](#) 100 mg/day due to a [relapse](#) of depression. [Lamotrigine](#) brought her out of the depression, but did not help her [binge-eating disorder](#) or her efforts to lose weight. Because of these latter effects, adjunctive [topiramate](#) 50 mg at bedtime was added to therapy. Within a week of beginning [topiramate](#),

she started waking up in the early morning hours feeling sudden and intense anxiety; attacks also occurred during the day. Manifestations included shortness of breath, increased heart rate, muscle tightness, and a flushing sensation. She reported having rare but similar attacks 8 years earlier. [Topiramate](#) was withdrawn and the attacks ceased after about 14 days ([lamotrigine](#) was continued). [Topiramate](#) was reintroduced a month later at 25 mg/day, and the panic attacks recurred. Again, the attacks disappeared when [topiramate](#) was stopped, while [lamotrigine](#) was continued [83].

3.3.12.J] Personality disorder

1) Incidence: pediatrics, 3% to 11% [1] [20]

2) Pediatrics

a) The incidence of personality disorder (behavior problems) was 3% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 0% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#) [20].

b) Personality disorder (behavior problems) was reported in 11% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 9% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.12.K] Psychotic disorder

1) In a retrospective chart review of 80 patients treated with [topiramate](#), five patients were found who developed psychotic symptoms 2 to 46 days after beginning therapy. Effects included auditory hallucinations (3 patients), [paranoid delusions](#) (4 patients), violent and hostile moods, confusion, fear, agitation, and bizarre thinking. Three patients improved when [topiramate](#) was discontinued, one with dose reduction, and the third received neuroleptics and [topiramate](#) was continued. Three of the patients had no history of psychiatric problems, one had a history of auditory hallucination, and another of aggressive and suicidal thoughts (Khan et al, 1999).

3.3.12.L] Suicidal thoughts

1) An increased risk of suicidal behavior or ideation may exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled clinical studies (monotherapy and adjunctive therapy) of 11 different AEDs used for several different indications such as [epilepsy](#), selected psychiatric illnesses, and other conditions. The analysis included 27,863 patients treated with AEDs and 16,029 patients who received placebo; patients were 5 years or older. There were 4 completed suicides among patients in the AED treatment groups compared with none in the placebo groups. Suicidal behavior or ideation occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebo groups, corresponding to an increase of about 1 case of suicidal thinking or behavior for every 530 patients treated. The increased risk of suicidality was noted at 1 week after starting an AED and continued to at least 24 weeks. Results were generally consistent among the drugs across a range of indications and among varying mechanisms of action and did not vary substantially by age (5 to 100 years). Closely monitor patients treated with AEDs for emergence or worsening of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior [1] [20].

3.3.13] Renal Effects

3.3.13.A] Nephrolithiasis

1) Summary

a) **Kidney stones** have been reported in patients treated with **topiramate**, an effect attributed to carbonic anhydrase inhibition. **Kidney stones** occurred more commonly in men. **Kidney stones** have been reported in pediatric patients also. **Topiramate** should be avoided in patients at greater risk of **kidney stone** formation including concomitant use of drugs producing **metabolic acidosis** or patients on a ketogenic diet [1] [20].

1) Adults

a) Kidney stones were reported in 1.3% of adult patients on topiramate (4 of 319 patients) during a double-blind monotherapy epilepsy study [1] [20].

b) Kidney stones were reported in 3% of adult patients on topiramate 400 mg/day (n=159) compared with 0% on 50 mg/day (n=160) in a monotherapy epilepsy trial [1] [20].

c) Kidney stones were reported in 1.5% of adult patients on topiramate (32 of 2086 patients) during adjunctive epilepsy therapy development [1] [20].

d) Kidney stones were reported in 1% of patients on topiramate 100 mg/day (n=386) compared with 0% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

2) Incidence: adults, 1% to 3% [1] [20]

3.3.15] Respiratory Effects

3.3.15.A] **Bronchitis**

1) Incidence: 3% to 7% [1] [20]

2) Adults

a) **Bronchitis** was reported in 4% of adult patients on **topiramate** 400 mg/day (n=159) compared with 3% of patients on 50 mg/day (n=160), in a monotherapy **epilepsy** trial [1] [20].

b) **Bronchitis** was reported in 3% of patients on **topiramate** 100 mg/day (n=386) compared with 2% on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) **Bronchitis** was reported in 7% of pediatric patients (ages 10 to 16 years) who received immediate-release **topiramate** 400 mg/day (n=57) compared with 2% on immediate-release **topiramate** 50 mg/day (n=57) in a monotherapy **epilepsy** trial [1].

b) The incidence of **bronchitis** was 5% in pediatric patients (age 6 to less than 16 years) who received monotherapy with **topiramate** 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of **epilepsy** [20].

3.3.15.B] **Pharyngitis**

1) Incidence: adults, 6% [1] [20]

2) Adults

a) **Pharyngitis** was reported in 6% of adult patients on immediate-release **topiramate** 200 to 400 mg/day (n=183) compared with 2% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for **epilepsy** (partial onset seizures, primary generalized tonic-clonic seizures, or **Lennox-Gastaut syndrome**) [1] [20].

b) **Pharyngitis** was reported in 6% of patients on **topiramate** 100 mg/day (n=386) compared with 4% of patients on placebo (n=445), in placebo-controlled, migraine trials [20].

3.3.15.C) **Pneumonia**

1) Incidence: pediatrics, 5% [1] [20]

2) Pediatrics

a) **Pneumonia** was reported in 5% of pediatric patients 2 to 16 years of age on **topiramate** (n=98) compared with 1% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.15.D) **Rhinitis**

1) Incidence: 2% to 7% [1] [20]

2) Adults

a) **Rhinitis** was reported in 4% of adult patients on **topiramate** 400 mg/day (n=159) compared with 2% on 50 mg/day (n=160), in a monotherapy **epilepsy** trial [1] [20].

b) **Rhinitis** was reported in 7% of adult patients on immediate-release **topiramate** 200 to 400 mg/day (n=183) compared with 6% on placebo (n=291), in randomized, double-blind, clinical trials of adjunctive therapy for **epilepsy** (partial onset seizures, primary generalized tonic-clonic seizures, or **Lennox-Gastaut syndrome**) [1] [20].

c) **Rhinitis** was reported in 2% of patients on **topiramate** 100 mg/day (n=386) compared with 1% on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) **Rhinitis** was reported in 7% of pediatric patients (ages 10 to 16 years) who received immediate-release **topiramate** 400 mg/day (n=57) compared with 2% on immediate-release **topiramate** 50 mg/day (n=57) in a monotherapy **epilepsy** trial [1].

b) The incidence of **rhinitis** was 6% in pediatric patients (age 6 to less than 16 years) who received monotherapy with **topiramate** 400 mg/day (n=77) and 5% in those who received 50 mg/day (n=74) for the treatment of **epilepsy** [20].

3.3.15.E) **Sinusitis**

1) Incidence: 4% to 6% [1] [20]

2) Adults

a) **Sinusitis** was reported in 5% of adult patients on immediate-release **topiramate** 200 to 400 mg/day (n=183) compared with 4% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for **epilepsy** (partial onset seizures, primary generalized tonic-clonic seizures, or **Lennox-Gastaut syndrome**) [1] [20].

b) **Sinusitis** was reported in 6% of patients on **topiramate** 100 mg/day (n=386) and 6% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) The incidence of **sinusitis** was 4% in pediatric patients (age 6 to less than 16 years) who received monotherapy with **topiramate** 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of **epilepsy** [20].

b) **Sinusitis** was reported in 5% of pediatric patients (ages 10 to 16 years) who received immediate-release **topiramate** 400 mg/day (n=57) compared with 2% on immediate release **topiramate** 50 mg/day (n=57) in a monotherapy **epilepsy** trial [1].

3.3.15.F] **Upper respiratory infection**

1) Incidence: 14% to 18% [1] [20]

2) Adults

a) **Upper respiratory tract infection** was reported in 14% of patients on **topiramate** 100 mg/day (n=386) compared with 12% on placebo (n=445), in placebo-controlled, migraine trials [20].

3) Pediatrics

a) **Upper respiratory tract infection** was reported in 18% of pediatric patients (ages 10 to 16 years) who received immediate-release **topiramate** 400 mg/day (n=57) compared with 16% on immediate-release **topiramate** 50 mg/day (n=57) in a monotherapy **epilepsy** trial [1].

b) The incidence of **upper respiratory tract infection** was 18% in pediatric patients (age 6 to less than 16 years) who received monotherapy with **topiramate** 400 mg/day (n=77) and 16% in those who received 50 mg/day (n=74) for the treatment of **epilepsy** [20].

3.3.16] **Other**

3.3.16.A] **Fatigue**

1) Incidence: 15% to 16% [1] [20]

2) Adults

a) Somnolence and fatigue were the adverse effects reported most frequently during clinical trials of **topiramate** for adjunctive **epilepsy**. [1] [20]. In the adjunctive **epilepsy** population, fatigue was dose-related and the incidence increased at dosages above 400 mg/day. In the monotherapy **epilepsy** population, the incidence of fatigue was 14% in patients who received 50 mg/day and in patients who received 400 mg/day. In the migraine population, fatigue was dose-related and more common in the titration phase [20].

b) Dose-related fatigue was reported in 9% of adult patients on immediate-release **topiramate** 50 mg/day and 15% for 400 mg/day in the monotherapy **epilepsy** population [1] [20]. Fatigue was one of the most common adverse reactions causing therapy discontinuation [20].

c) Fatigue was reported in 15% of adult patients on immediate-release **topiramate** 200 to 400 mg/day (n=183) compared with 13% of patients on placebo (n=291) in randomized, double-blind, clinical trials of adjunctive therapy for **epilepsy** (partial onset seizures, primary generalized tonic-clonic seizures, or **Lennox-Gastaut syndrome**) [1] [20].

d) Fatigue was reported in 15% of adult patients on [topiramate](#) 100 mg/day (n=386) compared with 11% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) Somnolence and fatigue were the most frequently reported neuropsychiatric events reported in pediatric patients on [topiramate](#) during an adjunctive therapy double-blind study [1] [20]. In the monotherapy trial, somnolence was one of the most frequently reported neuropsychiatric reactions in patients who received [topiramate](#) 50 mg/day and in those who received 400 mg/day [20].

b) Fatigue was reported in 16% of pediatric patients 2 to 16 years of age on immediate-release [topiramate](#) (n=98) compared with 5% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.3.16.B] Fever

1) Incidence: 1% to 12% [1] [20]

2) Adults

a) Fever was reported in 1% of adult patients on [topiramate](#) 100 mg/day (n=386) and 1% of patients on placebo (n=445) in placebo-controlled, migraine trials [20].

3) Pediatrics

a) The incidence of fever was 12% in pediatric patients (age 6 to less than 16 years) who received monotherapy with [topiramate](#) 400 mg/day (n=77) and 1% in those who received 50 mg/day (n=74) for the treatment of [epilepsy](#). Fever was one of the most common adverse reactions resulting in therapy discontinuation [20].

b) Fever was reported in 9% of pediatric patients (ages 10 to 16 years) who received immediate-release [topiramate](#) 400 mg/day (n=57) compared with 0% on immediate-release [topiramate](#) 50 mg/day (n=57) in a monotherapy [epilepsy](#) trial [1].

3.3.16.C] Traumatic injury

1) Incidence: pediatrics, 14% [1] [20]

2) Pediatrics

a) Injury was reported in 14% of pediatric patients 2 to 16 years of age on [topiramate](#) (n=98) compared with 13% of patients on placebo (n=101) in a randomized, double-blind clinical trial of adjunctive therapy for partial onset seizures, with or without secondarily generalized seizures [1] [20].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category D (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

2) Australian Drug Evaluation Committee's (ADEC) Category: B3

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown**4) Clinical Management**

a) **Topiramate** monotherapy increases the risk for **cleft lip** and/or **cleft palate** (oral clefts) in babies born to women who use the medication during the first trimester of pregnancy. **Metabolic acidosis** may occur with **topiramate** use during pregnancy, which may cause decreased fetal growth and oxygenation and fetal death. Monitoring for **metabolic acidosis** in the mother and newborn is recommended when **topiramate** is used during pregnancy. Pregnant patients with **metabolic acidosis** should be treated as in the nonpregnant state [17]. **Hypospadias** in male infants exposed to **topiramate** monotherapy or polytherapy has also been reported [147]. Alternative medications that have a lower risk for oral clefts and congenital anomalies should be considered for pregnant women with **epilepsy**, and **topiramate** should only be used during pregnancy if the drug is clearly needed. If a woman becomes pregnant while taking **topiramate**, she should be advised of the potential for fetal harm, and women of childbearing potential should use effective birth control [145]. The North American Antiepileptic Drug Pregnancy Registry has been established to evaluate safety outcomes of pregnant women who are receiving antiepileptic therapy. Patients or their healthcare providers are encouraged to enroll. To enroll, contact the registry at 1-888-233-2334. To find out more about the North American Drug Pregnancy Registry, go to <http://www.massgeneral.org/aed/> [17].

5) Literature Reports

a) A cohort study of children between the ages of 3 and 6 years 11 months (n=9) who were exposed in utero to **topiramate** showed evidence of increased long term deficits in motor and cognitive functioning compared with a control group of unexposed children (n=18). Of the 9 children exposed to **topiramate** (dosage range: 25 mg to 425 mg) in utero, all 9 were exposed during the first trimester and 6 were exposed throughout the duration of the pregnancy. Treatment in child development centers, including occupational, physical, or speech therapy, was required for 56% of **topiramate** exposed children compared with 11% of children in the control group. Motor function test scores (Beery, M-FUN, and Little DCDQ) were significantly lower among the exposed children (n=7) compared with children in the control group (n=14) in 5 out of 10 areas assessed (visual perception, motor control, general coordination, fine motor, gross motor); the mean test scores of **topiramate** exposed children were 92, 78.56, 20.71, 6.78, and 7.78 respectively, compared with 110.41, 101.47, 23.57, 9, and 10.72 for children in the control group. Testing showed evidence of significant behavioral differences between groups based on the Conners' rating scale. Mean test scores for the cognitive problems/inattention test and perfectionism test among exposed children were 51.25 and 52.88 respectively and 46.8 and 44.67 among unexposed children [143].

b) In an analysis of data collected by the Australian Pregnancy Register from 1999 through 2010 (n=1317), the incidence of fetal malformations that occurred with prenatal exposure to

antiepileptic (AED) drug therapy during the first trimester was similar among women who used new AEDs (lamotrigine, levetiracetam, or topiramate), women with epilepsy untreated with AEDs, and women who used traditional AEDs (carbamazepine, clonazepam, or phenytoin), with the exception of valproic acid. The incidence of fetal malformations was 12/231 (5.2%), 0/22 (0%), and 1/31 (3.2%) among patients treated with lamotrigine, levetiracetam, and topiramate monotherapy, respectively, compared with 19/301 (6.3%), 0/24 (0%), 1/35 (2.9%) and 35/215 (16.3%) among patients treated with carbamazepine, clonazepam, phenytoin, or valproate monotherapy, respectively. Fetal malformations were reported in 6/139 (5.2%) of patients who were not treated with AEDs for at least the first trimester [144].

c) Topiramate monotherapy increases the risk for cleft lip and/or cleft palate (oral clefts) in babies born to women who use the medication during the first trimester of pregnancy. Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry indicate the prevalence of oral clefts was 1.2% for infants whose mothers used topiramate compared with 0.39% to 0.46% for infants who were exposed to other antiepileptic drugs (AEDs) or 0.12% for infants of mothers without epilepsy. The relative risk of oral clefts was 9.6 for infants exposed to topiramate when compared to infants who were not exposed to AEDs in utero (95% confidence interval, 3.6 to 25.7). Similar data have been reported from the United Kingdom Epilepsy and Pregnancy Register, with oral clefts occurring in 3.2% of infants exposed to topiramate compared with 0.2% of infants from the background population, a 16-fold increase in risk with topiramate exposure [17] [145].

d) Although not studied in pregnancy, topiramate can cause metabolic acidosis, which has been reported to cause decreased fetal growth and oxygenation and fetal death and may affect the ability of the fetus to tolerate labor. If topiramate use is required during pregnancy, monitoring for metabolic acidosis in the mother and newborn is recommended due to the risk of fetal transfer of topiramate and transient metabolic acidosis following birth [17].

e) In a 10-year, prospective study of pregnancies in which mothers called a teratogen information service following topiramate exposure during the first trimester or longer (n=52) compared with a control group with no exposure to nonteratogenic agents (n=212), there were significant differences in gestational age at call, number of deliveries, median birth weight, and birth weight of term infants without multiple gestations. Median gestational week at time of call was significantly lower in the topiramate group compared to the control group (7 weeks vs 11 weeks; p value not given). Among pregnancies in the topiramate group, 41 (77.4%) resulted in live birth deliveries compared to 196 (92.5%) in the control group (p=0.001). Median birth weight was 2932 g for the topiramate group compared to 3300 g for the control group (p=0.024). The birth weight of term infants without multiple gestations was lower in the topiramate group (3084 g vs 3356 g; p=0.001). Spontaneous abortions occurred at a higher frequency in the topiramate group compared to the control group (11.3% vs 2.8%; p=0.017). However, the odds ratio for miscarriage adjusted for gestational age at call, maternal age, previous miscarriages, and smoking was 3.07 (95% confidence interval, 0.796 to 11.832). A regression analysis, performed to determine the cause of increased miscarriages, revealed that gestational age at contact was a significant predictor, but not treatment. Frequency of major anomalies was not significant between the groups. Two of 4 anomalies in the topiramate group were non-genetic (pulmonary artery stenosis with maternal topiramate exposure and fatal multiple brain cysts with neonatal seizures with maternal exposure to topiramate, valproic acid, and clonazepam) [146].

f) In a prospective, observational study of 203 pregnancies in which the mothers had received topiramate as monotherapy (n=70) or as part of an antiepileptic drug (AED) polytherapy regimen (n=133) during the first trimester, major congenital malformations (MCMs) were reported in 16

[topiramate](#) exposures. An MCM was defined as an anomaly of a vital embryonic structure present at birth or during the first 6 weeks of life requiring significant treatment. Of the 203 pregnancies, 178 (87.7%) resulted in a live birth. Abnormalities were observed in 31 of the 178 live births (17.4%; 95% confidence interval (CI), 12.5% to 23.7%). Of the 16 MCMs, 3 occurred with monotherapy (4.8%; 95% CI, 1.7 to 13.3%) and 13 with polytherapy (19.8%; CI, 13.6 to 28%). Four of the MCMs were oral [cleft palate](#) (2.2%; 95% CI, 5.6% to 14.1%), 3 were [cleft lip](#) plus [cleft palate](#), and 4 were [hypospadias](#) (5.1%; 95% CI, 0.2% to 10.1%), 2 of which were classified as major, among 78 live male births. High MCM rates were associated with [valproate](#) either as duotherapy with [topiramate](#) (n=12; 36.4%; 95% CI, 15.2% to 64.6%) or as part of a 3 or more AED regimen (n=23; 23.8%, 10.6% to 45.1%). Mean [topiramate](#) daily doses were not significantly different between those with or without MCMs for monotherapy or polytherapy exposure (p=0.123 and p=0.539, respectively). In the monotherapy and polytherapy groups, there were 6 (9.8%) and 17 (15.3%) infants born at 37 weeks or less, respectively, and 8 (14.3%) and 20 (19.4%) infants, respectively, that were small for gestational age. Among the 25 outcomes not resulting in live births, [spontaneous abortions](#) (6 monotherapy, 12 polytherapy), induced abortions (2 monotherapy, 3 polytherapy), and stillbirths (2 polytherapy) were reported [147].

g) In a preclinical trial involving eight exposed pregnancies, 5 fetuses were electively aborted and 3 normal infants resulted. In one case, reported only in abstract, an infant with multiple minor anomalies was born to a mother treated with [topiramate](#) monotherapy 700 mg twice daily throughout gestation. The infant girl was delivered by elective [cesarean section](#) at 40 weeks' gestation. At birth, anomalies noted included prenatal onset growth deficiency, generalized hirsutism, a [third fontanelle](#), short nose with anteverted nares, blunt distal phalanges and generalized blunting of the nails, with fifth nail [hypoplasia](#). This collection of defects is consistent with anomalies found in infants exposed to a number of different anticonvulsants prenatally [148].

B) Breastfeeding

1) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) In limited data of nursing infants (n=5), infant plasma [topiramate](#) levels were 10% to 20% of the maternal plasma levels; however, the effects of [topiramate](#) use in nursing infants are not known. Therefore, exercise caution when administering [topiramate](#) to a nursing woman [17].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] [Acetazolamide](#)

1) Interaction Effect: an increased risk of [nephrolithiasis](#)

2) Summary: [Topiramate](#) is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (ie, [acetazolamide](#)) promote [renal stone](#) formation. Concomitant use of carbonic anhydrase inhibitors and [topiramate](#) should be avoided as the combination may increase the risk of [renal stone](#) formation [18].

3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of carbonic anhydrase inhibitors and [topiramate](#) (ie, [acetazolamide](#)) should be avoided. The combination of carbonic anhydrase inhibitors and [topiramate](#) may increase the risk of [renal stone](#) formation [18].
- 7) Probable Mechanism: additive effects of carbonic anhydrase inhibition
- 8) Literature Reports

a) In a study of 15 patients with drug refractory [partial epilepsy](#) or [Lennox-Gastaut syndrome](#), subjects were placed on [topiramate](#) in addition to their previous antiepileptic drug regimens. One patient passed a [renal stone](#) during the study, which is consistent with the documented increased risk of [nephrolithiasis](#) [129].

3.5.1.B) [Amiodarone](#)

- 1) Interaction Effect: decreased exposure of [amiodarone](#)
- 2) Summary: The concomitant use of [amiodarone](#) (a CYP3A4 substrate) with a CYP3A inducer may decrease [amiodarone](#) exposure. Coadministration of [rifampin](#), a strong CYP3A inducer, has shown to decrease serum concentrations of [amiodarone](#) and its major active metabolite, desethylamiodarone [90]. Additional monitoring and [amiodarone](#) dose adjustment of [amiodarone](#) may be warranted when [amiodarone](#) is used concomitantly with CYP3A inducers.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [amiodarone](#) (a CYP3A4 substrate) with a CYP3A inducer may decrease [amiodarone](#) exposure [90]. Additional monitoring and [amiodarone](#) dose adjustment may be warranted.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of [amiodarone](#)

3.5.1.C) [Amitriptyline](#)

- 1) Interaction Effect: increased [amitriptyline](#) exposure
- 2) Summary: Compared with [topiramate](#) alone, the concurrent administration of [amitriptyline](#) (25 mg/day) and [topiramate](#) (200 mg/day) in 18 normal subjects resulted in increases of 12% in both the steady-state maximum concentration and area under the concentration-time curve of [amitriptyline](#). If [amitriptyline](#) and [topiramate](#) are co-administered, adjusting the [amitriptyline](#) dose based on the patient's clinical response may be necessary [18].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [amitriptyline](#) and [topiramate](#) may increase plasma concentrations of [amitriptyline](#). If [amitriptyline](#) and [topiramate](#) are co-administered, adjust [amitriptyline](#) dose as necessary based on the patient's clinical response, and monitor for increased [amitriptyline](#) adverse effects [18].
- 7) Probable Mechanism: unknown

3.5.1.D) [Carbamazepine](#)

- 1) Interaction Effect: decreased [topiramate](#) concentrations
- 2) Summary: In controlled, clinical [pharmacokinetic studies](#), patients with [epilepsy](#) showed a 40% decrease in [topiramate](#) concentrations when [carbamazepine](#) was added to [topiramate](#) therapy [18]. [Topiramate](#)

oral and nonrenal clearance is twofold to threefold higher during concurrent [carbamazepine](#) therapy. The renal clearance of [topiramate](#), however, is not affected by concomitant [carbamazepine](#) therapy. No significant changes in [carbamazepine](#) pharmacokinetic parameters were evident upon coadministration with [topiramate](#) [126]. In another study, addition of [topiramate](#) to existing [carbamazepine](#) regimens in epileptic patients resulted in no significant pharmacokinetic changes in either drug [127].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Upon the addition of [carbamazepine](#) to a drug regimen involving [topiramate](#), the dose of [topiramate](#) may need to be increased to accommodate for the decreased concentration of [topiramate](#) that occurs with concomitant therapy [18].

7) Probable Mechanism: unknown

8) Literature Reports

a) Twelve patients with [partial epilepsy](#) receiving chronic stable doses of [carbamazepine](#) were enrolled in a study to determine the steady-state pharmacokinetic profile of [topiramate](#) and the effects of comedication with [carbamazepine](#). All subjects were receiving [carbamazepine](#) in doses of 300 mg to 800 mg every eight hours. [Topiramate](#) was added and doses were increased at approximately two week intervals until the highest tolerated dose was reached. [Carbamazepine](#) was then tapered off over the next four weeks, and [topiramate](#) was maintained as monotherapy for two more weeks. Results showed that the mean [topiramate](#) area under the concentration-time curve (AUC), C_{max}, C_{min}, and C_{avg} values were all approximately 40% lower during [carbamazepine](#) treatment as compared to [topiramate](#) monotherapy. These results suggest that the metabolic clearance of [topiramate](#) increases when [carbamazepine](#) is coadministered. There were no significant changes in the [carbamazepine](#) pharmacokinetic profile during [topiramate](#) administration [124].

b) The interaction between [carbamazepine](#) and [topiramate](#) was assessed in eight epileptic patients. Pharmacokinetic profiles were evaluated after a single dose of [topiramate](#), after two weeks at three different doses of [topiramate](#), and after each subject had taken [topiramate](#) at its highest tolerated dose for two months. No significant changes in [topiramate](#), [carbamazepine](#), or [carbamazepine](#) metabolite pharmacokinetics were observed at any dose level [125].

3.5.1.E] [Carbinoxamine](#)

1) Interaction Effect: additive CNS effects

2) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects [101] [102]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [carbinoxamine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may have additive effects and is therefore not recommended [101] [102]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.

7) Probable Mechanism: additive effects on the CNS

3.5.1.F] [Citalopram](#)

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation
- 2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [topiramate](#) (a mild CYP2C19 inhibitor) [17] has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [topiramate](#) is required, do not exceed [citalopram](#) doses of 20 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds (ms) [140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with [topiramate](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) (a CYP2C19 substrate) with [topiramate](#) (a mild CYP2C19 inhibitor) is required [17], do not exceed [citalopram](#) doses of 20 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds (ms) [140].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [topiramate](#)

3.5.1.G] Clozapine

- 1) Interaction Effect: reduced [clozapine](#) exposure and reduced efficacy
- 2) Summary: Reduced [clozapine](#) plasma concentrations may occur when [clozapine](#), a CYP1A2 and CYP3A4 substrate, is administered concomitantly with drugs that are moderate or weak CYP1A2 or CYP3A4 inducers. Use caution, monitor for decreased [clozapine](#) effectiveness, and consider increasing the [clozapine](#) dose during concurrent therapy. When weak CYP1A2 or CYP3A4 inducers are discontinued, monitor for [clozapine](#) adverse reactions and consider a [clozapine](#) dose reduction [98].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution and monitor for decreased [clozapine](#) effectiveness during concurrent use of [clozapine](#) and moderate or weak CYP1A2 or CYP3A4 inducers. Consider increasing the [clozapine](#) dose during concurrent use. When weak CYP1A2 or CYP3A4 inducers are discontinued, monitor for [clozapine](#) adverse reactions and reduce the [clozapine](#) dose, if necessary [98].
- 7) Probable Mechanism: induction of CYP1A2- or CYP3A4-mediated metabolism of [clozapine](#)

3.5.1.H] Cobicistat

- 1) Interaction Effect: decreased cobicistat exposure
- 2) Summary: Cobicistat is metabolized by CYP3A. Caution is advised when using cobicistat together with a CYP3A inducer as this may cause decreased plasma concentrations of cobicistat resulting in a loss of therapeutic effect and the development of viral resistance [128]. If concomitant use is required, consider monitoring HIV virologic response.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised when using cobicistat together with a CYP3A inducer as this may cause decreased plasma concentrations of cobicistat resulting in a loss of therapeutic effect and the development of viral resistance [128]. If concomitant use is required, consider monitoring HIV virologic response.

7J) Probable Mechanism: induction of CYP3A-mediated cobicistat metabolism

3.5.1.1J) **Desogestrel**

1J) Interaction Effect: reduced contraceptive efficacy

2J) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) ([Ortho-Novum\(R\)](#) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

bJ) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and oral contraception with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200

mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.J] [Dichlorphenamide](#)

- 1J) Interaction Effect: an increased risk of [nephrolithiasis](#)
- 2J) Summary: [Topiramate](#) is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (ie, [dichlorphenamide](#)) promote [renal stone](#) formation. Concomitant use of carbonic anhydrase inhibitors and [topiramate](#) should be avoided as the combination may increase the risk of [renal stone](#) formation [18].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of carbonic anhydrase inhibitors and [topiramate](#) (ie, [dichlorphenamide](#)) should be avoided. The combination of carbonic anhydrase inhibitors and [topiramate](#) may increase the risk of [renal stone](#) formation [18].
- 7J) Probable Mechanism: additive effects of carbonic anhydrase inhibition
- 8J) Literature Reports

aJ) In a study of 15 patients with drug refractory [partial epilepsy](#) or [Lennox-Gastaut syndrome](#), subjects were placed on [topiramate](#) in addition to their previous antiepileptic drug regimens. One patient passed a [renal stone](#) during the study, which is consistent with the documented increased risk of [nephrolithiasis](#) [141].

3.5.1.K] [Dienogest](#)

- 1J) Interaction Effect: reduced contraceptive efficacy
- 2J) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].
- 7J) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.L] [Dorzolamide](#)

1) Interaction Effect: an increased risk of [nephrolithiasis](#)

2) Summary: [Topiramate](#) is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (ie, [dorzolamide](#)) promote [renal stone](#) formation. Concomitant use of carbonic anhydrase inhibitors and [topiramate](#) should be avoided as the combination may increase the risk of [renal stone](#) formation [18].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of carbonic anhydrase inhibitors and [topiramate](#) (ie, [dorzolamide](#)) should be avoided. The combination of carbonic anhydrase inhibitors and [topiramate](#) may increase the risk of [renal stone](#) formation [18].

7) Probable Mechanism: additive effects of carbonic anhydrase inhibition

8) Literature Reports

a) In a study of 15 patients with drug refractory [partial epilepsy](#) or [Lennox-Gastaut syndrome](#), subjects were placed on [topiramate](#) in addition to their previous antiepileptic drug regimens. One patient passed a [renal stone](#) during the study, which is consistent with the documented increased risk of [nephrolithiasis](#) [85].

3.5.1.M] [Drospirenone](#)

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.N] Estradiol Cypionate

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle)

and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.O] [Estradiol Valerate](#)

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) ([Ortho-Novum\(R\)](#) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and oral contraception with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the

addition of **topiramate** did not change the **norethindrone** pharmacokinetic parameters, the mean AUC of **ethinyl estradiol** was decreased by 18%, 21%, and 30% with daily **topiramate** doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of **ethinyl estradiol** was 14.7% to 33% higher. It is suggested that the modest effect of **topiramate** on **ethinyl estradiol** pharmacokinetics may be due to **topiramate** being a weak inducer of cytochrome P450 [123].

3.5.1.P] Ethinyl Estradiol

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of **ethinyl estradiol/norethindrone** with **topiramate** 50 to 200 mg/day (n=45) did not significantly change the AUC of **ethinyl estradiol** or the AUC or plasma levels of **norethindrone** [122]. However, in another study (n=12), coadministration of **topiramate** with **ethinyl estradiol/norethindrone** decreased the mean **ethinyl estradiol** AUC by 18% to 30% with daily **topiramate** doses of 200 mg to 800 mg [123]. **Topiramate** is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as **topiramate**, with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using **topiramate** as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of **topiramate** and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if **topiramate** is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking **topiramate** concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of **topiramate** with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that **topiramate** doses less than or equal to 200 mg/day do not interact with oral contraceptives containing **ethinyl estradiol** and **norethindrone**. In two 28-day cycles, 5 groups of female subjects received oral doses of **ethinyl estradiol/norethindrone** (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with **topiramate** or **carbamazepine** during the second cycle. Coadministration of daily **topiramate** in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; **topiramate** 200 mg) women resulted in nonsignificant changes in the AUC of **ethinyl estradiol** and nonsignificant changes in the AUC and plasma concentrations of **norethindrone** compared with the contraceptive alone (p greater than 0.05). When **carbamazepine** 600 mg/day was coadministered with **ethinyl estradiol/norethindrone** (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). **Carbamazepine** increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with **epilepsy** who were receiving stable **valproic acid** monotherapy and **oral contraception** with **ethinyl estradiol** 35 mcg/**norethindrone** 1 mg (21 days on/7 days

off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.Q] [Ethinodiol Diacetate](#)

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) ([Ortho-Novum\(R\)](#) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b)) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.R] [Etonogestrel](#)

1)) Interaction Effect: reduced contraceptive efficacy

2)) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) ([Ortho-Novum\(R\)](#) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day

was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b)) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.S] Evening Primrose

- 1)) Interaction Effect: reduced anticonvulsant effectiveness
- 2)) Summary: Evening primrose oil contains gamma-linolenic acid (GLA), which may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [87]. Evening primrose oil is contraindicated in patients with [epilepsy](#) [88] [89].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants. Evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [87].
- 7)) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.T] Fentanyl

- 1)) Interaction Effect: increased risk of CNS depression
- 2)) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death [112]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [113]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [112].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents [112].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.U] Fosphenytoin

- 1) Interaction Effect: altered [phenytoin](#) or [topiramate](#) concentrations
- 2) Summary: Controlled, clinical [pharmacokinetic studies](#) in some patients with [epilepsy](#) showed a 25% increase in the concentration of [phenytoin](#) when [topiramate](#) was added. This increase was seen mostly in patients taking [phenytoin](#) twice daily. However, when [topiramate](#) was given alone, the concentration of [topiramate](#) decreased by 48% when [phenytoin](#) was added [18]. The enhanced clearance of [topiramate](#) is most likely a result of phenytoin-induced enzyme induction [115]. In two controlled studies involving a total of nine epileptic patients already receiving [phenytoin](#), the addition of [topiramate](#) did not significantly change the serum concentration of [phenytoin](#) or the trough [phenytoin](#) plasma concentration [116] [117].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Upon the coadministration of [phenytoin](#) and [topiramate](#), dosing adjustments may be required for either or both drugs. Consider monitoring patients for seizure control and excessive adverse effects [18].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a controlled study, interactions with [topiramate](#) were assessed in six epileptic patients already taking [phenytoin](#) and three epileptic patients already taking [valproic acid](#). The patients were given [topiramate](#) 100 mg every morning, which was increased to the maximum tolerated dose (no greater than 1200 mg per day). Plasma concentration-time profiles were then observed over the next eight weeks. No apparent changes were observed in [phenytoin](#) or [valproic acid](#) area under the concentration-time curve (AUC) profiles or trough plasma concentrations [114].

3.5.1.V] Ginkgo

- 1) Interaction Effect: decreased anticonvulsant effectiveness
- 2) Summary: In a case report, 2 patients with [epilepsy](#) previously well controlled by [valproate](#) sodium developed a recurrence of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn [108]. An infant developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds [109]. The compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as in leaves, the ginkgo component from which commercially available extracts are derived [110]. The majority of ginkgo leaf products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly assayed to assure that 4'-O-methylpyridoxine is not contained in the commercial product. Of concern are those instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known seizure disorders).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with [epilepsy](#). If seizures occur for the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of ginkgo seed or leaf extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxine is present.
- 7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may cause seizures
- 8) Literature Reports

a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridoxine levels. The serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible for the tonic/clonic convulsions and loss of consciousness observed. They further observed that infants are particularly vulnerable [105].

b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of Ginkgo biloba leaves which is the source of commercially-available products. Highest amounts were found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was detected in medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested [106].

c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without changing anticonvulsant therapy) after discontinuing Gb [107].

3.5.1.W) Hydrochlorothiazide

1) Interaction Effect: increased topiramate exposure

2) Summary: Compared with topiramate alone, the concurrent administration of hydrochlorothiazide (25 milligrams (mg) every 24 hours) and topiramate (96 mg every 12 hours) in healthy volunteers resulted in increases of 27% and 29% in topiramate steady-state maximum concentration (C_{max}) and area under the concentration-time curve (AUC), respectively. In addition, serum potassium levels decreased to a greater extent with the combination of hydrochlorothiazide and topiramate than with either agent alone. However, the steady-state pharmacokinetics of hydrochlorothiazide were not significantly altered by concurrent administration of topiramate. If hydrochlorothiazide is added to topiramate therapy, adjusting the topiramate dose may be necessary. Patients may need to be monitored for increased topiramate adverse effects and decreased serum potassium levels [18].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of hydrochlorothiazide and topiramate may decrease serum potassium levels and increase plasma concentrations of topiramate. If hydrochlorothiazide is added to

[topiramate](#) therapy, adjust [topiramate](#) dose as necessary and monitor for increased [topiramate](#) adverse effects [18].

7J) Probable Mechanism: unknown

3.5.1.X] [Hydrocodone](#)

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension [138].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension [138].

7J) Probable Mechanism: additive effects on the CNS

3.5.1.Y] [Ketorolac](#)

1J) Interaction Effect: reduced anticonvulsant effectiveness

2J) Summary: The concomitant use of ketorolac and an anticonvulsant (such as [phenytoin](#) or [carbamazepine](#)) may cause an increased risk of seizures. Sporadic cases of seizures have been reported in patients who received ketorolac together with an antiepileptic drug [86].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing ketorolac to patients who take anticonvulsants. The concomitant use of ketorolac and an anticonvulsant (such as [phenytoin](#) or [carbamazepine](#)) may cause an increased risk of seizures [86].

7J) Probable Mechanism: unknown

3.5.1.Z] [Levonorgestrel](#)

1J) Interaction Effect: reduced contraceptive efficacy

2J) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3J) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.AA] [Medroxyprogesterone Acetate](#)

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended

pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.AB] [Mestranol](#)

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration

of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.AC] [Metformin](#)

1) Interaction Effect: additive risk of [metabolic acidosis](#)

2) Summary: [Topiramate](#), a carbonic anhydrase inhibitor, may decrease [sodium bicarbonate](#) levels and cause [metabolic acidosis](#) [130]. In healthy volunteers, coadministration of [metformin](#) 500 mg/day and

topiramate 100 mg/day resulted in **metformin** AUC and Cmax increases of 25% and 17%, respectively, compared with **metformin** monotherapy [1] [130]. Oral plasma clearance of **topiramate** also occurred with **metformin** coadministration, with unknown clinical significance [1] [131]. Use of **metformin** is contraindicated in the presence of **metabolic acidosis**. Accordingly, coadministration of **metformin** and **topiramate** is contraindicated [1].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of **metformin** and **topiramate** is contraindicated. **Topiramate** therapy can frequently cause **metabolic acidosis**, a condition for which **metformin** is contraindicated [1].

7) Probable Mechanism: unknown

8) Literature Reports

a) Compared with healthy volunteers administered **metformin** monotherapy, coadministration of **metformin** 500 mg every 12 hours and **topiramate** 100 mg every 12 hours in healthy volunteers resulted in **metformin** AUC and Cmax increases of 25% and 17%, respectively [1] [130]; **metformin** Tmax was not affected. Oral plasma clearance of **topiramate** was decreased with **metformin** coadministration, with unknown clinical significance [1] [131].

3.5.1.AD] **Methazolamide**

1) Interaction Effect: an increased risk of **nephrolithiasis**

2) Summary: **Topiramate** is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (ie, **methazolamide**) promote **renal stone** formation. Concomitant use of carbonic anhydrase inhibitors and **topiramate** should be avoided as the combination may increase the risk of **renal stone** formation [18].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of carbonic anhydrase inhibitors (ie **methazolamide**) and **topiramate** should be avoided. The combination of carbonic anhydrase inhibitors and **topiramate** may increase the risk of **renal stone** formation [18].

7) Probable Mechanism: additive effects of carbonic anhydrase inhibition

8) Literature Reports

a) In a study of 15 patients with drug refractory **partial epilepsy** or **Lennox-Gastaut syndrome**, subjects were placed on **topiramate** in addition to their previous antiepileptic drug regimens. One patient passed a **renal stone** during the study, which is consistent with the documented increased risk of **nephrolithiasis** [99].

3.5.1.AE] **Nifedipine**

1) Interaction Effect: decreased **nifedipine** exposure

2) Summary: **Nifedipine** is metabolized by CYP3A4. Concomitant administration of **nifedipine** and CYP3A4 inducers reduced the AUC and Cmax of **nifedipine** by approximately 70%. Using **nifedipine** together with any known CYP3A4 inducer may significantly reduce the effectiveness of **nifedipine**, and should be avoided. Alternate antihypertensive treatment should be considered [91] [92]. Case reports and studies suggest concomitant administration of **nifedipine** and CYP3A4 inducers may result in reduced effectiveness of **nifedipine** [93] [94] [97] [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6j) Clinical Management: Coadministration of [nifedipine](#) and CYP3A4 inducers may significantly reduce the effectiveness of [nifedipine](#). Avoid concomitant use of [nifedipine](#) and any known CYP3A4 inducer. Alternate antihypertensive treatment should be considered [91] [92].

7j) Probable Mechanism: induction of CYP3A4-mediated [nifedipine](#) metabolism

8j) Literature Reports

a) St John's wort, a CYP3A4 inducer, reduced the mean plasma concentration of [nifedipine](#), a CYP3A4 substrate, by 53% at 30 minutes in an open trial of 22 healthy subjects. Subjects received oral St John's wort 900 mg/day for 18 days and then received a single oral dose of [nifedipine](#) 10 mg. The mean plasma concentration of [nifedipine](#) at 30 minutes was reduced by 53% compared with [nifedipine](#) alone (statistical significance not stated) [93].

b) A 75-year-old hypertensive woman had been well controlled with [nifedipine](#), a CYP3A4 substrate. After she developed [tuberculosis](#) and was treated with [rifampin](#), a CYP3A4 inducer, both peak plasma concentration and AUC of [nifedipine](#) decreased to about 40% of previous levels; control of the [hypertension](#) was significantly affected. Another [calcium](#) channel blocker, [nisoldipine](#), was administered concurrently with [rifampin](#), but it also was unable to lower her blood pressure [94].

c) Eight healthy subjects were administered [nifedipine](#), a CYP3A4 substrate, sparteine, and [phenytoin](#), a CYP3A4 inducer, separately and as a "cocktail" on separate occasions. There were no significant differences in clearance of any of the substrates after separate or "cocktail" administration [95].

d) Concomitant administration of [nifedipine](#), a CYP3A4 substrate, and [rifampin](#), a CYP3A4 inducer, resulted in exacerbation of [variant angina](#) in one case, presumably due to enhanced [nifedipine](#) elimination from rifampin-induced enzyme induction [96].

3.5.1.AF] [Norelgestromin](#)

1j) Interaction Effect: reduced contraceptive efficacy

2j) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3j) Severity: moderate

4j) Onset: delayed

5j) Substantiation: probable

6j) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid

the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.AG] [Norethindrone](#)

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-

only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7) Probable Mechanism: unknown

8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.AH] Norgestimate

1) Interaction Effect: reduced contraceptive efficacy

2) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6j) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].

7j) Probable Mechanism: unknown

8j) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.Aj) [Norgestrel](#)

1j) Interaction Effect: reduced contraceptive efficacy

2j) Summary: Coadministration of [ethinyl estradiol/norethindrone](#) with [topiramate](#) 50 to 200 mg/day (n=45) did not significantly change the AUC of [ethinyl estradiol](#) or the AUC or plasma levels of [norethindrone](#) [122]. However, in another study (n=12), coadministration of [topiramate](#) with [ethinyl estradiol/norethindrone](#) decreased the mean [ethinyl estradiol](#) AUC by 18% to 30% with daily [topiramate](#) doses of 200 mg to 800 mg [123]. [Topiramate](#) is a mild inducer of CYP3A4 [20]. Coadministration of CYP3A4 inducers, such as [topiramate](#), with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method if using [topiramate](#) as long-term therapy [118] [119] [120].

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [topiramate](#) and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if [topiramate](#) is used concomitantly with estrogen-containing contraceptives [20]. In women who are taking [topiramate](#) concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [118] [119] [120]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of [topiramate](#) with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [121].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that [topiramate](#) doses less than or equal to 200 mg/day do not interact with oral contraceptives containing [ethinyl estradiol](#) and [norethindrone](#). In two 28-day cycles, 5 groups of female subjects received oral doses of [ethinyl estradiol/norethindrone](#) (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with [topiramate](#) or [carbamazepine](#) during the second cycle. Coadministration of daily [topiramate](#) in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; [topiramate](#) 200 mg) women resulted in nonsignificant changes in the AUC of [ethinyl estradiol](#) and nonsignificant changes in the AUC and plasma concentrations of [norethindrone](#) compared with the contraceptive alone (p greater than 0.05). When [carbamazepine](#) 600 mg/day was coadministered with [ethinyl estradiol/norethindrone](#) (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively (p less than 0.05). [Carbamazepine](#) increased oral clearance in both contraceptives by 127% and 69%, respectively (p less than 0.05) [122].

b) In a study of 12 women with [epilepsy](#) who were receiving stable [valproic acid](#) monotherapy and [oral contraception](#) with [ethinyl estradiol](#) 35 mcg/[norethindrone](#) 1 mg (21 days on/7 days off), the coadministration of [topiramate](#) (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to [ethinyl estradiol](#). Starting on the first 3 days of cycle 2 through cycle 4, [topiramate](#) 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of [topiramate](#) did not change the [norethindrone](#) pharmacokinetic parameters, the mean AUC of [ethinyl estradiol](#) was decreased by 18%, 21%, and 30% with daily [topiramate](#) doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of [ethinyl estradiol](#) was 14.7% to 33% higher. It is suggested that the modest effect of [topiramate](#) on [ethinyl estradiol](#) pharmacokinetics may be due to [topiramate](#) being a weak inducer of cytochrome P450 [123].

3.5.1.AJ] [Orlistat](#)

- 1) Interaction Effect: [orlistat](#) may reduce anticonvulsant efficacy
- 2) Summary: Concomitant use of [orlistat](#) with [anticonvulsant therapy](#) has resulted in reports of convulsions during postmarketing surveillance of [orlistat](#). Therefore, if coadministration is necessary, monitor patients for changes in the frequency and severity of their seizures [84].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable

6) Clinical Management: Concomitant use of [orlistat](#) with an anticonvulsant may result in reduced efficacy of the anticonvulsant. If coadministration is necessary, monitor patients for changes in the frequency and severity of their seizures [84].

7) Probable Mechanism: unknown

3.5.1.AK] [Phenobarbital](#)

1) Interaction Effect: a decrease in serum concentrations of [topiramate](#)

2) Summary: Concurrent use of [topiramate](#) and [phenobarbital](#) may result in a shorter half-life and a higher total clearance of [topiramate](#) [104]. Coadministered [phenobarbital](#) and [topiramate](#) resulted in a less than 10% change in the plasma concentration of [phenobarbital](#). The pharmacokinetics of [topiramate](#) were not evaluated [18].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Dosage adjustments of [topiramate](#) are usually necessary during addition or discontinuation of enzyme-inducing antiepileptic drugs.

7) Probable Mechanism: unknown

8) Literature Reports

a) When concomitantly administered with enzyme-inducing antiepileptic drugs, such as [phenobarbital](#), the proportion of [topiramate](#) metabolized by the liver increases resulting in a shorter half-life and a higher total clearance [103].

3.5.1.AL] [Phenytoin](#)

1) Interaction Effect: altered [phenytoin](#) or [topiramate](#) concentrations

2) Summary: Controlled, clinical [pharmacokinetic studies](#) in some patients with [epilepsy](#) showed a 25% increase in the concentration of [phenytoin](#) when [topiramate](#) was added. This increase was seen mostly in patients taking [phenytoin](#) twice daily. However, when [topiramate](#) was given alone, the concentration of [topiramate](#) decreased by 48% when [phenytoin](#) was added [18]. The enhanced clearance of [topiramate](#) is most likely a result of phenytoin-induced enzyme induction [115]. In two controlled studies involving a total of nine epileptic patients already receiving [phenytoin](#), the addition of [topiramate](#) did not significantly change the serum concentration of [phenytoin](#) or the trough [phenytoin](#) plasma concentration [116] [117].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Upon the coadministration of [phenytoin](#) and [topiramate](#), dosing adjustments may be required for either or both drugs. Consider monitoring patients for seizure control and excessive adverse effects [18].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a controlled study, interactions with [topiramate](#) were assessed in six epileptic patients already taking [phenytoin](#) and three epileptic patients already taking [valproic acid](#). The patients were given [topiramate](#) 100 mg every morning, which was increased to the maximum tolerated dose (no greater than 1200 mg per day). Plasma concentration-time profiles were then observed over the next eight weeks. No apparent changes were observed in [phenytoin](#) or [valproic acid](#) area under the concentration-time curve (AUC) profiles or trough plasma concentrations [114].

3.5.1.AM] Pioglitazone

- 1) Interaction Effect: decreased pioglitazone exposure
- 2) Summary: The concurrent administration of pioglitazone and topiramate in healthy subjects resulted in a 15% decrease in the steady-state area under the concentration-time curve (AUC) of pioglitazone but no change in the steady-state maximum concentration (C_{max}). Additionally, there was a 13% and 16% decrease in C_{max} and AUC, respectively for the active hydroxy-metabolite, and a 60% decrease in C_{max} and AUC for the active keto-metabolite of pioglitazone. Although the clinical significance of these results is unknown, if pioglitazone and topiramate are administered concurrently, routinely monitor patients for adequate control of their diabetic state [18].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If topiramate and pioglitazone are administered concurrently, routinely monitor patients for adequate control of their diabetes [18].
- 7) Probable Mechanism: unknown

3.5.1.AN] Piperaquine

- 1) Interaction Effect: decreased exposure of piperaquine
- 2) Summary: The concomitant use of piperaquine (a CYP3A4 substrate) with a CYP3A4 inducer may decrease piperaquine exposure and is not recommended [111].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of piperaquine (a CYP3A4 substrate) with a CYP3A4 inducer may decrease piperaquine exposure and is not recommended [111].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of piperaquine

3.5.1.AO] Posaconazole

- 1) Interaction Effect: elevated topiramate plasma concentrations and topiramate toxicity
- 2) Summary: Use caution when posaconazole is coadministered with topiramate. A case report described probable posaconazole-induced topiramate in a 48-year-old male [139]. Monitor the patient for increased topiramate adverse events (anorexia, somnolence, stupor).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when posaconazole is coadministered with topiramate as this may result in increased topiramate plasma concentrations, leading to excessive toxicity. Monitor the patient for increased topiramate adverse events (anorexia, somnolence, stupor).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A case was reported of a 48-year-old male who experienced probable posaconazole-induced topiramate toxicity. Following pneumectomy for invasive aspergillosis, the patient had been initiated on posaconazole at hospital discharge. Two weeks after discharge, he presented with 10 days of progressive stupor, daytime somnolence, anorexia, decreased oral intake, weight loss, and a "catatonic state". Past medical history was significant for long-standing epilepsy, stabilized with valproic acid and topiramate, and hemiglossectomy for lingual squamous cell

carcinoma. Medications on admission were [topiramate](#) (100 mg twice daily), [valproate](#) (700 mg twice daily); [posaconazole](#) (200 mg four times daily) was discontinued 2 days prior to admission based on clinical discussion. The [topiramate](#) plasma level on admission was 27.34 micromol/L, which was highly elevated for the patient's dose (pharmacokinetic modeling suggests a peak plasma concentration of 5 micromol/L may be expected for a 100-mg dose). Eleven days after discontinuing [posaconazole](#), the [topiramate](#) level had decreased to 11.51 micromol/L, which coincided with symptom resolution. [Valproate](#) levels were normal throughout hospital stay. The patient's stupor and appetite improved slowly over 10 days, and he was discharged 3 weeks after admission. The patient received [amphotericin B](#), followed by [voriconazole](#), and completed antifungal treatment without further incident [139].

3.5.1.AP| Ulipristal Acetate

- 1) Interaction Effect: decreased ulipristal acetate plasma concentrations
- 2) Summary: Studies to evaluate drug interactions with ulipristal acetate have not been performed. Because ulipristal acetate is metabolized by CYP3A4, concomitant use of [topiramate](#), a CYP3A4 inducer, and ulipristal acetate may result in decreased plasma concentrations of ulipristal acetate, thereby decreasing its effectiveness [100].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [topiramate](#) and ulipristal acetate may result in decreased plasma concentrations of ulipristal acetate which may reduce its effectiveness [100].
- 7) Probable Mechanism: induction of CYP3A4-mediated ulipristal acetate metabolism by [topiramate](#)

3.5.1.AQ| Valproic Acid

- 1) Interaction Effect: decreased [topiramate](#) or [valproic acid](#) concentrations and increased risk of [hyperammonemia](#), [encephalopathy](#), and [hypothermia](#)
- 2) Summary: Controlled, clinical [pharmacokinetic studies](#) in patients with [epilepsy](#) showed an 11% decrease in the concentration of [valproic acid](#) when [topiramate](#) was added. However, when [topiramate](#) was given alone, the concentration of [topiramate](#) decreased by 14% when [valproic acid](#) was added [17]. In two controlled studies involving a total of seven epileptic patients already receiving [valproic acid](#), the addition of [topiramate](#) did not significantly change the serum concentration of [valproic acid](#) or [valproic acid](#) trough concentrations [135] [136]. The coadministration of [valproic acid](#) and [topiramate](#) has also been implicated in the development of [hyperammonemic encephalopathy](#) [137]. As described in a series of case reports, stuporous [encephalopathy](#) developed in 5 patients with drug-resistant [epilepsy](#), shortly after beginning a combination anticonvulsant regimen comprising [topiramate](#) and [valproic acid](#). Symptoms largely resolved after either drug was reduced in dose or completely withdrawn [133]. Although not studied, concomitant use of [topiramate](#) and [valproic acid](#) may exacerbate existing defects or unmask deficiencies in susceptible patients. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for [hyperammonemia](#) with or without [encephalopathy](#) and [hypothermia](#) (with or without [hyperammonemia](#)). If concomitant use of [topiramate](#) with [valproic acid](#) is required, monitor for [hyperammonemia](#), [encephalopathy](#), and [hypothermia](#). Assessment of plasma ammonia levels and discontinuation of either drug may be warranted [17].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [topiramate](#) and [valproic acid](#) may result in [hyperammonemia](#), [encephalopathy](#), and [hypothermia](#). It may also result in decreased plasma

concentrations of one or both drugs. Upon the coadministration of [topiramate](#) and [valproic acid](#), dosing adjustments may be required for either or both drugs. Consider monitoring patients for seizure control and excessive adverse effects. Assess blood ammonia levels if patient develops [hypothermia](#); if confirmed, discontinuation of [topiramate](#) or [valproic acid](#) may be warranted [17].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a controlled study, interactions with [topiramate](#) were assessed in six epileptic patients already taking [phenytoin](#) and three epileptic patients already taking [valproic acid](#). The patients were given [topiramate](#) 100 mg every morning, which was increased to the maximum tolerated dose (no greater than 1200 mg per day). Plasma concentration-time profiles were then observed over the next eight weeks. No apparent changes were observed in either [phenytoin](#) or [valproic acid](#) area under the concentration-time curve (AUC) profiles or trough plasma concentrations [132].

b) Stuporous [encephalopathy](#) developed in 5 patients with drug-resistant [epilepsy](#), shortly after beginning combination anticonvulsant regimens comprising [topiramate](#) (TPM) and [valproic acid](#) (VPA). [Hyperammonemia](#) was observed in 4 of the patients (age ranging from 29 to 41 years). Blood ammonia levels ranged from 62 to 146 mcmol/L. After a reduction in dose or withdrawal of TPM or VPA, blood ammonia levels returned to normal. In the 5th case report, a 17-year-old boy developed impaired consciousness, 10 days after VPA 1500 mg/day was added to a stable [dose regimen](#) comprising TPM 300 mg/day, [phenytoin](#) (PHT) 300 mg/day, and [carbamazepine](#) 6 mg/day. Blood ammonia concentrations were within normal limits; however, elevations were observed in plasma concentrations of [gamma glutamyl-transferase](#) and [alkaline phosphatase](#). The patient's cognitive status returned to baseline after TPM was tapered and withdrawn, in conjunction with a reduction of PHT dose [133].

c) A 32-year-old male with centro-temporal [epilepsy](#) was controlled on [phenobarbital](#) 200 mg daily and [topiramate](#) 600 mg daily when [valproic acid](#) was added to his regimen. Two days prior to hospital admission, [valproic acid](#) was increased to 1500 mg daily and the patient became drowsy with nausea and slurred speech. The [phenobarbital](#) concentration was 35 mcg/mL (therapeutic range 15 mcg/mL to 40 mcg/mL) and the [valproic acid](#) level was 38 mcg/mL (therapeutic range 50 mcg/mL to 100 mcg/mL) at hospital admission. The ammonia concentration was elevated at 116 mcmol/L (normal 15 mcmol/L to 60 mcmol/L), as was the gamma glutamyl transpeptidase ([GGT](#)) level. Acute [valproic acid encephalopathy](#) was suspected, and [valproic acid](#) was discontinued. The patient recovered within the next three days and the ammonia concentration decreased to within normal limits [134].

d) A 37-year-old female with [focal epilepsy](#) was receiving [topiramate](#) 400 mg daily, [carbamazepine](#) 1000 mg daily, and [lamotrigine](#) 150 mg daily with little effect on her seizure frequency. [Valproic acid](#) 1200 mg daily was slowly substituted for [lamotrigine](#), and the patient became somnolent and dysarthric within three weeks. Laboratory results showed a [valproic acid](#) level of 47 mcg/mL (therapeutic range 50 mcg/mL to 100 mcg/mL) and a [carbamazepine](#) level of 5.2 mcg/mL (therapeutic range 8 mcg/mL to 12 mcg/mL). The ammonia level was increased to 88 mmol/L and valproate-induced [hyperammonemic encephalopathy](#) was suspected. [Topiramate](#) was slowly discontinued over a seven-day period, and the patient completely recovered, although the ammonia level remained elevated. [Valproic acid](#) was then also discontinued, and the ammonia concentration returned to a normal range [134].

3.5.2] Drug-Food Combinations

3.5.2.A) Ethanol

- 1) Interaction Effect: erratic [topiramate](#) plasma concentrations and additive CNS depressant effects
- 2) Summary: The presence of alcohol within 6 hours before or 6 hours after administration of [topiramate](#) extended-release capsules is contraindicated due to erratic [topiramate](#) plasma concentrations caused by altered [topiramate](#) release from the extended-release capsule formulation. Therefore alcohol should be completely avoided within 6 hours prior to and 6 hours after [topiramate](#) extended-release capsule administration to avoid a spike in [topiramate](#) plasma levels that may occur soon after dosing, followed by subtherapeutic [topiramate](#) plasma levels hours later. Additionally, the use of any dose form of [topiramate](#) with alcohol may increase the risk of significant additive CNS depression [1].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The presence of alcohol within 6 hours before or 6 hours after administration of [topiramate](#) extended-release capsules is contraindicated. Therefore alcohol should be completely avoided within 6 hours prior to and 6 hours after [topiramate](#) extended-release capsule administration to avoid a spike in [topiramate](#) plasma levels that may occur soon after dosing, followed by subtherapeutic [topiramate](#) plasma levels hours later. Use of any dose form of [topiramate](#) with alcohol may increase the risk of significant additive CNS depression [1].
- 7) Probable Mechanism: altered [topiramate](#) release from extended-release capsules

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

- a) In women who plan on becoming pregnant, obtaining concentrations of [topiramate](#) before becoming pregnant and during the pregnancy may be beneficial. Although, therapeutic concentrations have not been established, prepregnancy concentrations in an optimally-treated woman provide a reference concentration for comparison to concentrations during pregnancy, when concentrations may change [165].

2) Physical Findings

- a) A reduction in seizure frequency and severity is indicative of efficacy.

B) Toxic

1) Laboratory Parameters

- a)) Measure renal function prior to treatment in elderly patients and patients with high risk of [renal insufficiency](#) [1] [20].
- b)) Measure ammonia levels in any patient experiencing unexplained lethargy, vomiting, or changes in mental status, which may be indicative of [hyperammonemia](#) with or without [encephalopathy](#) [1] [20].
- c)) Monitor serum bicarbonate levels, at baseline and periodically during treatment [1] [20].
- d)) Monitor for [metabolic acidosis](#) in pregnant patients and newborns exposed to drug during pregnancy [1] [20].

2)) Physical Findings

- a)) Closely monitor patients treated with AEDs for emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior [1] [20].
- b)) Monitor for decreased sweating and [hyperthermia](#), especially in pediatric patients, and during hot weather or concomitant drug therapy predisposing patients to heat-related disorders (eg, other carbonic anhydrase inhibitors, anticholinergics) [1] [20].

4.2) Patient Instructions

A)) [Topiramate](#) (By mouth)

[Topiramate](#)

Treats and prevents seizures and prevents migraine headaches. This medicine is an anticonvulsant.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use if you had an [allergic reaction](#) to [topiramate](#), or if you are pregnant.

How to Use This Medicine:

Capsule, Long Acting Capsule, Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. You may take this medicine with or without food.

Extended-release capsule: Swallow whole. Do not open, crush, or chew it.

Tablet: Swallow whole. Do not break, crush, or chew it. The tablet has a very bitter taste.

Sprinkle capsule: Swallow whole or open the capsule and pour the medicine into a small amount (1 teaspoon) of soft food, such as applesauce. Swallow the food mixture right away without chewing. Do not store the mixture for use at a later time.

Drink extra fluids so you will urinate more often and help prevent kidney problems.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not drink alcohol for 6 hours before and 6 hours after you take the Trokendi XR™ capsule.

Some foods and medicines can affect how [topiramate](#) works. Tell your doctor if you are using [acetazolamide](#), [digoxin](#), [lithium](#), [zonisamide](#), [metformin](#), other medicine for seizures (such as [carbamazepine](#), [phenytoin](#), [valproic acid](#)), or [birth control pills](#).

Tell your doctor if you drink alcohol or if you are using any medicine that makes you sleepy, such as allergy medicine or narcotic pain medicine.

Warnings While Using This Medicine:

It is not safe to take this medicine during pregnancy. It could harm an unborn baby. Tell your doctor right away if you become pregnant.

Tell your doctor if you are breastfeeding, or if you have [kidney disease](#), liver disease, [glaucoma](#), or a history of depression or mood disorders.

This medicine may cause the following problems:

- Eye pain or vision changes, including [glaucoma](#)
- Changes in body temperature, high or low
- [Metabolic acidosis](#) (too much acid in the blood)
- High levels of ammonia in the blood
- [Kidney stones](#)

This medicine may increase depression or thoughts of suicide. Tell your doctor right away if you start to feel more depressed or think about hurting yourself.

Your doctor may want to monitor your child's weight and height, because this medicine may cause slow growth in children.

This medicine may make you dizzy, drowsy, confused, or tired. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

- [Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
- Blistering, [peeling](#), or red skin rash
- Bloody or cloudy urine, painful urination, sudden lower back or stomach pain
- Changes in vision, eye pain
- Feeling agitated, depressed, nervous, or irritable, thoughts of hurting yourself or others, unusual mood or behavior
- Fever, decreased sweating
- Numbness, tingling, or burning pain in your hands, arms, legs, or feet
- Problems with walking, clumsiness, dizziness
- Rapid, deep breathing, tiredness, loss of appetite, fast or uneven heartbeat
- Trouble talking, concentrating, or remembering
- Unusual drowsiness, tiredness, or weakness, vomiting

If you notice these less serious side effects, talk with your doctor:

- Change in taste or bitter taste
- Loss of appetite, weight loss
- Nausea, constipation, diarrhea

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) Trokendi XR(TM)

1) **Topiramate** extended-release oral capsule is indicated as initial monotherapy in patients 10 years of age or older with partial onset or primary generalized tonic-clonic seizures, and as adjunctive therapy in patients 6 years of age or older for partial seizures, primary generalized tonic-clonic seizures, or seizures associated with **Lennox-Gastaut syndrome**. Approval is based upon demonstration of pharmacokinetic equivalence to immediate-release **topiramate** [1].

2) Safety and efficacy are not established in patients converted from previous anticonvulsant regimens to **topiramate** monotherapy [1].

B) Topamax(R)

1) Epilepsy

a) **Topiramate** is indicated as initial monotherapy in patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures, and as add-on therapy for partial seizures, primary generalized tonic-clonic seizures, or seizures associated with **Lennox-Gastaut syndrome** [17]. **Topiramate** is considered one of the newer antiepileptic drugs along with **gabapentin**, **lamotrigine**, **levetiracetam**, **oxcarbazepine**, **tiagabine** and vigabatrin. These newer antiepileptics are recommended (within their licensed indications) for management of **epilepsy** in people who have not benefited from treatment with the older antiepileptic drugs, such as **carbamazepine**, or when treatment with the older antiepileptic drugs is not suitable because of contraindications, drug interactions, tolerability or pregnancy [166]. Potential advantages of **topiramate** are its apparent lack of effect on serum levels of conventional antiepileptic agents (although **phenytoin** and **carbamazepine** can decrease **topiramate** serum concentrations), relatively long elimination half-life, and overall better tolerability compared to conventional agents; hematotoxicity or hepatotoxicity has not been reported in available trials. A disadvantage of **topiramate** is its propensity to induce cognitive disturbances. the clinical significance of this effect with respect to continuation of therapy and long-term **sequelae** require further evaluation.

2) Migraine Prophylaxis

a) **Topiramate** is indicated for adults in the **prophylaxis of migraine** headache [17]. **Topiramate** is currently not indicated for **prophylaxis of migraine** headaches in children, but clinical trials have shown benefit in both pediatric and adolescent patients [35] [34] [37] [36]. The usefulness of **topiramate** in the acute treatment of migraine headache has not been studied [17].

3) Off-label Use

a) Appetite suppression and weight loss can be of concern with **topiramate** therapy, especially in children. However, beneficial weight loss has been seen in clinical trials of weight loss in obese and type 2 diabetic patients. In type 2 diabetic patients, **topiramate** as add-on treatment to diet and life style changes produced significant weight loss and improvements in **HbA1C** [3] [4] [2]. The frequency of adverse events experienced in these weight loss studies, suggest its usefulness in clinical practice may be limited, but with few good options available for weight loss, further studies are needed to clarify its role. Studies with **topiramate** in **bulimia** [10] [11] [12], essential tremor [167], and smoking and alcohol dependence [168] have shown benefits; while studies with **topiramate** in **diabetic peripheral neuropathy** [54] [53], **bipolar disorder** [169] [170] [171] [172], and **post traumatic**

stress disorder [173] [174] [175] do not support a role for [topiramate](#) in the management of these disorders.

4.4] Mechanism of Action / Pharmacology

A) Mechanism of Action

1) [Topiramate](#) is a sulfamate-substituted monosaccharide with antiepileptic activity [161] [153]. It is a derivative of D-fructose, structurally distinct from other antiepileptic agents.

2) The exact mechanism of action is unknown, but 4 properties that may contribute to [topiramate's](#) antiepileptic and antimigraine efficacy are a blockage of voltage-dependent sodium channels, an augmentation of gamma-aminobutyrate acid activity at some subtypes of the [GABA-A](#) receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV [1] [20].

3) Although the drug is a weak carbonic anhydrase inhibitor, this does not appear to contribute significantly to anticonvulsant effects [162] [161] [160]. Rapid neuronal firing in the rat hippocampus is decreased by [topiramate](#), an effect possibly related to inhibition of [calcium](#) or sodium channels [160]. [Topiramate](#) does not interact with [gamma-aminobutyric acid \(GABA\)](#), benzodiazepine, serotonin, adrenergic, muscarinic, or [dopamine](#) receptor binding sites, although it has been reported to potentiate GABA-mediated [chloride](#) currents [160] [161]. [Topiramate](#) has also been reported to inhibit release of excitatory amino acids in spontaneously epileptic rats [160] and to block voltage-dependent sodium channels and the activity of [adenosine](#) monophosphate (AMP) and kainic acid by antagonism at receptor sites [162].

4) [Topiramate](#) significantly increases human cerebral [GABA](#) concentrations within 3 hours and maintains these levels for at least 6 hours [163]. Increases in brain and cerebral spinal fluid [GABA](#) correlate with seizure protection in patients with complex partial seizures. [Topiramate](#) also increases human brain homocarnosine levels and pyrrolidinone concentrations [164]. Both of these increases should contribute to [topiramate's](#) ability to protect the brain from seizure activity.

5) In preclinical studies, [topiramate](#) has effectively abolished electroshock-induced seizure activity, but had minimal to no effect on seizures induced by pentylenetetrazol, picrotoxin, or bicuculline [154] [160]. These data suggest the drug acts primarily via prevention of seizure spread as opposed to an elevation of seizure threshold.

4.5] Therapeutic Uses

4.5.A] Alcoholism

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Topiramate was more efficacious than placebo in reducing the percentage of heavy drinking days in a 14-week, double-blind, placebo-controlled clinical trial (n=371). [7]

Topiramate was more efficacious than placebo in treating alcohol dependence when given with behavioral compliance-enhancement treatment [8].

3) Adult:

a) Topiramate treatment was more efficacious than placebo in reducing the percentage of heavy drinking days in a 14-week, double-blind, placebo-controlled clinical trial. In this multicenter trial, patients with alcohol dependence according to DSM-IV and who drank 35 or more (men) or 28 or more (women) drinks per week were randomized to receive **topiramate** (n=183; mean age 46.7 years, 74.3% male) or placebo (n=188; mean age 47.8 years, 71.9% male), along with weekly compliance enhancement intervention. Patients who enrolled had to express a desire to stop or reduce their alcohol consumption with the possible goal of long-term abstinence. The primary efficacy measure was self-reported percentage of heavy drinking days defined as the number of days men consumed 5 or more drinks per day and women consumed 4 or more drinks per day divided by the number of study days. Plasma **gamma-glutamyl transferase** levels were collected to provide a laboratory measure of drinking reduction. **Topiramate** therapy was started at 25 mg once daily, and increased at weekly intervals for 5 weeks to a total dose of 300 mg, divided twice daily (a minimum daily dose of 50 mg was required to remain in the trial). Patients remained on this dose from week 6 to the beginning of week 14, and then tapered off by week 16. All randomized patients were included in the primary analysis with the data from dropouts imputed as **relapse** to baseline measure. There was a greater lowering in the percentage of heavy drinking days from baseline to week 14 with **topiramate** compared with placebo ((81.91% to 43.81% vs 81.97% to 51.76%; between-group difference, 8.44%; 95% CI, 3.07% to 13.8%; p=0.002). Onset was evident by week 4 and maintained through week 14. Abstinence increased to 37.56 days (baseline, 9.64 days) with **topiramate** compared with 29.06 days (baseline, 9.35 days) with placebo (between-group difference, -7.68; 95% CI, -12.49 to -2.87; p=0.002). The number of drinks per drinking day also decreased from 11.04 to 6.53 with **topiramate** compared with a reduction from 10.9 to 7.46 with placebo (between-group difference, 0.88; 95% CI, 0.25 to 1.51; p=0.006). Attrition due to adverse events was higher in the **topiramate** group compared with placebo (18.6% vs 4.3%; p less than 0.001), with paresthesia, headache, taste perversion, fatigue, anorexia and insomnia being the most frequently reported events [7].

b) Topiramate was found to be more effective than placebo in reducing the number of drinks per day, drinks per drinking day, cravings and the percentage of heavy drinking days. In a 12-week, double-blinded, placebo-controlled trial, 150 patients were randomized to receive **topiramate** (n=75) or matching placebo (n=75) in conjunction with behavioral compliance- enhancement treatment. **Topiramate** was titrated from an initial dose of 25 mg once daily to 300 mg/day given in 2 divided doses over an 8-week dose-escalation schedule, and was maintained during the rest of the trial. Abstinence was not a requirement for study entry but participants were encouraged to attempt drinking cessation. Participants were considered heavy drinkers if they consume on average at least 21 drinks per week for women and at least 35 per week for men. The number of drinks per day decreased an average of 2.88 drinks more in the **topiramate** arm compared with placebo (p=0.0006). Drinks per drinking day and percentage of heavy drinking days also decreased an average of 3.1 drinks and 27.61% further with **topiramate** (p=0.0009 and p=0.0003, respectively). Other variables measured showed a significant increase in the percentage of days abstinent in the **topiramate** arm compared with placebo (p=0.0003) as well as a greater decrease in the log plasma **gamma-glutamyl transferase** ratios with **topiramate** (p=0.0046). Cravings were measured as a secondary variable using a 14-item obsessive-compulsive drinking scale and were also found to have improved to a greater degree with **topiramate** (p equal to or less than 0.0031). No serious adverse events were reported. Dizziness, paraesthesia, psychomotor

slowing, memory or concentration impairment and weight loss were reported with greater frequency in the [topiramate](#) arm [8].

4.5.B] Bipolar I disorder, Acute manic or mixed episodes

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

There was no significant difference between [topiramate](#) monotherapy and placebo for the treatment of acute mania, and [lithium](#) was superior to both, in 4 multicenter, randomized, double-blind, placebo-controlled, parallel-group trials in patients with bipolar I disorder (manic or mixed episodes) [13].

There was no significant difference between [topiramate](#) and placebo as adjunct to [lithium](#) or [valproate](#) for the treatment of adults with bipolar I disorder (manic or mixed episodes) in a 12-week, multicenter, randomized, double-blind, parallel-group trial (n=287) [14].

3) Adult:

a) General Information

1) Results from randomized, double-blind, placebo- and active-controlled studies demonstrated that adjunctive therapy or monotherapy with [topiramate](#) was ineffective for the treatment of acute manic or mixed episodes of bipolar I disorder in adults [13] [14]. In 4 randomized, double-blind, placebo- and active-controlled ([lithium](#)) studies, there was no significant difference between [topiramate](#) monotherapy compared with placebo for the treatment of acute mania in hospitalized patients with bipolar I disorder [13]. Ineffectiveness of [topiramate](#) was further substantiated when analysis of pooled data from these 4 studies also failed to show a significant difference; superiority of [lithium](#) to both [topiramate](#) and placebo was established in the primary and pooled analysis [13]. Additionally, in a 12-week, multicenter, randomized, double-blind, parallel-group trial (n=287), there was no significant difference between [topiramate](#) and placebo as adjunctive therapy to [lithium](#) or [valproate](#) for the treatment of bipolar I disorder (manic or mixed episodes) in adult outpatients [14].

b) Clinical Trials

1) In 4 multicenter, randomized, double-blind, placebo-controlled, parallel-group trials in patients with bipolar I disorder (manic or mixed episodes), there was no significant difference between [topiramate](#) monotherapy and placebo for the treatment of acute mania, and [lithium](#) was superior to both. Hospitalized patients aged 16 years or older experiencing acute manic or mixed episodes of bipolar I disorder (DSM-IV and Structured Clinical Interview for DSM-IV Axis I Disorders), and with a history of at least 1 previous manic or mixed episode were eligible. A Young Mania Rating Scale (YMRS) score of 20 or greater was required at screening and randomization. Patients with rapid cycling [bipolar disorder](#), as well as a primary diagnosis of schizoaffective, [impulse control](#), [antisocial](#), or [borderline personality disorder](#)

were excluded. During a 2-week screening/wash-out phase, all prior psychotropic medications were discontinued, and use of short-acting benzodiazepines was allowed only for agitation and insomnia. Following wash-out, eligible patients were randomized to receive [topiramate](#), placebo, or [lithium](#) (studies 1 and 4), or either [topiramate](#) or placebo (studies 2 and 3) for 3 weeks. [Topiramate](#) was initiated at a dose of 50 mg/day, and titrated in daily increments of 50 mg (day 2) and 100 mg (next 1 to 5 days) to achieve a target dose of 200 mg/day, 400 mg/day, or 600 mg/day (mean modal dose, 176 +/- 25 mg/day, 313 +/- 71 mg/day, and 409 +/- 118 mg/day, respectively). In studies 1 and 4, the target [lithium](#) dose was 1500 mg/day (serum level range: 0.8 to 1.2 mEq/L at titration, 0.6 to 1.2 mEq/L at stabilization; mean modal dose, 1258 +/- 221 mg/day). In a modified intention-to-treat analysis at 3 weeks (included all randomized patients with at least 1 post baseline efficacy assessment), the mean reduction in YMRS score from baseline (primary outcome) was not significantly different in the [topiramate](#) (range, 5.1 to 8.2) and placebo arms (range, 6.4 to 8.4) in all 4 studies. Additionally, in studies 1 and 4, [lithium](#) was superior to both placebo and [topiramate](#) for the primary outcome. Key baseline characteristics and details for the primary outcome in the individual studies are shown in the table. Exploratory analysis of pooled data from all 4 studies also showed no significant difference in mean change in YMRS score from baseline to 3 weeks between the [topiramate](#) and placebo arms (least squares mean difference, 0.6 +/- 0.73; p=0.41). The proportion of patients who achieved 50% or greater reduction in YMRS at 3 weeks in pooled analysis was 27%, 28%, and 46% in the [topiramate](#), placebo, and [lithium](#) arms, respectively; response (DSM-IV classified) was observed in 25%, 22%, and 37% of patients, respectively. Notably, a significant difference in favor of placebo over [topiramate](#) was observed for change in the Montgomery-Asberg Depression Rating Scale and the Brief Psychiatric Rating Scale scores in pooled analysis. Studies 1, 2, and 4 also included a 9-week, double-blind, extension phase following the 3-week core study phase; in studies 1 and 4 that had a lithium-treatment arm, patients in the placebo group were crossed over to either [topiramate](#) (placebo/[topiramate](#) group) or [lithium](#) for the extension phase. At 12 weeks, there was no significant difference in mean reduction of YMRS score from baseline between the [topiramate](#) (range, -7.4 to -10) and the placebo or placebo/[topiramate](#) groups (range, -7.4 to -9.4). In studies 1 and 4, mean reductions in YMRS score from baseline to 12 weeks in the [lithium](#) arms (-16.3 and -18.4, respectively) were significantly greater than those obtained in patients who continued on or crossed over to [topiramate](#) (p less than 0.001 for both), but not in patients who crossed over to [lithium](#) (p=0.098). [Topiramate](#) adverse events were dose-related, with paresthesia, decreased appetite, dry mouth, and weight loss occurring at an incidence of 3% or greater in pooled analysis. Both suicidal attempt and [suicidal ideation](#) were reported in less than 1% of topiramate-treated patients during the 3-week core study period, with the same incidence noted in the placebo group [14]:

Study 1 Topiramate vs Placebo vs

Lithium

Core 3-week Double-blind

Treatment Phase

Topiramate	Lithium	Placebo		
Dose	200 mg/day	400 mg/day	600 mg/day	1500 mg/day
n	107	107	-	113
Mean age (years)	42 +/- 14	43 +/- 14	-	43 +/- 14
Current episode manic	83%	83%	-	82%
Baseline mean YMRS score	30.8 +/- 7.8	30.2 +/- 7.1	-	30.1 +/- 7.4
Mean change in YMRS score at 3 weeks	-5.8 +/- 12.3	-6.2 +/- 11.9	-	-12.9 +/- 11.8
p value vs placebo	0.223	0.324	-	0.001

p value vs lithium less than 0.001 less than 0.001 - -

KEY: YMRS = Young Mania Rating Scale; n = number of patients

Study 2 Topiramate vs Placebo

Core 3-week Double-blind Treatment Phase

Topiramate	Placebo			
Dose	200 mg/day	400 mg/day	600 mg/day	
n	-	107	98	
Mean age (years)	-	40 +/- 12	39 +/- 11	
Current episode manic	-	47%	51%	
Baseline mean YMRS score	-	29 +/- 5.5	29.2 +/- 5.8	
Mean change in YMRS score at 3 weeks	-	-8.2 +/- 9.6	-7.9 +/- 11.4	
p value vs placebo	-	0.729	0.808	

KEY: YMRS = Young Mania Rating Scale; n = number of patients

Study 3 Topiramate vs Placebo

Core 3-week Double-blind Treatment Phase

Topiramate	Placebo			
Dose	200 mg/day	400 mg/day	600 mg/day	
n	-	105	-	
Mean age (years)	-	41 +/- 12	-	
Current episode manic	-	64%	-	
Baseline mean YMRS score	-	30.2 +/- 7.3	-	
Mean change in YMRS score at 3 weeks	-	-5.1 +/- 10.1	-	
p value vs placebo	-	0.263	-	

KEY: YMRS = Young Mania Rating Scale; n = number of patients

Study 4 Topiramate vs Placebo vs

Lithium

Core 3-week Double-blind

Treatment Phase

Topiramate	Lithium	Placebo		
Dose	200 mg/day	400 mg/day	600 mg/day	1500 mg/day
n	-	115	-	114
Mean age (years)	-	40 +/- 12	-	42 +/- 11
Current episode manic	-	88%	-	90%
Baseline mean YMRS score	-	30.8 +/- 6.8	-	30.7 +/- 7.5
Mean change in YMRS score at 3 weeks	-	-8.2 +/- 11.8	-	-13.8 +/- 11.9
p value vs placebo	-	0.976	-	less than 0.001
p value vs lithium	-	less than 0.001	-	-

KEY: YMRS = Young Mania Rating Scale; n = number of patients

2) There was no significant difference between [topiramate](#) and placebo as adjunct to [lithium](#) or [valproate](#) for the treatment of adults with bipolar I disorder (manic or mixed episodes) in a 12-week, multicenter, randomized, double-blind, parallel-group trial (n=287). Adult outpatients (age range, 18 to 70 years) with bipolar I disorder (DSM-IV and Structured Clinical Interview for DSM-IV Axis I Disorders) and a score of 18 or greater on the Young Mania Rating Scale (YMRS) were eligible if they had received either [lithium](#) or [valproate](#) for 6 weeks or more, with stable doses 2 weeks prior to screening. The required serum levels of [lithium](#) and [valproate](#) at screening were 0.5 to 1.2 mEq/L and 45 to 100 mg/L, respectively. Patients were randomized

to receive either adjunctive [topiramate](#) (n=143; mean age, 41 +/- 12.2 years; 73.4% current episode mania) or placebo (n=144; mean age, 39 +/- 11.9 years; 70.8% current episode mania) for 12 weeks. During the first 8 weeks (titration period), [topiramate](#) was initiated at 25 mg/day (minimum required dosage of 50 mg/day after week 1), with weekly titrations at a twice-daily schedule up to 400 mg/day as tolerated. The dosage of [topiramate](#) at the end of the titration period was continued for 4 additional weeks (mean dose, 254.7 mg/day; 42% received a dose of greater than 200 mg/day). The mean treatment duration was 70.8 +/- 31.6 days for [topiramate](#) and 74.7 +/- 30 days for placebo. Use of an oral antipsychotic, at a stable dosage, was permitted during the study, and short-acting benzodiazepines for sleep or agitation were completely weaned during the first 4 weeks of the titration period. At baseline, rapid cycling was present in 27.3% and 29.9% of patients in the [topiramate](#) and placebo groups, respectively, and 29.4% (mean, 7.3 episodes) and 25% (mean, 7.8 episodes) of patients, respectively, had a history of psychotic episodes; the mean baseline YMRS scores were 24.9 +/- 5 and 24 +/- 4.3, respectively. A modified intention-to-treat analysis (included all randomized patients who received at least 1 study dose and had at least 1 post baseline assessment) revealed that the mean improvement in total YMRS score from baseline to last visit (primary outcome) was not significantly different between the [topiramate](#) (-10.1 +/- 8.7; -40.1% from baseline) and placebo groups (-9.6 +/- 8.2; -40.2% from baseline; p=0.797). Similarly, the response rate (greater than 50% reduction in total YMRS score from baseline) was not significantly different between the [topiramate](#) and placebo groups (39% vs 38%, respectively; p=0.914). Additionally, there were no significant differences from placebo for improvements noted in secondary measures (Clinical Global Impressions-Severity of Illness Scale, Brief Psychiatric Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Global Assessment Scale). [Topiramate](#) was not associated with worsening of mania or induction of depression. [Lithium](#) and [valproate](#) levels during the study remained within ranges required at screening. Commonly reported adverse events that occurred more frequently in the [topiramate](#) arm were paresthesia (23.1% vs 3.5%), diarrhea (16.8% vs 8.4%), and anorexia (13.3% vs 5.6%). There was significantly greater reduction in body weight and BMI in the [topiramate](#) arm compared with placebo (p less than 0.001 for both). [Suicidal ideation](#), possibly treatment-associated, was reported in 1 patient in the [topiramate](#) arm [14].

4.5.C] [Diabetes mellitus type 2](#) in obese; Adjunct

1) Overview

FDA Approval: Adult, no; [Pediatric](#), no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) as add-on treatment to diet and lifestyle changes produced significant benefits (weight loss, improvements in [HbA1C](#), and reductions in blood pressure) compared with placebo; however, CNS and psychiatric adverse events limit its usefulness [2] [3] [4].

[Topiramate](#) controlled-release (CR) as add-on treatment to diet and lifestyle programs in obese patients with [type 2 diabetes](#) produced similar beneficial effects (weight loss, improvements in [HbA1C](#), and

reductions in blood pressure) to immediate-release [topiramate](#); however, it did not show improved tolerability [2]

3) Adult:

a) Immediate-release

1) In a multicenter, randomized, double-blind, placebo-controlled trial (n=229), [topiramate](#) as add-on treatment to diet and lifestyle changes produced significant benefits (weight loss, improvements in [HbA1C](#), and reductions in blood pressure) compared with placebo in obese, type 2 drug-naïve diabetic patients. Patients (aged 18 to 75 years, mean 53 years; 99% Caucasian; 39% male) with a BMI between 27 and 50 kg/m², following a 600 kcal deficit diabetic diet and participating in behavior modification and physical activity programs were randomized to [topiramate](#) 96 mg/day (n=74), [topiramate](#) 192 mg/day (n=77) or placebo (n=78). The trial consisted of a 6-week placebo run-in phase, followed by randomization, an 8-week titration phase and a 52-week maintenance phase. This was to be a 72-week study, but was ended at 40 weeks when the sponsor discontinued the [topiramate](#) immediate-release clinical program in [obesity](#) and [diabetes](#) to develop a controlled-release [topiramate](#) formulation. Due to early termination of the study, efficacy data were based on a predefined (prior to unblinding) population (n=229) consisting of subjects who enrolled early enough to have completed at least 40 weeks of double-blind treatment before the decision to stop the study was made. The safety data included all subjects (n=535) who had at least one dose of study medication and provided any post baseline safety data. Two co-primary endpoints were identified: mean percent weight change and mean change in [HbA1C](#) from baseline. Five hundred forty-one subjects were randomized, 535 were included in the safety analysis and 229 (42% of the total number of randomized subjects) were included in the efficacy analysis. At week 40, both primary endpoints of percent weight change and mean change in [HbA1C](#) were met [3].

Coprimary Endpoints	Placebo	Topiramate 96 mg/day	Topiramate 192 mg/day
Weight (baseline)	104.1 kg	104.9 kg	101.9 kg
Weight change at 40 weeks	-2.5%	-6.6%*	-9.1%*
HbA1C (baseline)	6.6%	6.8%	6.7%
HbA1C change at 40 weeks	-0.2%	-0.6%*	-0.7%*

*p less than 0.001 vs placebo

Topiramate-treated patients experienced a significant improvement in body weight and HbA1C compared with placebo (p less than 0.001). A drop in HbA1C was observed up until week 20, after which it plateaued and weight loss was ongoing at week 40. Overall, 24% of patients in the placebo, 57% in the topiramate 96 mg/day and 77% in the topiramate 192 mg/day group lost at least 5% of their baseline body weight by week 40. Adverse events were generally related to central or peripheral nervous system, or were psychiatric in nature. The majority of CNS-related adverse events occurred early during treatment and generally resolved with either ongoing treatment or after discontinuation. Paresthesia (46%), fatigue (26%), hypoesthesia (15%), difficulty with concentration/attention (9%), and difficulty with memory (8%) were some of the more commonly reported events. Twenty-one percent of subjects in the topiramate 192 mg/day, 17% of subjects in the topiramate 96 mg/day and 12% of subjects in the placebo group withdrew from the study due to adverse events [3].

2) [Topiramate](#), in addition to diet and lifestyle changes produced significant benefits (weight loss, improvements in [HbA1C](#) and reductions in systolic blood pressure) compared with placebo in obese type 2 diabetic patients in combination with [metformin](#) in a multicenter,

randomized, double-blind, placebo-controlled trial (n=307). Patients (aged 18 to 75 years; mean 53.3 +/- 9.6 years; 96% Caucasians; 59% female) with a BMI between 27 and 50 kg/m(2) (mean 36.2 +/- 5.4 kg/m(2)) on metformin monotherapy (not to exceed 2.1 g/day) for at least 4 months (on a stable dose for the past 2 months), following a 600 kcal deficit diabetic diet and participating in nonpharmacologic lifestyle intervention programs, were randomized to topiramate 96 mg/day (n=102), topiramate 192 mg/day (n=105) or placebo (n=100). Patients with hypertension were allowed into the study, provided the dose of antihypertensive had been stable for at least 2 months and were maintained for the duration of the study. The trial consisted of a 6-week placebo run-in phase, followed by randomization, an 8-week titration phase and a 52-week maintenance phase. This was a 72-week study, but was ended at 24 weeks when the sponsor discontinued the immediate-release clinical program of topiramate in obesity and diabetes in order to develop a controlled-release topiramate formulation. Due to early termination of the study, efficacy data were based on a predefined (prior to unblinding) population (n=307) consisting of subjects who were enrolled early enough to have completed at least 24 weeks of double-blind treatment before the decision to stop the study was made. The safety data included all subjects (n=640) who had at least one dose of study medication and provided any post baseline safety data. At 24 weeks, statistically significant improvements in both primary endpoints (mean percent weight change and mean change in HbA1C from baseline) were met by the topiramate-treated patients [4].

Coprimary Endpoints	Placebo	Topiramate 96 mg/day	Topiramate 9
Weight (baseline)	103.2 kg	102.4 kg	99.4 kg
Weight change at 24 weeks	-1.7%	-4.5%*	-6.5%*
HbA1C (baseline)	6.7%	6.9%	6.8%
HbA1C change at 40 weeks	-0.2%	-0.6%*	-0.7%*

*p less than 0.001 vs placebo

Topiramate resulted in greater mean weight change and mean HbA1C levels improvement compared with the placebo group (p less than 0.001). Paresthesia (32%), fatigue (12%), hypoesthesia (8%), depression (8%), and difficulty with concentration/attention (5%) were some of the more commonly reported events. Eighteen percent of subjects in the topiramate 192 mg/day, 9% of subjects in the topiramate 96 mg/day and 7% of subjects in the placebo group withdrew from the study due to adverse events. Two patients experienced serious adverse events possibly related to study drug. The first patient experienced increased hepatic enzymes and alkaline phosphatase, while the second patient died of hemorrhage secondary to preexisting liver disease and hepatic failure [4].

b) Controlled-Release

1) Topiramate controlled-release (CR) as add-on treatment to diet and lifestyle programs in obese patients with type 2 diabetes produced similar beneficial effects (weight loss, improvements in HbA1C, and reductions in blood pressure) to immediate-release topiramate; however, it did not show improved tolerability in this multicenter, double-blind, placebo-controlled study (n=111). Patients (aged 40 to 65 years; mean, 52.7 +/- 11.3 years; 75% Caucasians; 32% male) with a BMI between 27 and 50 kg/m(2) and HbA1C levels between 6.5% and 11% were randomized to receive topiramate CR 175 mg/day (n=54) or placebo (n=57) in addition to diet and exercise alone or in combination with metformin for 16 weeks. The primary end point was mean percentage change in body weight from baseline to week 16. After a 1-week screening phase, randomized patients entered a 7-week titration phase followed by a 9-

week maintenance phase, a 2-week taper, and a 2-week follow up. All patients were instructed to follow a 600 kcal deficit diabetic diet, a [behavioral modification](#) and a physical activity program. Patients in the [topiramate](#) group started on [topiramate](#) controlled-release 25 mg/day, and increased by 25 mg increments each week to a dose of 175 mg/day; with options to down-titrate dose for intolerable adverse effects. A total of 39 patients in the [topiramate](#) group and 46 in the placebo group completed the study. Patients in the [topiramate](#) group lost 6 kg (-5.8% from baseline of 106 kg) compared with 2.5 kg (-2.3% from baseline of 109.7 kg) in the placebo group (p less than 0.001). Differences in weight loss were seen by week 2 of titration. [HbA1C](#) levels improved to 6.7% (from a baseline of 7.6%) in the [topiramate](#) compared with 7.1% (baseline, 7.4%) in the placebo group (p less than 0.001). The majority of adverse events were related to central and peripheral nervous system (43% [topiramate](#) vs 21% placebo) or psychiatric in nature (33% [topiramate](#) vs 11% placebo). The onset of most CNS and psychiatric adverse events occurred during the 7 week titration phase. Paresthesia (28%) was the most frequently reported adverse event. A serious case of [renal calculus](#) that was considered possibly drug-related occurred in the [topiramate](#) group. One patient in the placebo group and 7 patients in the [topiramate](#) group had dose reduction or interruption of treatment due to intolerable adverse events. The final dosing of [topiramate](#) in the study was 175 mg (n=34), 150 mg (n=1), 75 mg (n=3) and 50 mg (n=1) [2].

4.5.D) [Diabetic peripheral neuropathy](#)

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) was not statistically more effective than placebo in reducing pain scores in patients with [painful diabetic neuropathy](#) in 3 similarly designed, double-blind placebo-controlled trials (n=1259) [52]

[Topiramate](#) monotherapy was more effective than placebo in reducing pain associated with [diabetic peripheral neuropathy](#) in a 12-week multicenter, randomized, double-blind trial (n=322). Of note in this trial, there was a 48% drop out rate with the vast majority of subjects dropping out because of adverse events [53]

3) Adult:

a) [Topiramate](#) was not statistically more effective than placebo in reducing pain scores in patients with [painful diabetic neuropathy](#) in 3 similarly designed, double-blind placebo-controlled trials (n=1259). Diabetic patients (mean age, 58 years; 58% male; 87% with [type 2 diabetes](#)) with at least a 6-month history of painful [peripheral neuropathy](#) (mean, 4.2 years) were enrolled in 1 of 3 studies using identical inclusion/exclusion criteria. During a 28-day baseline phase, patients were continued on their stable antidiabetic regimens, and all medications being used to treat neuropathic pain were discontinued at least 7 days before randomization. Rescue medication was allowed, but could not be used during the 12-hour period before randomization or before treatment visits. At randomization, patients rated

their neuropathic pain on a 100-mm Visual Analog Scale (VAS) (0 mm = no pain; 100 mm = the worst pain imaginable). There were a total of 4 treatment groups throughout these 3 studies: placebo (n=381), [topiramate](#) 100 mg/day (n=250), [topiramate](#) 200 mg/day (n=369), and [topiramate](#) 400 mg/day (n=259). The study design consisted of a baseline phase, a titration phase (6 to 10 weeks depending on target dose) and a 12 week maintenance period. Two of the 3 trials were 22 weeks in duration and 1 trial was 18 weeks in duration. The starting dose of [topiramate](#) was 25 mg/day at bedtime during the first week, followed by weekly increases of 25 mg/day to 100 mg/day, and then weekly 50-mg increment increases until target or maximum tolerated dosages were achieved. The primary efficacy measure was reduction in pain at the final visit compared with baseline scores on the VAS. The intent-to-treat population was defined as all randomized patients who received at least 1 dose of study drug and provided at least one efficacy evaluation. For patients who withdrew from the study early, the last pain evaluation was carried forward. Completion rates were similar across studies, and for each treatment group. At final visit, VAS scores were lower versus baseline for all treatment groups, but the differences did not meet statistical significance in any of the 3 studies. Discontinuation rates due to inadequate pain control were lower in topiramate-treated patients (12% to 17%) compared with the placebo treated patients (20% to 24%) although discontinuation rates due to adverse events were greater in the topiramate-treated patients and were dose-dependent (16% to 31%) compared with placebo-treated patients (8%). The most frequently reported adverse events in the topiramate-treated patients were fatigue, nausea, paresthesia, somnolence, appetite decrease, weight loss, taste perversion, memory difficulty and confusion. Of interest, diabetic control improved in all 3 topiramate-treated groups, with clinically significant reductions in [HbA1c](#) levels (0.5% or greater improvement) in 55% of the [topiramate](#) 100-mg treated patients, 60% of the [topiramate](#) 200-mg treated patients, and 62% of the [topiramate](#) 400-mg treated patients compared with 29% of placebo-treated patients; and clinically significant weight loss (5% or greater of baseline body weight) in 19% to 38% of topiramate-treated patients compared with 7% of placebo-treated patients. The authors reported that although [topiramate](#) therapy did not achieve statistically significant differences in pain control in this study, there were findings, specifically lower discontinuation rates for lack of effect in topiramate-treated patients, improved glycemic control, and beneficial weight loss, that may warrant further studies evaluating the potential therapeutic benefit of [topiramate](#) [52].

b) [Topiramate](#) monotherapy was more effective than placebo in reducing pain associated with [diabetic peripheral neuropathy](#) in a 12-week multicenter, randomized, double-blind trial (n=322). Diabetic patients (18 to 75 years) with stable glycemic control, discontinued their current pain treatments following set protocols and then rated their pain on a pain visual analog (PVA) scale from 0 to 100 (0=no pain; 100=worse possible pain). Patients with moderate or severe pain (PVA scale scores of 40 or more) were randomly assigned to treatment with [topiramate](#) or placebo in a 2:1 ratio. [Topiramate](#) was started at 25 mg once a day and increased in increments of 25 mg/week on weeks 2, 3, and 4, followed by 50 mg/week increments on weeks 5 and 6, and 100 mg/week increments on weeks 7 and 8. The final [topiramate](#) dosage was 400 mg/day (or maximum tolerated dose), and this dosage was maintained through the maintenance phase (weeks 8 to 12) of the trial. The mean daily [topiramate](#) dosage during the 4-week maintenance phase was 320 mg/day, and 161.2 mg over the course of the entire study. The primary efficacy measure was the difference in pain intensity from baseline to the last evaluation as measured on the PVA scale. Efficacy analysis was preformed on the modified intent-to-treat (mITT) population defined as all subjects who received at least one dose of study medication and completed at least one follow-up efficacy assessment. Three hundred twenty three subjects met eligibility criteria and were randomized to [topiramate](#) (n=214, mITT=208) or placebo (n=109, mITT=109). After 12 weeks, topiramate-treated patients experienced a significantly (p=0.038) greater mean decrease in PVA scores (baseline, 68; 12 weeks, 46.2) compared with placebo-treated patients (baseline, 69.1; 12 weeks, 54). Notably, there was a 48% dropout rate; only 112 topiramate-treated subjects and 80 placebo-treated subjects completed the 12-week study. One hundred and 2 topiramate-treated subjects discontinued

the study early; 52 of whom due to adverse events and 31 of them due to lack of efficacy. The most common treatment-emergent adverse events were diarrhea (11.4%), loss of appetite (10.9%) and somnolence (10%). The most common adverse events that lead to early discontinuation: were: nausea (3.3%), somnolence (2.8%), dizziness (2.4%), paresthesia (1.9%), and difficulty with concentration and attention (1.9%) [53]. In an attempt to further assess long-term safety and efficacy of [topiramate](#) in painful [diabetic peripheral neuropathy](#), an open-label extension to this study was undertaken. The following paragraph summarizes these findings:

1) Patients were eligible for this open-label extension study if they completed the above double-blinded [topiramate](#) monotherapy trial or if they had been in the double-blinded [topiramate](#) monotherapy trial for 8 or more weeks, but had discontinued due to lack of effect. Two hundred five patients (118 previously treated with [topiramate](#) and 87 placebo-treated patients) entered this 26-week open-label extension study. Patients entering the open-label extension were tapered from their double-blind regimen ([topiramate](#) or placebo) in the same increments as the [topiramate](#) was increased which allowed the titration to occur without revealing the original study medication to the subjects or investigators. In the 8-week titration phase, patients were titrated to a maximum of 400 mg/day as tolerated. After the initial 8-week titration period, open-label [topiramate](#) was administered without concealment and the dose could be titrated up to 600 mg/day at the discretion of the investigator. The mean dosage of [topiramate](#) during the maintenance phase of this open-label [topiramate](#) study was 312.1 +/- 137.3 mg/day. The primary efficacy measure was the change in pain visual analog (PVA) scores which were recorded at each visit. Patients rated their pain on a PVA scale from 0 to 100 (0=no pain; 100=the worse pain possible). Of the 205 patients who enrolled in the open-label extension study, 124 (60.5%) completed the study. The most common reason for discontinuing the study early was adverse reactions. Mean PVA scores at the end of the open-label extension trial were significantly decreased from the start of the open-label [topiramate](#) trial (p less than 0.001 for both groups). PVA scores in the previously topiramate-treated subjects dropped from 43.3 to 21.8, and from 52.5 to 26.1 for previously placebo-treated patients. The difference in PVA scores between subjects by the end of the open-label extension was not significant. The most commonly reported adverse events associated with [topiramate](#) during double-blind, placebo-controlled or open-label trials were [upper respiratory tract infection](#) (16.1%), anorexia (15.1%), diarrhea (12.8%), nausea (12.8%) and paresthesia (10.7%). Participants in the open-label extension study were asked to rate the effectiveness of long-term [topiramate](#) therapy, 143 out of 199 patients (71.9%) rated [topiramate](#) treatment as good, very good, or excellent overall. Further studies are needed to determine the optimal target dose for [topiramate](#) in [painful diabetic neuropathy](#) [54].

4.5.E] Eating disorder

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

In a 16-week, double-blind, parallel-group, multicenter study (n=394) of obese adult outpatients with [binge-eating disorder](#), [topiramate](#) reduced binge eating episodes and body mass compared with placebo, and was well tolerated [9].

[Quetiapine](#) reduced weight, improved the weekly frequency of bingeing and/or purging, and improved health-related quality of life compared with placebo in women with [bulimia nervosa](#) according to a randomized, double-blind clinical trial (n=60) [10].

[Topiramate](#) was associated with a greater reduction in the mean weekly number of binge and/or purge days when compared with placebo, and may have beneficial effects on some behavioral symptoms of [bulimia](#) [11] [12].

3) Adult:

a) In a 16-week, double-blind, parallel-group, multicenter study among 394 adult outpatients (84% female) with [binge-eating disorder](#) (BED) and [obesity](#), [topiramate](#) was effective in improving the features of BED and in reducing [obesity](#) compared with placebo. After a screening period, eligible patients with 3 or more binge eating days/week and a BMI between 30 and 50 kg/m(2) were randomized to receive placebo (n=199) or [topiramate](#) (n=195) 25 mg daily titrated over an 8-week period to 400 mg/day or the maximum tolerated dose. Seventy percent of patients completed 16 weeks of double-blind treatment in each group. The median final daily dose of [topiramate](#) was 300 mg/day (range, 25 to 400 mg/day), with a mean duration of treatment of 93.6 +/- 33 days for [topiramate](#) and 93.3 +/-33.6 days for placebo. The study met its primary efficacy endpoint in a statistically significant improvement in the mean number of binge eating days/week in the [topiramate](#) group compared with placebo (p less than 0.001) [9].

Change from Baseline to Week 16	Topiramate	Placebo	p values vs placebo
Binge eating days/week (Mean)	-3.7 (from 4.6 to 0.9)	-2.4 (from 4.6 to 2.2)	less than 0.001
Binge eating episodes/week (Mean)	-5.3 (from 6.6 to 1.3)	-3.5 (from 6.3 to 2.8)	less than 0.001

1) Median binge eating days/week also decreased from 4.5 at baseline to 0 beginning at week 5 and lasting throughout the remainder of the study in the [topiramate](#) group. [Topiramate](#) was associated with higher rate of binge eating remission (58% vs 29%; p less than 0.001) compared with placebo , and greater rate of improvement in body weight, BMI, Clinical Global Impression (CGI)-Severity scores, and Yale-Brown Obsessive-Compulsive, modified to binge-eating scores (all p less than 0.001). Treatment discontinuation due to adverse events occurred in 15% of patients in the [topiramate](#) group and 8% of patients in the placebo group. The most common adverse events reported in the [topiramate](#) group compared with the placebo group were paresthesia, [upper respiratory tract infection](#), taste perversion, difficulty with concentration/attention, and difficulty with memory. Serious adverse events occurred in 3 patients in each group (acute [cholecystitis](#), [major depression](#), and tibial fracture in [topiramate](#) group; [asthma](#) exacerbation, stomach virus, and [arrhythmia](#) in placebo group) [9].

b) The percentage reduction in the mean weekly number of binge and/or purge days was greater in the [topiramate](#) arm compared with placebo in a randomized, double-blind trial. Patients (n=64) with DSM-IV [bulimia nervosa](#) were randomized to receive either [topiramate](#) (n=31) or placebo (n=33) for 10 weeks. [Topiramate](#) was initiated at 25 mg/day for 1 week and then was titrated by 25 to 50 mg per week to 400 mg/day or to the maximally tolerated dose (median dose 100 mg/day). Patients recorded the incidence of binge and purge episodes as well as time and quantity of medication taken in a daily diary. From a baseline mean of 5 binge and/or purge days per week, the intent-to-treat

analysis demonstrated a 44.8% reduction in the [topiramate](#) arm compared with a 10.7% reduction in the placebo arm (primary outcome; $p=0.004$). [Topiramate](#) was associated with a greater reduction in mean weekly number of binge days alone (48.2% vs 17.7%; $p=0.015$) and mean weekly binge frequency (49.2% vs 28%; $p=0.071$) compared with placebo. Similarly greater reduction in the mean weekly purge days (43.4% vs 16.6%; $p=0.016$) and weekly purge frequency (49.8% vs 21.6%; $p=0.016$) was observed in the [topiramate](#) arm compared with placebo. Fatigue, flu-like symptoms, and paresthesias were the most common adverse effects associated with [topiramate](#) use [11]. Further analysis on Eating Disorder Inventory (EDI) and Eating Attitudes Test (EAT) revealed that [topiramate](#) alleviated other behavioral attributes central to [bulimia nervosa](#). Improvements in EDI subscale scores for [bulimia](#)/uncontrollable overeating, body dissatisfaction and drive for thinness were better among patients receiving [topiramate](#) compared with cohorts receiving placebo ($p=0.005$, 0.007 and 0.002 , respectively). However changes in ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness and maturity fears were not statistically different between groups. Percent change in EAT subscale scores from baseline for [bulimia](#)/food preoccupation and dieting were significantly higher with [topiramate](#) compared with placebo ($p=0.019$ and 0.031); however oral control was not. Comparison studies with psychotherapy and/or antidepressants are needed to elucidate what role, if any, [topiramate](#) has in the treatment of [bulimia nervosa](#) [12].

Change from Baseline to Endpoint	Topiramate	Placebo	p values vs placebo
Eating Disorder Inventory (EDI)			
Subscale Scores			
Bulimia /Uncontrollable Overeating	10.4 to 5.9	11.5 to 10.3	0.005
Body Dissatisfaction	16.7 to 14.2	19.1 to 19.9	0.007
Drive for Thinness	14.1 to 10.9	16.2 to 15.3	0.002
Eating Attitudes Test (EAT)			
Subscale Scores			
Bulimia /Food Preoccupation	11.5 to 7.9	12.4 to 10.9	0.019
Dieting	18.3 to 15.2	22.5 to 20.6	0.031

[12]

c) [Topiramate](#) produced greater reductions in the frequency of bingeing and/or purging and weight loss, and a greater improvement in health-related quality of life (HRQOL) compared with placebo in women with [bulimia nervosa](#) in a randomized, double-blind clinical trial. Women ($n=60$; 18 years or older) with a 12-month history of DSM-IV [bulimia nervosa](#), were randomized to [topiramate](#) 25 mg daily ($n=30$; titrated up to 250 mg/day in week 6) or placebo ($n=30$) for 10 weeks. Mean weekly bingeing and/or purging episodes at the end of 10 weeks improved from 8 at baseline to 4.6 in the [topiramate](#) arm, and remained stable from 8 at baseline to 7.9 in the placebo arm (between group difference, -3.3 ; 95% CI, -4.3 to -2.1 ; p less than 0.001). Mean body weight was reduced from 64.9 kg at baseline to 60.9 kg at endpoint in the [topiramate](#) arm compared with a relatively stable weight from 64.5 kg at baseline to 64.2 kg at endpoint in the placebo arm (p less than 0.001). Each component of the SF-36 Health Survey, including physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health were significantly improved in the [topiramate](#) arm compared with the placebo arm (p less than 0.001 for each subscale). For all outcome measures, improvements in the [topiramate](#) arm increased more rapidly starting after week 5 of treatment. Sedation, dizziness, headache, and paresthesia were reported in isolated cases in both groups [10].

4.5.F] Essential tremor

1)) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2)) Summary:

Significant decreases seen in overall Fahn-Tolosa-Marin Tremor Rating Scale (TRS) compared with placebo, according 4 randomized, double-blind, studies (pooled data from 3 crossover trials, 1 parallel-design) of adults with moderate to severe essential tremor [15] [16]

3)) Adult:

a)) In pooled analysis from 3 randomized, double-blind, crossover trials of 64 adults with moderate to severe essential tremor of the hands, head, or voice, topiramate-treated patients had a significant decrease in the overall Fahn-Tolosa-Marin Tremor Rating Scale (TRS) score compared with placebo at 22 week follow-up. Overall TRS scores (range of 0 to 100, with 100 being most severe) were based on an average of the 3 normalized subscale scores (upper limb tremor severity, motor tasks, and functional disability). Patients with a mean age of 62 +/- 15 years were randomized to receive either [topiramate](#) or placebo in the 10-week period 1 (n=32), and following a 2-week washout period, were crossed-over to receive placebo or [topiramate](#) in the 10 week period 2 (n=30). Concomitant tremor ameliorating drugs were permitted (77% of patients), with beta-blockers accounting for 46% of use. Topiramate-treated patients initially received 25 mg/day for 1 week, with weekly titrations in increments of 25 or 50 mg/day up to 200 mg/day, then 100 mg/day weekly increments to a clinical response, up to a maximum of 400 mg/day. It was required that all patients receive a stabilized maintenance dose for at least 2 weeks; the mean dose of [topiramate](#) was 215 mg/day (range, 25 to 400 mg/day). An analysis of patients on-treatment (completion of period 1 with efficacy data, and at least one efficacy assessment in period 2) revealed a mean overall TRS score in topiramate-treated patients of 28.7 +/- 1 compared with 37 +/- 1 in placebo, representing a corresponding mean score reduction of 9.1 vs 0.8 from baseline (p less than 0.0001). Treatment-limiting adverse events occurred in 24% (n=13) of [topiramate](#) patients and 10% (n=5) in placebo. Adverse events in [topiramate](#)- compared with placebo-treated patients included paresthesia (16% vs 2%), concentration/attention difficulties (13% vs 0%), and decreased appetite (10% vs 0%) [15].

b)) Topiramate-treated adults had a significant decrease in the overall Fahn-Tolosa-Marin Tremor Rating Scale (TRS) score compared with placebo, according to a 24-week, randomized, double-blind, parallel-design study of 208 patients with moderate to severe essential tremor of the hands or forearms. Overall TRS scores (range of 0 to 100) were based on an average of the three normalized subscale scores (upper limb tremor severity, motor function, and functional disability). Patients included in the study had a mean age of 62 +/- 13 years with a baseline tremor severity score of greater than 2 in the dominant hand/arm, and a mean TRS score of 38.7 +/-12.4 and 37.3 +/- 12 in the [topiramate](#) and placebo groups, respectively. Following discontinuation of any tremor-genic medications for at least 5 half-lives, patients were randomized to receive either placebo (n=106), or [topiramate](#) (n=117) 25 mg/day with titration over 12 weeks in 25-mg weekly increments to 100 mg/day, and then in 50-mg increments to a maximum of 400 mg/day, as tolerated, or the tremor ameliorating dose. Total daily [topiramate](#) doses of 50 mg or greater were administered twice daily. It was required that all patients

receive at least 50 mg/day from week 2 forward and the maximum achieved dose continue during the 12-week maintenance phase. The mean [topiramate](#) dose administered was 292 +/- 129 mg/day (median, 375 mg/day). In a modified intent-to-treat analysis of patients receiving at least 1 dose of study medication and 1 postbaseline assessment (n=208), the overall TRS score at week 24 was 27.9 +/- 13.2 in the [topiramate](#) group compared with 31.5 +/- 13.4 in placebo, indicating a mean reduction of 10.8 +/- 9.5 vs 5.8 +/- 7.5 (95% CI, 2.5 to 6.7, p less than 0.001), respectively. In an analysis of the individual subscales, there was a significant change between [topiramate](#) and placebo in the motor function and functional disability scores (p less than 0.001). Significant improvement in the overall TRS score was seen in the [topiramate](#) group at the twenty-eighth day on-treatment visit and continued for the duration of the study (compared with placebo, p less than 0.001). The incidence of treatment-limiting adverse events was 31.9% in evaluable topiramate-treated patients (n=116) compared with 9.5% in placebo (n=105). Adverse events in [topiramate](#)- compared with placebo-treated patients included paresthesia (28% vs 5%), weight loss (22% vs 3%), and memory difficulties (13% vs 1%). In the [topiramate](#) group, body weight was reduced by 3.6 kg, with a reduction of BMI of 1.3 kg/m(2) from baseline [16].

4.5.G] [Lennox-Gastaut syndrome; Adjunct](#)

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(Topamax\(R\), 2 years or older; Trokendi XR\(TM\), 6 years or older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) immediate-release oral tablets and capsules ([Topamax\(R\)](#)) are indicated for adjunctive therapy in the treatment of generalized seizures associated with [Lennox-Gastaut syndrome](#) in patients 2 years or older [17] [29] [30].

[Topiramate](#) extended-release oral capsule ([Trokendi XR\(TM\)](#)) is indicated for adjunctive therapy in patients 6 years or older with [Lennox-Gastaut syndrome](#). Approval is based upon demonstration of pharmacokinetic equivalence to immediate-release [topiramate](#) [1].

The effectiveness of [topiramate](#) as an adjunctive treatment for seizures associated with [Lennox-Gastaut syndrome](#) was established in a multicenter, randomized, double-blind, placebo-controlled trial (n=98) [18] [29].

3) Adult:

a) Adjunctive [topiramate](#) therapy was effective in reducing the number of drop attacks or tonic-atonic seizures associated with [Lennox-Gastaut syndrome](#). In a double-blind trial, patients (aged 1 to 30 years old) with [Lennox-Gastaut syndrome](#) were randomized to receive either [topiramate](#) (n=48) or placebo (n=50) as adjunctive therapy to their current antiepileptic therapy. [Topiramate](#) was initially administered as 1 mg/kg/day twice daily. By the third week it was titrated up to 6 mg/kg/day. This dose or the maximal tolerated dosage was maintained for an 8-week maintenance period. The median average dosage of [topiramate](#) during the maintenance period was 5.8 mg/kg/day. The median percentage reduction in drop attacks from baseline in the average monthly seizure rate was significantly greater in the [topiramate](#) group as compared with the placebo group (14.8% vs 5.1%, p=0.041). Parents

also judged (utilizing a global evaluation) the children in the [topiramate](#) group as twice as likely to have a significant improvement in seizure severity ($p=0.037$). When all seizures were reviewed (generalized and partial), there was no significant reduction in median percentage decline from baseline. However, when [atypical absence seizures](#) were excluded, the median percentage reduction in the average monthly seizure rate was 23.9% for [topiramate](#) and 2% for placebo. Common adverse effects in the [topiramate](#) group included somnolence, anorexia, nervousness, behavioral problems, fatigue, dizziness, and weight loss. This study suggests that [topiramate](#) is an important addition for the treatment of [Lennox-Gastaut syndrome](#) [29].

b) In a long-term study of the efficacy and safety of [topiramate](#) as add-on therapy for refractory [epilepsy](#) or [Lennox-Gastaut syndrome](#), 6 of 15 patients (46%) experienced a reduction in seizure frequency of 50% or greater after 2 months of treatment and 9 of 15 (69%) during the last 2 months of treatment during the follow-up period of 14 to 21 months. [Topiramate](#) treatment was initiated with a dosage of 100 mg/day and was gradually increased to 600 mg/day, based upon the individual patient tolerance. Final dosages ranged from 400 to 800 mg/day. Patients continued treatment with their other antiseizure medications, including therapies with 2 or more of the following drugs: [carbamazepine](#), [phenobarbital/primidone](#), [valproic acid](#), vigabatrin, benzodiazepines, [phenytoin](#) [30].

4) Pediatric:

a) Adjunctive [topiramate](#) therapy was effective in reducing the number of drop attacks or tonic-atonic seizures associated with [Lennox-Gastaut syndrome](#). In a double-blind trial, patients (aged 1 to 30 years) with [Lennox-Gastaut syndrome](#) were randomized to receive either [topiramate](#) ($n=48$) or placebo ($n=50$) as adjunctive therapy to their current antiepileptic therapy. [Topiramate](#) was initially administered as 1 mg/kg/day twice daily. By the third week it was titrated up to 6 mg/kg/day. This dose or the maximal tolerated dosage was maintained for an 8-week maintenance period. The median average dosage of [topiramate](#) during the maintenance period was 5.8 mg/kg/day. The median percentage reduction in drop attacks from baseline in the average monthly seizure rate was significantly greater in the [topiramate](#) group as compared with the placebo group (14.8% vs 5.1%, $p=0.041$). Parents also judged (utilizing a global evaluation) the children in the [topiramate](#) group as twice as likely to have a significant improvement in seizure severity ($p=0.037$). When all seizures were reviewed (generalized and partial), there was no significant reduction in median percentage decline from baseline. However, when [atypical absence seizures](#) were excluded, the median percentage reduction in the average monthly seizure rate was 23.9% for [topiramate](#) and 2% for placebo. Common adverse effects in the [topiramate](#) group included somnolence, anorexia, nervousness, behavioral problems, fatigue, dizziness, and weight loss. This study suggests that [topiramate](#) is an important addition for the treatment of [Lennox-Gastaut syndrome](#) [29].

b) During the double-blind phase of a randomized, placebo-controlled trial ($n=98$) (average [topiramate](#) dose 4.8 mg/kg/day), significant reduction in drop attacks and significant improvement in global impression (by parents or guardians) of seizure severity was reported in topiramate-treated children compared with those treated with placebo ($p=0.04$). During the open-label portion of the study ($n=97$), a 50% or greater reduction in drop attacks was reported in 58% of patients treated with [topiramate](#) (mean dose of 11 mg/kg/day) and a 75% or greater reduction was reported in 37% of patients [31].

4.5.H] Migraine; Prophylaxis

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (([Topamax](#)(R) only)); [Pediatric, no](#)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) immediate-release oral tablet and capsule ([Topamax\(R\)](#)) are indicated in adults for the [prophylaxis of migraine](#) headache [17].

[Topiramate](#) efficacy for the prophylactic treatment of migraine headaches was established in 2 double-blind, randomized, controlled trials (n=937) [18] [32].

In an open-label study (n=58), the combination of a beta-blocker ([propranolol](#) or [nadolol](#)) plus [topiramate](#) was beneficial in approximately 60% of patients with migraine who had not previously responded to monotherapy with either agent [33].

[Topiramate](#) has shown benefit in [migraine prophylaxis](#) in children and adolescents [34] [35] [36] [37].

In a post hoc subset analysis of adolescent patients (n=51) pooled from three 26-week, randomized, double-blind, similarly designed, placebo-controlled trials of [topiramate](#) for [migraine prophylaxis](#), [topiramate](#) 100 mg/day and [topiramate](#) 200 mg/day were equally effective in decreasing monthly migraine frequency from baseline, but patients receiving [topiramate](#) 200 mg/day experienced more adverse events [36].

One year of [topiramate](#) therapy for [migraine prophylaxis](#) resulted in a significant reduction in migraine days compared with discontinuation of [topiramate](#) after 6 months; however, discontinuation of [topiramate](#) after 6 months was beneficial in reduction of migraine days compared with pretreatment values. Patients should be treated for 6 months with the option to continue treatment to 12 months based on patient efficacy and tolerability [38].

See Drug Consult reference: MIGRAINE -- RECOMMENDATIONS FOR PROPHYLAXIS IN ADULTS

See Drug Consult reference: MIGRAINE -- RECOMMENDATIONS FOR TREATMENT IN CHILDREN AND ADOLESCENTS

3) Adult:

a) Monotherapy

1) [Topiramate](#) efficacy for the prophylactic treatment of migraine headaches was established in 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials (n=937). These 2 identically designed clinical trials enrolled patients with at least a 6 month history of migraine headaches (with or without aura) as defined by the International Headache Society diagnostic criteria. Patients with a history of cluster headaches, basilar, ophthalmoplegic, hemiplegic or transformed migraine headaches were excluded. Patients were required to complete a 2-week washout prior to entering the baseline phase. Patients who experienced 3 to 12 migraine headaches over the 4 week baseline phase were randomized to [topiramate](#) 50 mg/day, [topiramate](#) 100 mg/day, [topiramate](#) 200 mg/day or placebo and treated for a total of 26 weeks (8-week titration period and 18-week maintenance period). [Topiramate](#) was initiated at 25 mg daily for 1 week, and increased by 25 mg weekly until reaching the assigned target dose or maximum tolerated dose (administered twice daily). Effectiveness of treatment was assessed as a change in 4-week migraine headache frequency from baseline phase to the double-blind treatment period in each of the [topiramate](#) groups and placebo in the intent-to-treat population. Patients on [topiramate](#) 100 mg/day and 200 mg/day experienced

statistically significant decreases in migraine days compared with placebo. The paragraphs below summarize these trials [18].

a) In the first trial, 469 patients (416 female, 53 males) ranging in age from 13 to 70 years were randomized to topiramate 50 mg/day, 100 mg/day, 200 mg/day, or placebo. The mean migraine headache frequency rate at baseline was similar across treatment groups at 5.5 migraine headaches in 28 days. Two hundred sixty-five patients completed the 26-week trial. The median average daily topiramate dosages were 47 mg/day (50 mg group), 88.3 mg/day (100 mg group) and 132.1 mg/day (200 mg group). The change in mean 28 day migraine headache frequency rates from baseline were; -1.3, -2.1, and -2.2 in the topiramate 50 mg, 100 mg and 200 mg groups respectively, compared with -0.8 in the placebo group. Patients treated with topiramate 100 mg/day and 200 mg/day experienced a statistically significant (p less than 0.001 for both comparisons) reduction in frequency of migraine headaches compared with placebo [18].

b) In the second trial, 468 patients (406 female, 62 males) ranging in age from 12 to 65 years were randomized to topiramate 50 mg, 100 mg, 200 mg or placebo. The mean migraine headache frequency rate at baseline was similar across treatment groups at 5.5 migraine headaches in 28 days. Two hundred fifty-five patients completed the 26-week trial. The median average daily topiramate dosages were 46.5 mg/day (50 mg group), 85.6 mg/day (100 mg group) and 150.2 mg/day (200 mg group). The change in mean 28 day migraine headache frequency rate from baseline was; -1.4, -2.1, and -2.4 in the topiramate 50 mg, 100 mg and 200 mg groups respectively; versus -1.1 in the placebo group. Patients treated with topiramate 100 mg/day and 200 mg/day experienced a statistically significant ($p=0.008$ and p less than 0.001, for topiramate 100 mg and 200 mg, respectively) reduction in frequency of migraine headaches compared with placebo. Adverse events reported in 10% or more of topiramate patients include paresthesia, fatigue, anorexia, diarrhea, weight loss, hypesthesia, difficulty with memory, and nausea [18] [32].

b) Combination Therapy

1) In an open-label study ($n=58$), the combination of a beta-blocker ([propranolol](#) or [nadolol](#)) plus [topiramate](#) was beneficial in approximately 60% of patients with migraine who had not previously responded to monotherapy with either agent. Patients (47 women; age, 25 to 76 years) with a history of International Headache Society-classified migraine of at least 1 year, who had not responded to a beta-blocker ([propranolol](#) or [nadolol](#)) and [topiramate](#) (for at least 1.5 months each as monotherapy), received the combination of beta-blocker and [topiramate](#). Response was defined as a greater than 50% decrease in the number of days with headache in the third month of combination therapy, compared with the number of days with headache the month before combination therapy. Twenty patients (34.5%) met the criteria for chronic migraine, 13 patients (22.4%) for medication overuse headache, 18 patients (31%) for migraine without aura, and 7 patients (12%) with aura. Ten patients (17%) discontinued therapy early due to adverse events (ie, cognitive impairment, paresthesias, depression, digestive symptoms, and exaggerated weight loss). After 3 months of therapy, the mean daily dosage for beta blockers ([propranolol](#), $n=24$; [nadolol](#), $n=34$) was 52 mg (median, 60 mg; range, 40 to 80 mg) and for [topiramate](#) was 82 mg (median, 100 mg; range, 50 to 200 mg). Thirty-six (75%, 62% of the total series) of the 48 patients who tolerated the combination, showed a response, while

12 (25%, 21% of the total series) patients did not. The frequency of headache decreased from 15.1 to 6.5 days per month (a 57% reduction). An excellent response (the reduction in headache days of greater than 75%) occurred in 16 patients (44% of responders). Overall, 18 patients (38%) experienced a total of 25 mild to moderate adverse events (ie, cognitive impairment, paresthesias, digestive symptoms, renal colic, and impotence) [33].

c) Duration of Therapy

1) The Prolonged Migraine Prevention with [Topiramate](#) trial (PROMPT), a multicenter, randomized, double-blind, placebo-controlled trial, showed that 1 year of [topiramate](#) therapy for [migraine prophylaxis](#) resulted in a significant reduction in migraine days compared with discontinuation of [topiramate](#) after 6 months; nonetheless, discontinuation of [topiramate](#) after 6 months resulted in a reduction of migraine days compared with pretreatment values. Patients (n=954) ranging in age from 18 to 80 years, with a history of migraine headaches (with or without aura) for at least 1 year and a mean of at least 4 migraine days per month in the previous 3 months, entered into the baseline phase. Patients were excluded if they received prophylactic medication in the month prior (or flunarizine in the 3 months prior), if they overused acute medication, if they had experienced poor or no efficacy with 2 or more regimens of migraine prophylactic medication, or had used [topiramate](#) regularly for 2 or more weeks before study entry. During the baseline phase, patients received no study medication (acute medication was allowed) and were required to record the occurrence of migraine headaches. Patients experiencing 4 migraine days in 4 weeks (or 8 migraine days in 8 weeks) entered into the open-label [topiramate](#) phase. Patients (n=818; aged 39.8 +/- 10.9 years; migraine duration of 13.2 +/- 12.3 hours) were started on [topiramate](#) 25 mg/day for one week, increasing in 25-mg increments weekly to a target dose of 100 mg/day (administered twice daily) or the maximum tolerated dose not to exceed 200 mg/day. During the final 4 weeks of the [topiramate](#) open-label phase, the [topiramate](#) dose was kept stable. The median modal dose of [topiramate](#) during the open-label treatment phase was 100 mg/day. After 26 weeks of [topiramate](#) therapy, 559 patients were eligible for the double-blind phase of the trial. Forty-five patients withdrew consent and 514 patients were then randomized to [topiramate](#) (n=255) or placebo (n=259). Two patients, one in each group, withdrew from the trial after randomization but before receiving study medication. Patients randomized to [topiramate](#) were continued on the same [topiramate](#) dose they received the final 4 weeks of the [topiramate](#) open-label phase. Patients assigned to placebo reduced their daily [topiramate](#) dose by 100 mg per week until discontinuation. Four hundred seventeen patients completed the double-blind phase (n=210 [topiramate](#), n=207, placebo). Efficacy analysis was by intention to treat (ITT) for all 514 patients in the double-blind phase who took at least one dose of study medication. The primary endpoint was the change in number of migraine days during the last 4 weeks of the double-blind phase compared with the last 4 weeks of the open-label phase. The mean number of migraine days increased for both groups in the double-blind phase, but the magnitude of increase was greater for patients switching from [topiramate](#) to placebo (+1.19 days; 95% CI, 0.71 to 1.66 days; p less than 0.0001) than those continuing on [topiramate](#) (+0.1 days; 95% CI, -0.36 to 0.56 days; p=0.0011), and the difference between increases was significant (-1.09 days; CI, -1.75 to -0.43 days; p=0.0011). Further, the number of mean migraine days in patients discontinuing [topiramate](#) prophylaxis after 26 weeks (patients switching to placebo) did not return to pretreatment values (baseline, 9 +/- 4.5 days; endpoint, 5.82 +/- 4.36 days), suggesting that 6 months of [topiramate](#) treatment is beneficial in reducing migraine frequency. During the study, patients maintained a diary recording migraine frequency, severity and duration, as well as use of acute medication. These diary entries showed treatment with [topiramate](#) had little or no effect on the intrinsic

properties of a migraine (severity and duration showed little to no change), but the threshold for occurrence of a migraine decreased with [topiramate](#) use. Adverse events were most common in the open-label phase of the trial with 21% (including patients who cited both insufficient tolerability and insufficient efficacy) discontinuing [topiramate](#) because of adverse events. The most frequently reported adverse events in the open-label phase were paraesthesias (50%), fatigue (12%), disturbance in attention (12%), anorexia/decreased appetite (11%), weight loss (9%), and nausea (9%). In the double-blind phase, paraesthesias continued to be the most frequently reported event [38].

4) Pediatric:

a) In a double-blind, randomized, placebo-controlled, single-center trial comparing the efficacy of [topiramate](#) (n=21) to placebo (n=21) in [migraine prophylaxis](#) in children (8 to 13 years of age), topiramate-treated subjects experienced a significantly greater reduction in mean monthly migraine frequency compared with placebo-treated subjects. Children were treated with [topiramate](#) for a total of 4 months, including a 1-month titration period. [Topiramate](#) was started at 25 mg/day and increased in 25-mg increments weekly to 100 mg/day (in 2 divided doses) or to the maximum tolerated dose. The primary outcome measures were the reduction in mean migraine frequency and severity of headache from baseline. [Topiramate](#) treated subjects experienced a reduction in migraine frequency from 16.14 +/- 9.35 per month at baseline to 4.27 +/- 1.95 per month at the end of the study compared with placebo-treated patients who experienced a reduction from 13.38 +/- 7.48 at baseline to 7.48 +/- 5.94 at the end of the study (p=0.025). There was no statistically significant difference in migraine severity. The percentage of children experiencing a greater than 50% reduction in monthly migraine days was significantly (p=0.002) greater in the topiramate-treated patients 20 of 21 (95.2%) compared with the placebo patients 11 of 21 (52.4%). Adverse events occurring more frequently in the topiramate-treated subjects were weight loss (81%), loss of appetite (23.8%), paraesthesias (23.8%), decreased concentration in school (19%), sedation (19%) and abdomen pain (14.3%). Most adverse events were mild to moderate and no subject dropped from the study because of an adverse event [35].

b) In a 20-week, double-blind, randomized, placebo-controlled, multicenter trial (n=162), [topiramate](#) was not different from placebo in reducing the mean number of migraine days per month; nonetheless, significantly more topiramate-treated children experienced a 75% or greater reduction in monthly migraine days compared with placebo during the last 4 weeks of the trial (50.9% vs 30.6%; p=0.024). Children (6 to 15 years old) with a history of pediatric migraine (with or without aura) experiencing 3 to 10 migraine days/month in the 3 months prior and during the 4-week baseline period, were randomized in a 2:1 ratio to receive [topiramate](#) (n=112) or placebo (n=50) for 20 weeks. [Topiramate](#) was started at 15 mg/day, increasing to 30 mg/day for 1 week and then 50 mg/day for one week. After week 3, [topiramate](#) was further increased at investigator discretion to a target dose of 2 to 3 mg/kilogram (kg)/day or to a maximum tolerated dose not exceeding 200 mg/day (administered twice a day in evenly divided doses). After an 8 week titration period, patients moved to a 12-week maintenance period. The average daily dose of [topiramate](#) during the maintenance period was 2 mg/kg/day. The primary efficacy analysis was based on a population defined as subjects receiving at least 1 dose of study medication and having at least 1 post baseline efficacy assessment ([topiramate](#), n=108; placebo, n=49). The primary efficacy analysis compared the reduction of migraine days/month (28 days) in both treatment groups from baseline to endpoint follow-up. Additional analysis included reduction in number of migraine days in the last 28 days of the maintenance period and categorical responses rates (eg. percentage of subjects with greater than 50% response, greater than 75% response and 100% response). During the 20-week study, topiramate-treated subjects experienced a mean reduction of 2.6 migraine days/month compared with a mean reduction of 2 migraine days/month in the placebo group (p=0.061). When looking at the last 28 days of this 20 week study, topiramate-treated subjects experienced a

reduction of 3.1 +/- 3 migraine days compared with a reduction of 2.4 +/- 2.8 migraine days in the placebo group ($p=0.023$). Of note, the reduction in migraine days/month was not significant over the 20-week trial, but was significant for the last 4 weeks of the 20-week trial. For medications such as [topiramate](#), which require an initial titration period, it may take time for maximal effect. The percentage of topiramate-treated patients showing a 50% or greater reduction in monthly migraine days during the last 28 days was not significant ([topiramate](#) 69.4% vs placebo 53%; $p=0.051$), but the percentage of children experiencing a 75% or greater reduction in monthly migraine days was significant ([topiramate](#) 50.9% vs placebo 30.6%; $p=0.024$). Adverse events occurring more frequently in the [topiramate](#) group were [upper respiratory tract infection](#) (19.4%), anorexia (13%), weight decrease (10.2%), [gastroenteritis](#) (9.3%), paraesthesias (8.3%) and somnolence (8.3%). Serious adverse events occurred in 4 [topiramate](#) subjects (infection ($n=2$), severe migraine ($n=1$) and [suicidal ideation](#) ($n=1$)) [37].

c) In a post hoc subset analysis of adolescent patients ($n=51$) pooled from three 26-week, randomized, double-blind, similarly designed, placebo-controlled trials of [topiramate](#) for [migraine prophylaxis](#), [topiramate](#) 100 mg/day and [topiramate](#) 200 mg/day were equally effective in decreasing monthly migraine frequency from baseline, but patients receiving [topiramate](#) 200 mg/day experienced more adverse events. One thousand five hundred forty-three subjects were randomized in these 3 original trials; of these, 51 were adolescents (12 to 17 years old) and received: placebo ($n=12$), [topiramate](#) 50 mg/day ($n=12$), [topiramate](#) 100 mg/day ($n=13$) or [topiramate](#) 200 mg/day ($n=14$). Forty-nine adolescents were included in the modified intent-to treat data set (no data were obtained for 2 subjects). [Topiramate](#) 100 mg/day produced a 63% reduction and [topiramate](#) 200 mg/day resulted in a 65% reduction in monthly migraine frequency compared with baseline (p less than or equal 0.04). [Topiramate](#) treatment reduced the mean number of monthly migraine days by 1, 4, and 5 days for [topiramate](#) 50, 100 and 200 mg/day, respectively, compared with 1 day with placebo treatment. The most common adverse events reported for topiramate-treated patients were paresthesia, [upper respiratory infection](#) and weight decrease. Cognitive adverse events (difficulty with concentration, memory or language problems) were reported in 7 patients (5 in the [topiramate](#) 200 mg/day and 2 in the placebo group). Adverse events were more frequent in the [topiramate](#) 200 mg/day group [36].

d) [Topiramate prophylaxis of migraine](#) headaches in dosages of 25 mg/day and 100 mg/day resulted in 86% of patients responding with greater than a 50% reduction in migraine frequency in a double-blind, single-center, dose comparison study ($n=14$) in children 6 to 18 years of age. Children (10 female, 4 male) with a history of [basilar type migraines](#) and a history of experiencing greater than 4 migraine headache days per month were randomized to either [topiramate](#) 25 mg/day or [topiramate](#) 100 mg/day (both given twice a day to maintain blinding). Fifteen patients enrolled, 14 completed the double-blind phase. The primary efficacy endpoint measure was reduction in overall monthly migraine days relative to the baseline phase with secondary efficacy outcome measures looking specifically at [basilar migraine](#) frequency and proportion of responders. During a 4 week prospective baseline period, patients were allowed abortive medicines to treat migraine attacks, but no other preventative therapies were permitted. The average monthly migraine days during this baseline phase were 4.5 (25 mg) and 4.8 (100 mg) days. After completion of the baseline phase, [topiramate](#) was titrated over 4 weeks to target doses of 25 mg/day ($n=7$) or 100 mg/day ($n=7$), and continued for 12 weeks. All subjects experienced a decrease in overall monthly migraines days and [basilar migraine](#) days during the study. Children in the [topiramate](#) 25 mg/day group experienced an overall reduction of 2.9 mean monthly migraine days which included a reduction of 2.5 in mean monthly basilar headache days compared with baseline; and children in the [topiramate](#) 100 mg/day group experienced an overall reduction of 3.6 mean monthly migraine days/month which included a reduction of 2.3 mean monthly basilar headache days compared with baseline (all p less than 0.001). Overall, [basilar migraine](#) days were reduced from 2.84 to 0.59 days/month (p less than 0.0042), and the reduction in migraine days/month between the 2 dosages was not significant (p equal or higher than 0.83). All (100%) children in the [topiramate](#) 25 mg/day group

and 71% of children in the [topiramate](#) 100 mg/day group experienced a greater than 50% reduction in overall migraine frequency. Numbness and tingling in face and hands was the most commonly reported adverse event. No patients withdrew from the study because of this event. One patient in the [topiramate](#) 100 mg group reported learning difficulty, but no objective deterioration in school performance was noted [34].

e) According to the results of a retrospective study including 75 pediatric patients with very frequent migraine headaches, [topiramate](#) given at mean daily doses of 1.4 mg/kg/day reduced headache frequency from a mean of 16.5 headaches per month to 11.6 headaches per month (p less than 0.001). Mean headache duration, severity, and accompanying disability were also reduced. Common adverse effects included weight loss (5.6%), sensory symptoms (2.5%), and cognitive changes (12.5%) [39].

4.5.I] Obesity

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) treatment at 4 different doses produced significant reductions in body weight at week 60 compared with placebo in obese adults according to a randomized, double-blind, parallel-group study [5].

[Topiramate](#) at 4 different dosages produced greater weight loss among obese patients than placebo in a 6-month, randomized, double-blind study (n=385) [6].

3) Adult:

a) [Topiramate](#) treatment at 4 different doses produced significant reductions in body weight at week 60 compared with placebo in obese adults according to a multicenter, randomized, double-blind, parallel-group study. The study was originally planned for a duration of 2 years, but was terminated early to develop a controlled-release formulation to improve tolerability and simplify dosing; resulting in a total of 854 patients evaluable for efficacy and 1282 patients evaluable for safety. The longest duration of treatment received by any patient was 83 weeks. Patients included in the study had a mean age of 44.5 +/- 10.8 years (range, 18 to 75 years), a mean BMI of 37.3 +/- 5.2, and a mean body weight of 104.8 +/- 17.8 kg. Patients with controlled [hypertension](#) or [dyslipidemia](#) and minimum BMI of 27 kg/m² were permitted, but patients with [diabetes](#) were prohibited unless diagnosis of [type 2 diabetes](#) occurred at enrollment and antidiabetic agents were not necessary. Following a 6-week placebo run-in period, patients were randomized to receive either placebo (n=324; evaluable for efficacy n=215) or [topiramate](#) 96 mg (n=323; evaluable n=214), 192 mg (n=320; evaluable n=215), or 256 mg (n=322; evaluable n=210) in 2 divided daily doses. During an 8-week titration phase all [topiramate](#) patients were initialized with 16 mg/day and were up-titrated to their assigned doses before they entered the maintenance phase. One dose reduction was permitted for intolerable adverse events, but patients were discontinued from the study if events persisted. All patients received a lifestyle management program including nutrition, exercise, and psychosocial structuring, and were prescribed an individualized 600 kcal-deficit diet with a maximum of 30% fat. In an analysis of patients who completed at least 60 weeks

of treatment, had taken at least 1 dose and completed 1 follow-up visit, the mean change in body weight (primary endpoint) was -1.7% from 104 kg at baseline with placebo, -7% (baseline, 105.3 kg) with [topiramate](#) 96 mg, -9.1% (baseline, 103.3 kg) with [topiramate](#) 192 mg, and -9.7% (baseline, 106.3 kg) with [topiramate](#) 256 mg (all p less than 0.001 vs placebo). Secondary endpoint analysis demonstrated significantly greater percentage of patients in the 96, 192, and 256 mg [topiramate](#) groups achieved at least 5% reduction in weight loss at 60 weeks (54%, 61%, and 67%) compared with 18% in the placebo group (p=0.001 or less). [Topiramate](#) was associated with higher incidence of paraesthesia (57% vs 9%), language problems (6% vs 1%), difficulty with concentration/attention (11% vs 3%), fatigue (23% vs 20%), taste perversion (12% vs 1%), and abnormal vision (6% vs 2%). Due to early termination of the trial and adverse events, such as paraesthesia, depression, difficulty concentrating, difficulty with memory, fatigue, and mood problems, patients remaining in the study at 60 weeks were 102 in the placebo arm, 133 in [topiramate](#) 96-mg arm, 122 in [topiramate](#) 192-mg arm, and 124 in [topiramate](#) 256-mg arm [5].

b) [Topiramate](#) produced significantly (p less than 0.05 after week 4) greater weight loss than placebo in a 6-month, randomized, double-blind, dose-ranging study involving 385 obese patients (aged 18 to 75 years) with BMI between 27 to less than 50 kg/m². Patients were randomized to receive placebo or [topiramate](#) at 64, 96, 192, or 384 mg daily (doses began at 16 mg and were gradually increased to the target doses). After 24 weeks, all patients were tapered off treatment by a dose reduction of 50% per week and all patients participated in the same lifestyle program. Mean percent weight loss from baseline to week 24 (primary outcome) was -2.6% from 105.4 kg at baseline for placebo and -5% (baseline, 103.1 kg), -4.8% (baseline, 104.6 kg), -6.3% (baseline, 101 kg), and -6.3% (baseline, 104.5 kg) in the 64, 96, 192, and 384 mg/day treatment groups, respectively. The most frequent adverse events included paresthesia, somnolence, and difficulty with memory, concentration, and attention. Most events were dose-related and appeared early in treatment, and usually resolved spontaneously. Of patients receiving [topiramate](#), 21% withdrew due to adverse events compared with 11% on placebo. Lower doses warrant further clinical evaluation for long-term treatment of [obesity](#) [6].

4.5.J] Partial seizure, Initial monotherapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(Topamax\(R\), 2 years or older; Trokendi XR\(TM\), 10 years or older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) immediate-release oral tablet and capsule ([Topamax\(R\)](#)) are indicated as initial monotherapy in patients 2 years or older with partial-onset seizures [17].

[Topiramate](#) extended-release oral capsule ([Trokendi XR\(TM\)](#)) is indicated as initial monotherapy in patients 10 years or older with partial onset seizures. Approval is based upon demonstration of pharmacokinetic equivalence to immediate-release [topiramate](#) [1].

Safety and efficacy are not established in patients converted from previous anticonvulsant regimens to [topiramate](#) initial monotherapy [1].

In adults with partial onset seizures, doses above 400 mg/day (600, 800, or 1000 mg/day) have not been shown to improve responses in dose-response studies [17].

In a multinational, randomized, double-blind trial, [topiramate](#) was effective as monotherapy in children 6 years or older who had no more than 2 seizures in the 3 months prior to study enrollment [18] [19].

3) Adult:

a) Cumulative rates for time to first seizure significantly favored [topiramate](#) 400 mg/day compared with [topiramate](#) 50 mg/day in a randomized, double-blind, parallel-group trial in adults and children with [epilepsy](#) (n=470). Enrolled patients (median age, 22 years; range, 6 to 83 years) with partial onset or primary generalized seizures and 1 or 2 seizures in the 3 month retrospective baseline phase were entered into a 7-day open-label phase to receive 25 mg [topiramate](#) for 7 days and any additional anticonvulsants used were discontinued. Subsequently, in the double-blind phase, patients were randomized to receive titrated [topiramate](#) to 400 mg/day (n=236) or 50 mg/day (n=234). The primary efficacy endpoint was time to first partial onset or generalized onset tonic-clonic seizure during the double-blind phase and the secondary endpoint was the seizure-free rate at 6 and 12 months. The median duration of the study was approximately 266 days (range, 9 to 786 days). Based on Kaplan-Meier survival curves, time to first seizure favored [topiramate](#) 400 mg/day (p=0.0002). Fifty-eight percent of patients achieved the maximal dose of 400 mg/day. The probability of being seizure-free was 83% and 71% in the 400-mg and 50-mg groups, respectively, at 6 months (p=0.005), and 76% and 59%, respectively, at 12 months (p=0.001). The most common adverse effects were dose related and included paresthesia, weight loss, and decreased appetite. No deaths were reported in the study, overall, adverse events led to the withdrawal of 7% and 19% of patients in the 50-mg and 400-mg groups, respectively [18] [19].

4) Pediatric:

a) [Topiramate](#) is indicated as initial monotherapy for the treatment of partial onset seizures in patients 2 to younger than 10 years. Efficacy and dosing of [topiramate](#) in patients in this age group is based on extrapolated exposure response relationships of pediatric patients down to 2 years of age compared with adolescents and adults in [epilepsy](#) trials of [topiramate](#) as monotherapy and adjunct treatment [17].

b) Cumulative rates for time to first seizure significantly favored [topiramate](#) 400 mg/day compared with [topiramate](#) 50 mg/day in a randomized, double-blind, parallel-group trial in adults and children with [epilepsy](#) (n=470). Enrolled patients (median age, 22 years; range, 6 to 83 years) with partial onset or primary generalized seizures and 1 or 2 seizures in the 3-month retrospective baseline phase were entered into a 7-day open-label phase to receive 25 mg [topiramate](#) for 7 days and any additional anticonvulsants used were discontinued. Subsequently, in the double-blind phase, patients were randomized to receive titrated [topiramate](#) to 400 mg/day (n=236) or 50 mg/day (n=234). The primary efficacy endpoint was time to first partial onset or generalized onset tonic-clonic seizure during the double-blind phase and the secondary endpoint was the seizure-free rate at 6 and 12 months. The median duration of the study was approximately 266 days (range, 9 to 786 days). Based on Kaplan-Meier survival curves, time to first seizure favored [topiramate](#) 400 mg/day (p=0.0002). Fifty-eight percent of patients achieved the maximal dose of 400 mg/day. The probability of being seizure-free was 83% and 71% in the 400-mg and 50-mg groups, respectively, at 6 months (p=0.005), and 76% and 59%, respectively, at 12 months (p=0.001). The most common adverse effects were dose related and included paresthesia, weight loss, and decreased appetite. No deaths were reported in the study, overall, adverse events led to the withdrawal of 7% and 19% of patients in the 50-mg and 400-mg groups, respectively [18] [19].

4.5.K] Partial seizure; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; **Pediatric, yes (Topamax(R), 2 years or older; Trokendi XR(TM), 6 years or older)**

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category A; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Topiramate immediate-release oral tablet and capsule are indicated as adjunct therapy for the treatment of partial seizures in adults and children 2 years or older [17].

Topiramate extended-release oral capsule (Trokendi XR(TM)) is indicated as adjunct therapy for the treatment of partial seizures in patients 10 years or older. Approval is based upon demonstration of pharmacokinetic equivalence to immediate-release **topiramate** [1].

In dose-response studies in adults with partial onset seizures, doses above 400 mg/day (600, 800, or 1000 mg/day) have not been shown to improve responses [17].

Significant reductions in seizure frequency in adults and children [40]

3) Adult:

a) A meta-analysis of 6 double-blinded, placebo-controlled trials determined that adjunctive **topiramate** is effective in the treatment of refractory **partial epilepsy** with or without secondarily generalized seizures. Patients were between 18 and 65 years of age, were on stable treatment with 1 or 2 antiepileptic agents and had at least 3 to 4 partial onset seizures per month during the baseline period (4 to 12 weeks). EEGs were used to confirm the presence of a lateralized epileptiform pattern. Patients were randomized to receive placebo (n=265) or **topiramate** (n=481). Initial doses of **topiramate** ranged from 25 mg to 100 mg per day. Doses were titrated to either the maximally tolerated dose or the target dose over 2 to 8 weeks. Initial 100 mg doses were titrated weekly, up 100 mg per day after the first week and then 200 mg per day each week thereafter. Patients who were started at 25 or 50 mg doses were titrated in 25 or 50 mg increments. Maintenance doses ranged from 200 to 800 mg daily. Patients were maintained on these doses for 4 to 12 weeks. Baseline antiepileptic agents were continued throughout the trial period but were not adjusted. In 41% of **topiramate** patients, seizures were reduced by greater than 50% compared with 15% of placebo patients (p less than 0.001). Complete seizure reduction was achieved in 5% of **topiramate** patients compared with 0.8% of placebo patients (p=0.0024). This improvement was seen irrespective of the type of seizure. The median monthly seizure reduction was 55% with **topiramate** compared with -8% with placebo for simple partial seizures (p=0.002), 38% compared with 2% for complex partial seizures (p less than 0.001) and 56% compared with -3% with secondarily generalized seizures (p less than 0.001). Significant seizure reductions (greater than 50%) were seen irrespective of gender, age, baseline seizure rate, and number and type of concomitant antiepileptic agents (p less than 0.05). All dosage groups had similar responses. More patients tended to withdraw from treatment due to adverse reactions at doses greater than 600 mg daily (p less than 0.003 when compared with placebo). The authors conclude that a target dose of 200 mg daily is an adequate target dose to use when prescribing **topiramate** for adjunctive therapy in refractory **partial epilepsy** [18] [41].

b) In a double-blinded, randomized, concentration controlled study, examining adjunctive **topiramate** therapy, patients assigned to a target **topiramate** plasma level of 10.5 mg/L obtained better seizure

control than those assigned to target levels of 2 mg/L and 19 mg/L. Patients with refractory partial seizures were randomized to 1 of the 3 target plasma levels (n=65). **Topiramate** doses were then titrated over 8 weeks to attain these levels. Not all patients obtained their target plasma levels. Median doses were 100 mg for the 2 mg/L group, 450 mg for the 105 mg/L group and 677 mg for the 19 mg/L group. Patients randomized to 10.5 mg/L reduced seizure frequency by 85% compared with 39% in the 2 mg/L group (p=0.03) and 39% in the 19 mg/L group (p=0.05). Of note, lower target plasma levels were associated with higher study completion rates (85% compared with 78% and 50% in the 2, 10.5, and 19 mg/L groups, p=0.03). The occurrence of adverse events also was dose-related. Further studies involving larger numbers of subjects are required to establish target therapeutic levels [42].

c) **Topiramate**, as adjunct therapy, reduced seizure frequency and severity in patients with refractory **epilepsy** of a broad range of seizure types. In an open, 16-week, multicenter study, patients (n=201) 18 to 78 years of age experiencing at least 6 seizures within the previous 12 weeks despite a stable antiepileptic drug (AED) regimen were given **topiramate**, beginning at 50 mg per day, in addition to their established regimen. Doses were titrated to a clinically effective level over 8 weeks (final dose in the intent-to-treat population (ITT), 293 mg/day). In a comparison of frequency of seizures during the last 8 weeks of the trial to the frequency at baseline, 44% of patients experienced a reduction in frequency of 50% or more. Ten percent of patients had no seizures during the last 8 weeks. There were substantial reductions in the most common types of seizures: simple partial (p less than 0.0001), complex partial (p less than 0.0002), secondarily generalized (p less than 0.0001). There were also statistically significant reductions in absence seizures (p=0.0205) and tonic-clonic seizures (p=0.0002), but the numbers of patients experiencing these and other primary generalized seizures were small. Reductions in seizure severity scores were statistically (p less than 0.0001) and clinically significant. Statistically significant improvements in mental health were considered not of clinically significant magnitude. Of the 26% of patients who left the study before completion, about half withdrew because of adverse reactions. Anorexia, memory difficulties, nervousness, paresthesias, and increased number or intensity of seizures were the most common reasons for withdrawal. Weight loss (mean 3.5 kg) over the study was statistically significant (p less than 0.0001) [40].

d) Add-on therapy with **topiramate** in doses of 200 to 800 mg daily is effective in the treatment of refractory **partial epilepsy**, with or without secondary generalized seizures, in open and (primarily) placebo-controlled studies [43] [27] [44] [45] [46] [47] [48] [49] [26]. Patients in these studies had been receiving one to three antiepileptic agents (usually **phenytoin**, **carbamazepine**, **valproate**, and/or **primidone**) and mean reductions in seizure frequency after addition of **topiramate** ranged from 35 to 87%. An average of 50% of patients experienced a 50% or greater reduction in seizure frequency during **topiramate** therapy, which was superior to that observed with placebo. **Topiramate** was efficacious as monotherapy in one small study [50]. In open-label extensions of controlled studies, the efficacy of **topiramate** has been maintained for up to 2 years (mean seizure reduction rate, 69%) [43].

e) In a retrospective review of **topiramate** therapy, patients with **generalized epilepsies** had a greater decrease in seizure frequency than those with **partial epilepsy**. Patients, aged 12 to 75 years, received **topiramate** as add-on therapy with a mean dose of 352 mg daily. A greater than 50% seizure reduction rate was experienced by 33% of patients with **generalized epilepsy** and by 20% of those with **partial epilepsy** (p less than 0.03). Side effects leading to withdrawal occurred in 41% of patients. The most common adverse event was abnormal thinking [22].

4) Pediatric:

a) **Topiramate** add-on therapy was safe and effective during a 16-week double-blind study in children 2 to 16 years old. Children were randomized to either placebo (n=45) or a **topiramate** dose based on body weight to approximate 6 mg/kg/day: 125 mg daily for 16 to 24.9 kg (n=15), 175 mg for 25 to

33.9 kg (n=7), 225 for 34 to 42.9 kg (n=10), 400 mg for greater than 43 kg (n=9). The median percent reduction from baseline in the average monthly seizure rate was 33.1% for the [topiramate](#) group and 10.5% in the placebo group (p=0.034). In the [topiramate](#) group 7 out of 41 patients experienced a greater than 75% reduction in seizure rate while only 1 patient in the placebo group achieved this rate (p=0.019). Emotional lability, difficulty with concentration or attention, and fatigue were reported more frequently in the [topiramate](#) group. Two patients in the [topiramate](#) group reported weight decreases of 7.9% and 11.1% [18] [51].

b) During the double-blind phase of a randomized, placebo-controlled trial (n=86, [topiramate](#) target dose 6 mg/kg/day), significant reduction in partial onset seizures (p=0.034) and significant improvement in global impression (by parents or guardians) of seizure severity (0.03) was reported in topiramate-treated children compared with those treated with placebo. During the open-label portion of the study (n=83), a 50% or greater reduction in partial onset seizures was reported in 57% of patients treated with [topiramate](#) (mean dose of 9 mg/kg/day; mean treatment duration 440 days) and a 75% or greater reduction was reported in 42% of patients [31].

c) In a chart review of 49 children treated with [topiramate](#) for seizures, better efficacy was reported for treating complex partial seizures than generalized seizures. Children ages 1.5 to 19 years were retrospectively reviewed. [Topiramate](#) in doses of 2.5 to 7.5 mg/kg/day was the most efficacious. Half of the children with partial seizures experienced a greater than 50% reduction. Increased psychomotor dysfunction and decreased appetite were the most frequent adverse events [24].

d) Two infants were successfully treated with [topiramate](#) monotherapy. A 12-month-old child with partial seizures refractory to [phenobarbital](#), [valproic acid](#), [phenytoin](#), and [carbamazepine](#) was successfully treated with [topiramate](#) 7.7 mg/kg/day. His seizure frequency went from 5 to 10 seizures daily to 2 over the next 13 months. His [electroencephalogram](#) also normalized. A 9-month-old with partial seizures refractory to [phenobarbital](#) and [carbamazepine](#) received [topiramate](#) 6 mg/kg/day. His seizure frequency decreased from 1 to 2 weekly to 1 seizure over 11 months. He did experience initial appetite suppression (Kugler & Sachedo, 1998).

4.5.L] Tonic-clonic seizure, Primary generalized; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(Topamax\(R\), 2 years or older; Trokendi XR\(TM\), 6 years or older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) immediate-release oral tablets and capsules are indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 2 years or older [17]

[Topiramate](#) extended-release oral capsule (Trokendi XR(TM)) is indicated as adjunctive treatment of primary generalized-tonic [clonic seizures](#) in patients 6 years or older. Approval is based upon demonstration of pharmacokinetic equivalence to immediate-release [topiramate](#) [1].

[Topiramate](#) was effective as add-on therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures in a 20-week randomized, double-blind, placebo-controlled trial (n=83) [18] [21]

Weight loss and central nervous system effects may limit use [21] [22]

3) Adult:

a) [Topiramate](#) was effective as add-on therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures in a 20-week randomized, double-blind, placebo-controlled trial (n=83). Patients (aged 3 to 59 years) were allowed a maximum of 2 concomitant antiepileptic drugs (AEDs). During an 8-week baseline phase, patients experiencing at least 3 PGTC seizures were randomized to [topiramate](#) (n=39) or placebo (n=41). [Topiramate](#) was titrated over 8 weeks to 175 mg, 225 mg, or 400 mg (protocol specified target doses assigned based on weight to approximate 6 mg/kg/day) and maintained on this dose for 12 weeks. PGTC seizures decreased by 56.7% in the [topiramate](#) group versus the placebo group (p=0.019). A seizure reduction rate of at least 50% was experienced by 56% of the [topiramate](#) patients versus 20% of the placebo group (p=0.001). For all generalized seizures [topiramate](#) decreased the average monthly seizure rate by 42.1% versus 0.9% in the placebo group (p=0.003). One patient in the [topiramate](#) group experienced anorexia and weight loss that was treatment limiting. Other common adverse events were somnolence, fatigue, weight loss, difficulty with memory, and nervousness [18] [21].

b) As adjunct therapy, [topiramate](#) reduced seizure frequency, severity, and duration in mentally retarded, developmentally disabled patients with [intractable epilepsy](#). Twenty such patients, ages 21 to 57 years, with mixed types of seizures (mixed generalized seizures or mixed partial and generalized seizures) were given [topiramate](#) 25 mg/day for the first week; the dose was then titrated to a level providing clinical response (50 to 350 mg/day, mean 189 mg/day). Baseline antiepileptic drugs (AEDs) were gradually withdrawn when appropriate. Sixteen patients completed the study (range of duration of therapy 20 to 54 weeks, mean 42 weeks). Seizure frequency was reduced by more than 50% in 11 of 16 patients (69%). Seizures increased in 2 patients. Seizure duration and/or severity was decreased in 7 patients (44%). In 11 patients, at least 1 baseline AED was discontinued. Sixty-nine percent of patients experienced improved alertness. The most common adverse events were behavior problems and decreased alertness. Only one discontinuation was attributable to adverse events (disorientation and unsteadiness). The responsiveness of particular seizure types to [topiramate](#) was not reported [23].

c) In a retrospective review of [topiramate](#) therapy, patients with [generalized epilepsies](#) had a greater decrease in seizure frequency than those with [partial epilepsy](#). Patients, aged 12 to 75 years, received [topiramate](#) as add-on therapy with a mean dose of 352 mg daily. A greater than 50% seizure reduction rate was experienced by 33% of patients with [generalized epilepsy](#) and by 20% of those with [partial epilepsy](#) (p less than 0.03). Side effects leading to withdrawal occurred in 41% of patients. The most common adverse event was abnormal thinking [22].

4) Pediatric:

a) [Topiramate](#) was effective as add-on therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures in a 20-week randomized, double-blind study, placebo-controlled trial (n=83). Patients (aged 3 to 59 years) were allowed a maximum of 2 concomitant antiepileptic drugs (AEDs). During an 8-week baseline phase, patients experiencing at least 3 PGTC seizures were randomized to [topiramate](#) (n=39) or placebo (n=41). [Topiramate](#) was titrated over 8 weeks to 175 mg, 225 mg, or 400 mg (protocol specified target doses assigned based on weight to approximate 6 mg/kg/day) and maintained on this dose for 12 weeks. PGTC seizures decreased by 56.7% in the [topiramate](#) group versus the placebo group (p=0.019). A seizure reduction rate of at least 50% was experienced by 56% of the [topiramate](#) patients versus 20% of the placebo group (p=0.001). For all generalized seizures [topiramate](#) decreased the average monthly seizure rate by 42.1% versus 0.9% in the placebo group (p=0.003). One patient in the [topiramate](#) group experienced anorexia and weight loss that was

treatment limiting. Other common adverse events were somnolence, fatigue, weight loss, difficulty with memory, and nervousness [18] [18] [21].

b) In a chart review of 49 children treated with [topiramate](#) for seizures, better efficacy was reported for treating complex partial seizures than generalized seizures. Children ages 1.5 to 19 years were retrospectively reviewed. [Topiramate](#) in doses of 2.5 to 7.5 mg/kg/day was the most efficacious. Half of the children with partial seizures experienced a greater than 50% reduction. Increased psychomotor dysfunction and decreased appetite were the most frequent adverse events [24].

4.5.M] Tonic-clonic seizure, Primary generalized (initial monotherapy)

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(Topamax\(R\), 2 years or older; Trokendi XR\(TM\), 10 years or older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

[Topiramate](#) immediate-release oral capsules and tablets ([Topamax\(R\)](#)) are indicated as initial monotherapy in patients 2 years or older with primary generalized tonic-clonic seizures [17].

[Topiramate](#) extended-release oral capsule ([Trokendi XR\(TM\)](#)) is indicated as initial monotherapy in patients 10 years or older with primary generalized tonic-clonic seizures. Approval is based upon demonstration of pharmacokinetic equivalence to immediate-release [topiramate](#) [1].

Safety and efficacy are not established in patients converted from previous anticonvulsant regimens to [topiramate](#) initial monotherapy [1].

[Topiramate](#) efficacy for initial monotherapy in primary generalized tonic-clonic seizures was established in a multinational, randomized, double-blind trial in patients who had no more than 2 seizures in the 3 months prior to study enrollment [18] [19].

3) Adult:

a) Cumulative rates for time to first seizure significantly favored [topiramate](#) 400 mg/day compared with [topiramate](#) 50 mg/day in a randomized, double-blind, parallel-group trial in adults and children with [epilepsy](#) (n=470). Enrolled patients (median age, 22 years; range, 6 to 83 years) with partial onset or primary generalized seizures and 1 or 2 seizures in the 3-month retrospective baseline phase were entered into a 7-day open-label phase to receive 25 mg [topiramate](#) for 7 days and any additional anticonvulsants used were discontinued. Subsequently, in the double-blind phase, patients were randomized to receive titrated [topiramate](#) to 400 mg/day (n=236) or 50 mg/day (n=234). The primary efficacy endpoint was time to first partial onset or generalized onset tonic-clonic seizure during the double-blind phase and the secondary endpoint was the seizure-free rate at 6 and 12 months. The median duration of the study was approximately 266 days (range, 9 to 786 days). Based on Kaplan-Meier survival curves, time to first seizure favored [topiramate](#) 400 mg/day (p=0.0002). Fifty-eight percent of patients achieved the maximal dose of 400 mg/day. The probability of being seizure-free was 83% and 71% in the 400-mg and 50-mg groups, respectively, at 6 months (p=0.005), and 76% and 59%, respectively, at 12 months (p=0.001). The most common adverse effects were dose-related and included

paresthesia, weight loss, and decreased appetite. No deaths were reported in the study; overall, adverse events led to the withdrawal of 7% and 19% of patients in the 50-mg and 400-mg groups, respectively [1] [18] [19].

4)) Pediatric:

a)) **Topiramate** immediate-release oral capsule and tablet are indicated as initial monotherapy in patients 2 to younger than 10 years with primary generalized tonic-clonic seizures. Efficacy and dosing of **topiramate** in patients in this age group is based on extrapolated exposure response relationships of pediatric patients down to 2 years of age compared with adolescents and adults in **epilepsy** trials of **topiramate** as monotherapy and adjunct treatment [17].

b)) Cumulative rates for time to first seizure significantly favored **topiramate** 400 mg/day compared with **topiramate** 50 mg/day in a randomized, double-blind, parallel-group trial in adults and children with **epilepsy** (n=470). Enrolled patients (median age, 22 years; range, 6 to 83 years) with partial onset or primary generalized seizures and 1 or 2 seizures in the 3 month retrospective baseline phase were entered into a 7-day open-label phase to receive 25 mg **topiramate** for 7 days and any additional anticonvulsants used were discontinued. Subsequently, in the double-blind phase, patients were randomized to receive titrated **topiramate** to 400 mg/day (n=236) or 50 mg/day (n=234). The primary efficacy endpoint was time to first partial onset or generalized onset tonic-clonic seizure during the double-blind phase and the secondary endpoint was the seizure-free rate at 6 and 12 months. The median duration of the study was approximately 266 days (range, 9 to 786 days). Based on Kaplan-Meier survival curves, time to first seizure favored **topiramate** 400 mg/day (p=0.0002). Fifty-eight percent of patients achieved the maximal dose of 400 mg/day. The probability of being seizure-free was 83% and 71% in the 400-mg and 50-mg groups, respectively, at 6 months (p=0.005), and 76% and 59%, respectively, at 12 months (p=0.001). The most common adverse effects were dose-related and included paresthesia, weight loss, and decreased appetite. No deaths were reported in the study, overall, adverse events led to the withdrawal of 7% and 19% of patients in the 50-mg and 400-mg groups, respectively [1] [18] [19].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] **Amitriptyline**

4.6.A.1] **Migraine; Prophylaxis**

a)) Treatment for 26 weeks with **topiramate** was not inferior to **amitriptyline** for the **prophylaxis of migraine** headache measured by the mean monthly rate of migraine episodes according to a randomized, double-blind, double-dummy, parallel-group study of 331 adults. Included in the study were patients aged 38.8 +/- 11 years (range, 18 to 70 years) with at least a 6-month history of migraine with or without aura (International Headache Society class 1.1 and 1.2), 3 to 12 migraines/month in the 3 months prior to the screening and washout phase, and 3 to 12 migraine episodes and no more than 15 headache days during the 28-day prospective baseline phase. Patients who had previously failed more than 2 migraine prevention trials of at least 3 months duration were excluded from the study. A migraine episode was defined as painful migraine symptoms not exceeding 24 hours. Painful symptoms recurring within 24 hours of the initial onset was considered part of the initial migraine episode. Painful symptoms lasting longer than 24 hours was considered a new migraine episode. At baseline the mean monthly rate of migraine episodes was 6.2 +/- 2.7. Following a 14- to 28-day screening/washout phase and a 28-day prospective baseline period when patients maintained a headache diary, patients were randomized to receive 26 weeks of either **topiramate** (n=172) or **amitriptyline** (n=159). Both treatment groups received 25 milligrams (mg)/day for 7 days with weekly titrations of 25 mg/day to a maximum tolerated dose or up to 50 mg twice daily. The mean daily dose administered was **topiramate** 74.8 +/- 23.9 mg and **amitriptyline** 76.5 +/- 21.1 mg. Patients could receive concomitant acute headache agents including over-the-counter analgesics,

NSAIDs, triptans, ergot derivatives, and [dihydroergotamine](#) for up to 4 days/week, but other prophylactic migraine treatments were prohibited. Predetermined criteria for noninferiority was defined as the lower bound of the 95% confidence interval (CI) greater than -1. In an intent-to-treat analysis after 26 weeks of treatment, the least squares mean change from baseline in the monthly rate of migraine episodes was similar between the [topiramate](#) and [amitriptyline](#) group (-2.6 vs -2.7; 95% CI, -0.6 to 0.7, $p=0.874$). Treatment was discontinued prior to the end of the study in 42.7% ($n=76$) of topiramate-treated patients and in 43.8% ($n=74$) of amitriptyline-treated patients with intolerable adverse events as the most common reason for discontinuation in both groups. There were no significant differences between groups in any secondary endpoints, including change from baseline in monthly rate of migraine days (-3.1 days vs -3.2 days with [topiramate](#) and [amitriptyline](#), respectively; 95% CI, -0.9 to 0.7; $p=0.729$), total headache days or the rate of acute abortive medication use. The mean change from baseline in body mass index (BMI) in the [topiramate](#) and [amitriptyline](#) groups was -0.9 ± 1.5 kilograms/square meter (kg/m^2) and 0.9 ± 1.5 kg/m^2 , respectively. The most commonly occurring treatment-emergent adverse events in the [topiramate](#) group were paresthesia (29.9%) and fatigue (16.9%), and in the [amitriptyline](#) group were dry mouth (35.5%) and fatigue (24.3%) [176].

4.6.B] Carbamazepine

4.6.B.1] Epilepsy

a) In a double-blinded, randomized study, [topiramate](#), [carbamazepine](#) and [valproate](#) monotherapy demonstrated similar times to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months of follow-up. Newly diagnosed [epilepsy](#) patients were randomized to receive [topiramate](#) 100 milligrams (mg) daily ($n=210$), [topiramate](#) 200 mg daily ($n=199$), or traditional therapy ($n=204$). Patients in the traditional therapy arm were prescribed either [carbamazepine](#) 600 mg/day or [valproate](#) 1250 mg/day depending on the prescribing physician's treatment choice. Patients were followed until 6 months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse events accounted for 19% and 23% of discontinuations in the [topiramate](#) and traditional therapy arms, respectively. Ineffective treatment accounted for 11% and 12% of discontinuations in the [topiramate](#) and traditional therapy arms, respectively. The time to exit and the time to first seizure between the arms did not differ ($p=0.53$ and 0.35 , respectively). The proportion of patients who did not experience a seizure during the last 6 months of the study was 49% of [topiramate](#)-100 mg patients and 44% in each of the other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), language problems (3 to 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with [topiramate](#). [Carbamazepine](#) and [valproate](#) were associated with concentration and attention difficulty (4% and 1%), and language problems (6% and 4%). [Carbamazepine](#) was also associated with confusion (3%) [177].

4.6.C] Gabapentin

1) Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with [topiramate](#) while [gabapentin](#) and [lamotrigine](#) had only minimal effects [179]. Healthy young adults ($n=17$) were randomized to receive [topiramate](#) 5.7 milligrams/kilogram (mg/kg), [lamotrigine](#) 7.1 mg/kg , or [gabapentin](#) 35 mg/kg . Doses were titrated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 weeks. For the visual serial addition test, the [topiramate](#) group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004) than the [lamotrigine](#) or [gabapentin](#) groups. On the symbol digits modalities test, the [topiramate](#) group performed poorer than the [lamotrigine](#) and [gabapentin](#) at week 2 (p less than 0.005) and worse than the [lamotrigine](#) group at week 4 (p less than 0.04). On memory tests at week 2 the [topiramate](#) group was worse than the

[gabapentin](#) group (p less than 0.05). The [lamotrigine](#) group was below that of the [gabapentin](#) group but above the [topiramate](#) group. At week 4 the groups were similar. The [topiramate](#) group also reported more symptoms of depressed mood at week 4 compared to the [lamotrigine](#) and [gabapentin](#) groups (p less than 0.004), and had more anger-hostility symptoms than the [lamotrigine](#) group at week 4 (p less than 0.02). Further long-term drug effects should be evaluated.

4.6.D] [Lamotrigine](#)

1) Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with [topiramate](#) while [gabapentin](#) and [lamotrigine](#) had only minimal effects [180]. Healthy young adults (n=17) were randomized to receive [topiramate](#) 5.7 milligrams/kilogram (mg/kg), [lamotrigine](#) 7.1 mg/kg, or [gabapentin](#) 35 mg/kg. Doses were titrated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 weeks. For the visual serial addition test, the [topiramate](#) group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004) than the [lamotrigine](#) or [gabapentin](#) groups. On the symbol digits modalities test, the [topiramate](#) group performed poorer than the [lamotrigine](#) and [gabapentin](#) at week 2 (p less than 0.005) and worse than the [lamotrigine](#) group at week 4 (p less than 0.04). On memory tests at week 2 the [topiramate](#) group was worse than the [gabapentin](#) group (p less than 0.05). The [lamotrigine](#) group was below that of the [gabapentin](#) group but above the [topiramate](#) group. At week 4 the groups were similar. The [topiramate](#) group also reported more symptoms of depressed mood at week 4 compared to the [lamotrigine](#) and [gabapentin](#) groups (p less than 0.004), and had more anger-hostility symptoms than the [lamotrigine](#) group at week 4 (p less than 0.02). Further long-term drug effects should be evaluated.

4.6.E] [Phenytoin](#)

4.6.E.1] [Epilepsy](#)

a) [Topiramate](#) failed to meet the noninferiority criteria for the time to first complex-partial (CP) or generalized tonic-clonic (GTC) seizure when compared with [phenytoin](#) in patients with new-onset or relapsed [epilepsy](#) according to a randomized, double-blind study (n=254). Patients with a mean age 34.2 +/- 14.8 years (range, 12 to 65 years) weighing at least 50 kg with 1 to 20 unprovoked seizures within the past 3 months were included in the study. Following up to 7 days of screening, patients were randomized to receive 28 days of treatment with either [topiramate](#) 100 mg/day (n=128), or [phenytoin](#) 1000 mg on day 1 followed by 300 mg/day (n=126). At baseline the mean number of seizures within 3 months was 2 +/- 1.7 (GTC seizures) and 6.1 +/- 8.7 (CP seizures). [Topiramate](#) did not establish noninferiority to [phenytoin](#) as the [topiramate:phenytoin](#) hazard ratio for the time to first seizure (the primary endpoint) was 2 (95% confidence interval (CI), 0.98 to 4.12), and the an upper limit of the 95% CI exceeded the predefined criterion on 2.275 or less. At day 28, the seizure-free rate was 81.1% and 90.3% in the [topiramate](#) and [phenytoin](#) group, respectively. Adverse events in the [topiramate](#) and [phenytoin](#) groups, respectively, included paresthesia (22% vs 3.9%), confusion (6.1% vs 1.6%), and dizziness (19.7% vs 27.6%) [178].

4.6.F] [Valproic Acid](#)

4.6.F.1] [Epilepsy](#)

a) In a double-blinded, randomized study, [topiramate](#), [carbamazepine](#) and [valproate](#) monotherapy demonstrated similar times to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months of follow-up. Newly diagnosed [epilepsy](#) patients were randomized to receive [topiramate](#) 100 milligrams (mg) daily (n=210), [topiramate](#) 200 mg daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either [carbamazepine](#) 600 mg/

day or [valproate](#) 1250 mg/day depending on the prescribing physician's treatment choice. Patients were followed until 6 months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse events accounted for 19% and 23% of discontinuations in the [topiramate](#) and traditional therapy arms, respectively. Ineffective treatment accounted for 11% and 12% of discontinuations in the [topiramate](#) and traditional therapy arms, respectively. The time to exit and the time to first seizure between the arms did not differ ($p=0.53$ and 0.35 , respectively). The proportion of patients who did not experience a seizure during the last 6 months of the study was 49% of [topiramate](#)-100 mg patients and 44% in each of the other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), language problems (3 to 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with [topiramate](#). [Carbamazepine](#) and [valproate](#) were associated with concentration and attention difficulty (4% and 1%), and language problems (6% and 4%). [Carbamazepine](#) was also associated with confusion (3%) [181].

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