ASD IV: Evidence-based use of Newer ASDs and Their Interactions

Vineet Punia, MD, MS

Staff Physician,

Cleveland Clinic Epilepsy Center

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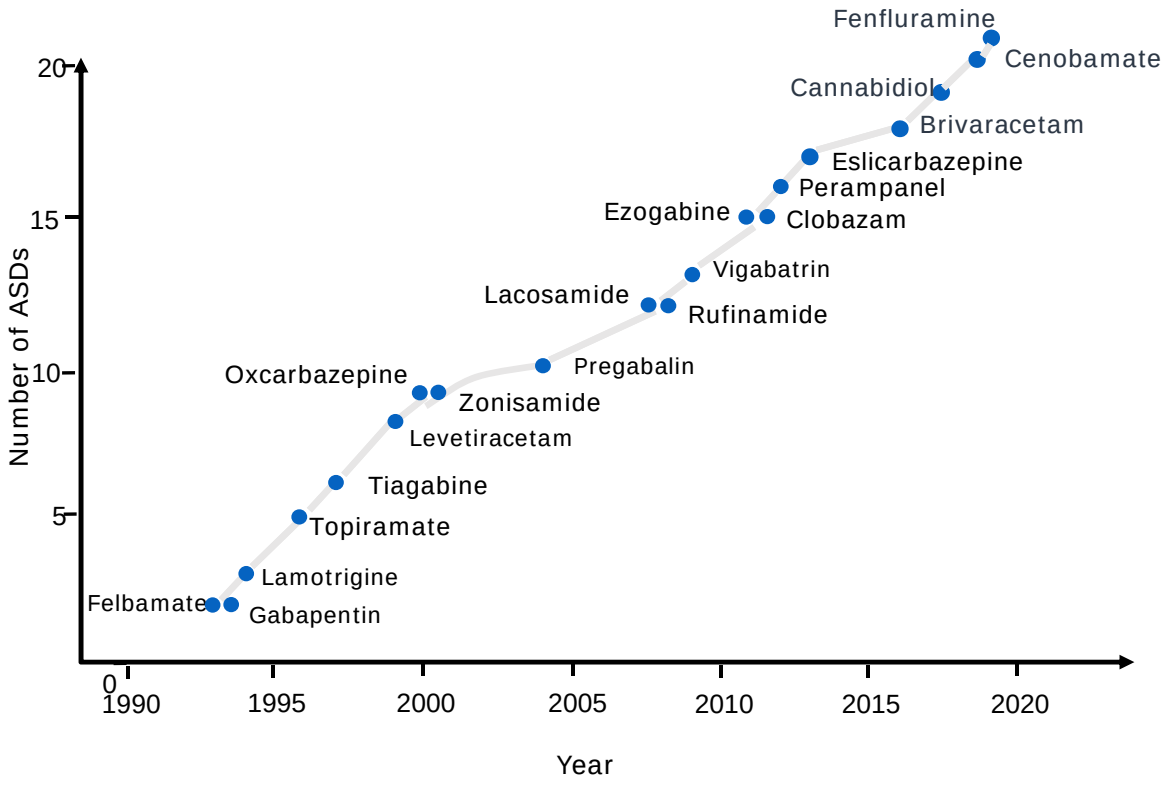
Abbreviations

- **FOS** Focal Onset Seizures
- **MOA** Mechanism of action
- **AED** Antiepileptic drug
- **YOA** Year of age
- **SZ** Seizure
- **PWE** People with epilepsy
- **GTC** Generalized tonic clonic (seizure)
- **RCT** Randomized control trial
- **CBZ** Carbamazepine
- **OXC** Oxcarbazepine
- **ESL** Eslicarbazepine
- **LEV** Levetiracetam
- **LTG** Lamotrigine
- **TPM** Topiramate
- **GBP** Gabapentin
- **PGB** Pregabalin

DEVELOPMENT OF ASDs



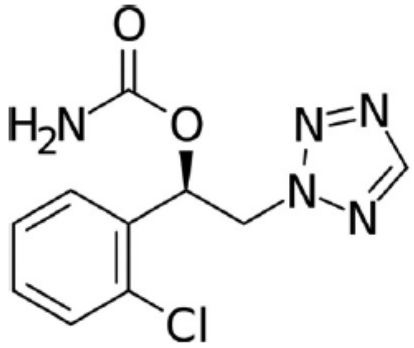
http://www.accessdata.fda.gov

New ASDs: Search for perfection

FEATURES OF AN IDEAL ASD	
Efficacy – Immediate and sustained	Broad spectrum
Good Tolerability	Ease of dosing
No adverse effects	No interaction with other meds
Serum levels monitoring	Linear pharmacokinetics

CENOBAMATE

- A novel tetrazole-derived carbamate compound
- Dual, complimentary MOA:
  - Sodium channel antagonist
  - Positive allosteric modulator of $GABA_A$ receptor
  - **<u>FDA approved for</u>**: FOS in adult patients.



Cenobamate Structure

CENOBAMATE: Pharmacological Properties

Characteristic	Effect
Protein bindings	**60%**
T_{max}	**1 – 4 hour**
Half-life ($t_{1/2}$)	**50 – 75 hours**
Metabolism	**Extensive. Glucronidation, Oxydation (CYP 2E1, 2A6, 2B6)**
Metabolites	**Not active**
Excretion	**90% renal**
Renal disease	**Mild-Mod impairment: ~1.5x increase. HD PK not tested**
Liver disease	**Mild-Mod impairment: ~2x increase. Severe not tested**

Characteristic	Effect
Effect on other ASDs	Inducer of CYP2B6 and CYP3A4 and an inhibitor of CYP2C19
Effect by other drugs	Phenobarbital reduced levels by 15%; PHT reduced levels by 28%
On OCPs	Affects Estrogen/Progestin metabolism. Use alternate means.
Cardiac effect	Shortens QT interval (dose dependent)
Interaction with EtOH	None
Intake with food	**High-fat meals do not show significant effects on rate and extent of absorption**

CENOBAMATE: Interactions

- Inducer of CYP2B6 and CYP3A4
- Inhibitor of CYP2C19
- Clinical implications unclear.
- No interactions:
  - Warfarin
  - Valproic acid
  - Lacosamide.
- Gradually decrease phenytoin dosage by up to 50%.

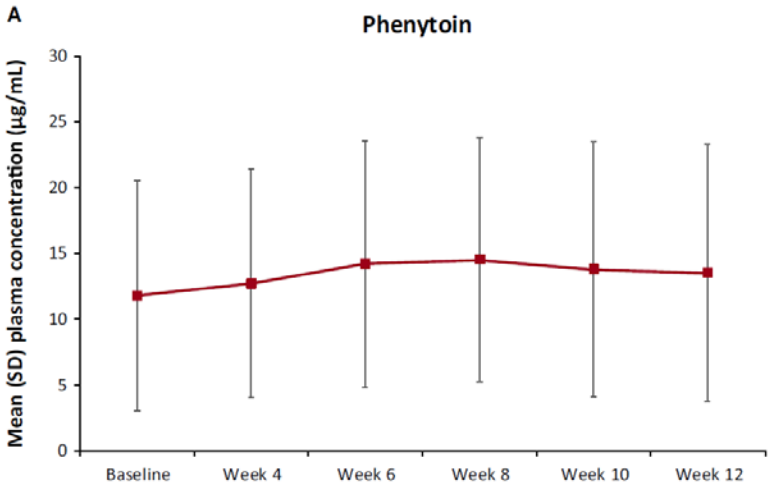
Medications	Plasma level	Dose change required
Bupropion	↓ ~40%	↑ likely needed
Midazolam	↓ ~70%	↑ needed
Lamotrigine*	↓ 20-50%	↑ likely needed
Carbamazepine^	↓ ~25%	↑ likely needed. Monitor levels.
Phenobarbital	↑ ~35%	↓ likely needed
Phenytoin	↑ ~85%	↓ definitely needed
Levetiracetam	↓ 5 – 15%	Monitor levels
Clobazam	↑ active metabolite	↓ may be needed

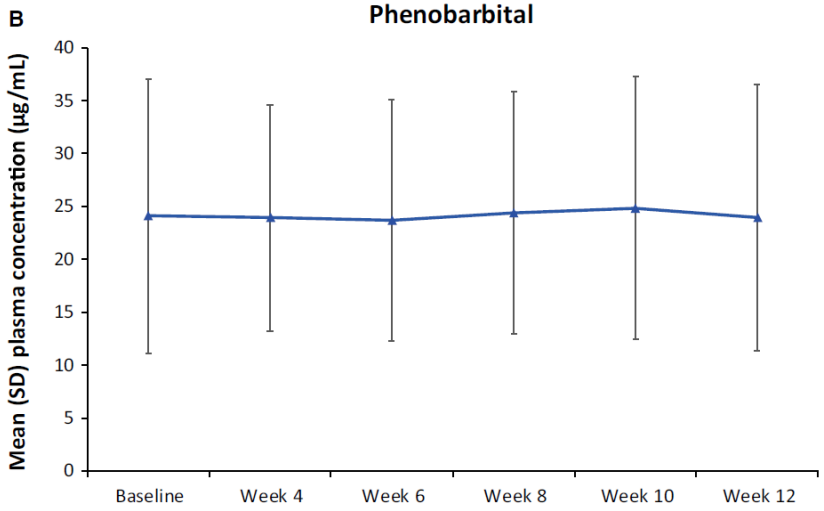
*Suggests induction of UGT metabolism

^ CBZ does not affect cenobamante plasma levels

CENOBAMATE: Interactions

- Open label study of 1339 patients
- PHT/PB doses could be decreased by 25%-33%.





Epilepsia . 2020 Jun;61(6):1099-1108.

CENOBAMATE: Efficacy Data

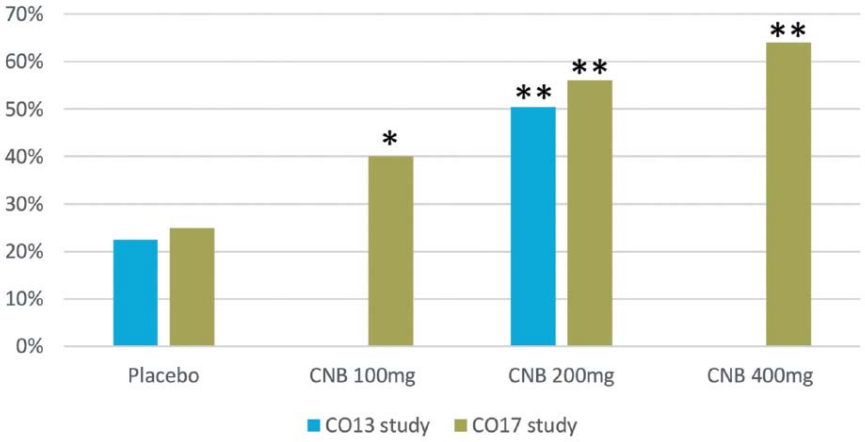
- FDA approval based on 2 RCTs

Study No	Study population	Study duration	Study groups	Median Sz reduction
CO13	N = 222 (ITT), 18 – 61 yrs	20 wks (4-8b + 6t + 6m)	Placebo vs. Cenobamate (CNB) 200 mg once daily	Placebo = 21.5% CNB: 55.6%
CO17	**N = 434 (mITT), 18 – 70 yrs**	**26 wks (8b + 6t + 12m)**	**Placebo vs. CNB 100 mg vs. CNB 200 mg vs. CNB 400 mg once a day**	**Placebo = 24% CNB 100 = 35.5% CNB 200 = 55% CNB 400 = 55%**

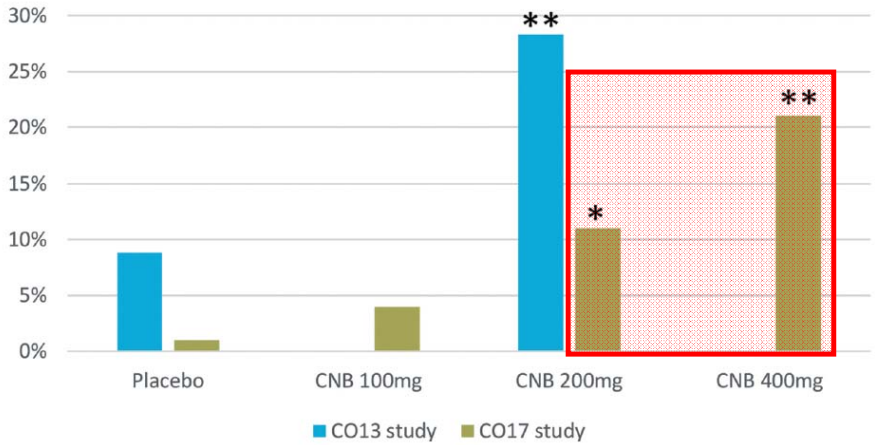
Neurology. 2020;94:e2311–e2322; Lancet Neurol. 2020;19:38–48

CENOBAMATE: Efficacy Data

- FDA approval based on 2 RCTs



≥50% Responder rate



Seizure freedom rate

Expert Opin Pharmacother. 2020 Aug 19:1-9. doi: 10.1080/14656566.2020.1803830

CENOBAMATE: Adverse Effects

Adverse Effects (combined 2 RCTs)	% patients
Somnolence	24.7
Dizziness	23.3
Headaches	11.1
Fatigue	16.1
Diplopia	10.9

- Dose dependent AEs.
- Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome: Noted in 3 out of 953 patients.
- Reduces QT interval (dose-dependent manner): Contraindicated in familial short-QT syndrome

CNS Drugs. 2020 Aug 26. doi: 10.1007/s40263-020-00759-9.

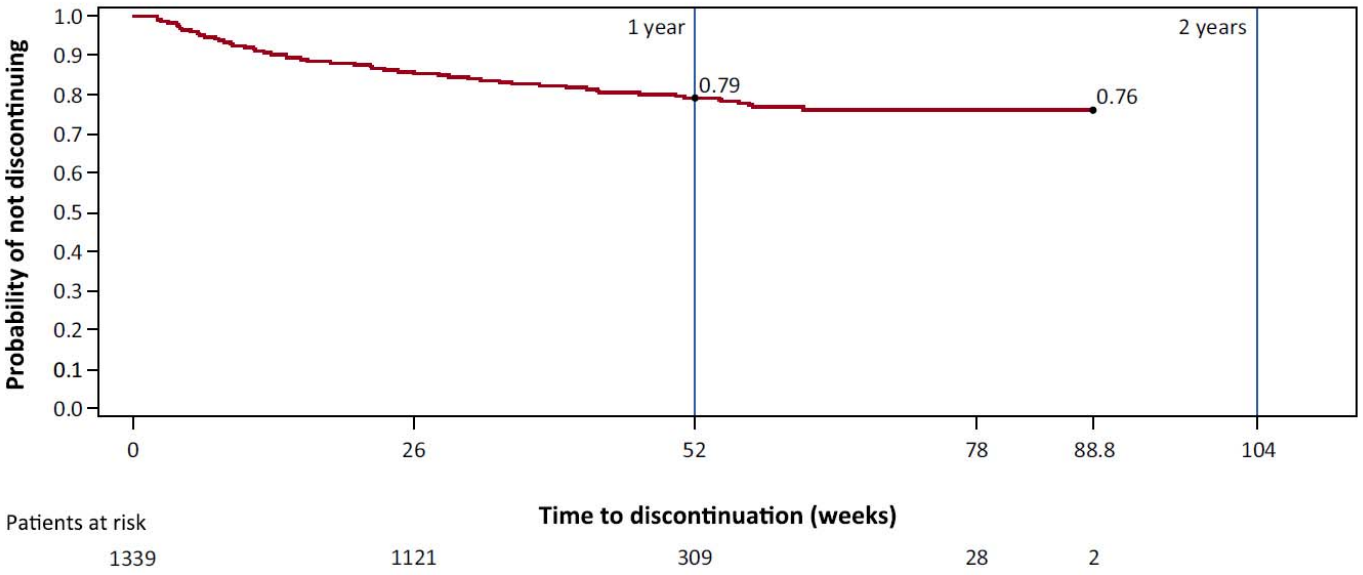
CENOBAMATE

- Available in:
  - Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg tablets
    - Swallow whole. Not to be chewed/crushed
- Dosage

Time	Dose
0 – 2 weeks	12.5 mg daily
Next 2 weeks	25 mg daily
Next 2 weeks	50 mg daily
2 weeks intervals	Increase by 50 mg
Maintenance dose	200 mg daily
Maximum dose	400 mg daily • Mild – Mod Hepatic impairment: 200 mg

CENOBAMATE: Adherence

- AEs very similar in open label study of 1339 patients
- 20% patients discontinued due to AEs



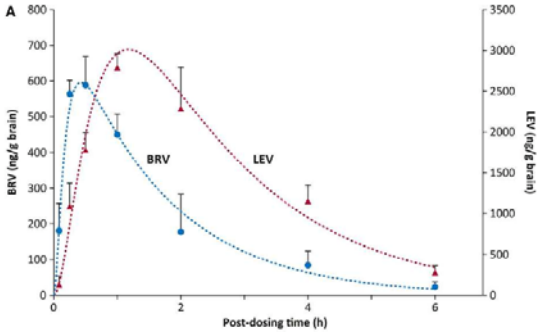
CNS Drugs. 2020 Aug 26. doi: 10.1007/s40263-020-00759-9.

CENOBAMATE: Summary

- Promising drug, specially at higher doses.
- Lower tolerability at higher doses
- Significant interactions with older ASDs
- Open-label safety study (N = 1348) starting at 12.5 mg/d and increased every 2 weeks: No DRESS reported
- “Start-low and go-slow”: can limit its use in certain situations.
- More experience needed.

BRIVARACETAM

- Selective, high-affinity binding with synaptic vesicle protein 2A ligand (SV2A).
- **FDA approved for**:
  - Adjunctive treatment FOS in patient ≥4 yoa.
  - Injection in patients ≥ 16 yoa
- Compared to Levetiracetam
  - 15-30 fold stronger binding to SV2A *in vitro*
  - Faster onset (quicker brain penetration) of action in audiogenic mouse model
  - Has sodium channel blocking properties as well



Epilepsia. 2016 Feb;57(2):201-9

BRIVARACETAM: Pharmacological Properties

Characteristic	Effect
Protein bindings	Weak (≤20%)
T_{max}	1 (0.25 – 3) hour
Metabolism	Hydrolysis with CYP2C19 playing major role
Half-life ($t_{1/2}$)	~9 hours
Liver disease	Dose reduction (25 -75 BID)
Metabolites	Not active
Excretion	95% renal
Renal disease	No dose adjustment needed

Characteristic	Effect
Effect on other ASDs	100 mg BID:~200% ↑in CBZ epoxide
Effect by other drugs	Rifampin ↓concentration by 45%
On OCPs	Not expected to be clinically significant.
Cardiac effect	No effect on QT prolongation (even at x4 recommended dose)
Interaction with EtOH	Added impairment in cognitive and psychomotor activity.

Epilepsia, 57(7):1139–1151, 2016

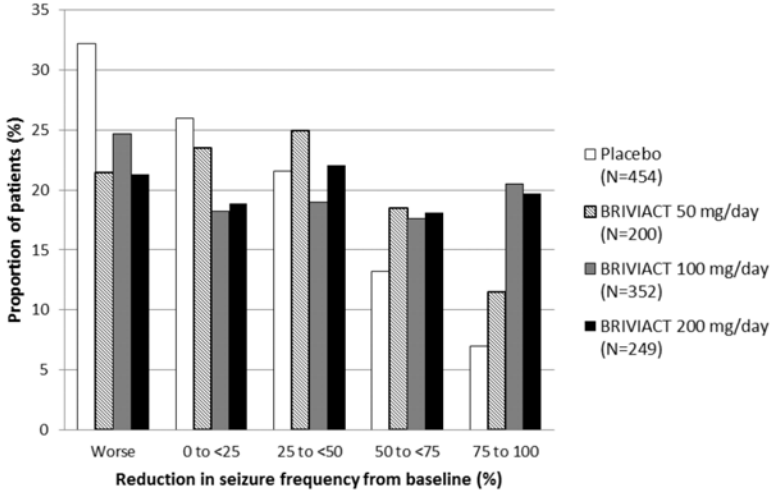
BRIVARACETAM

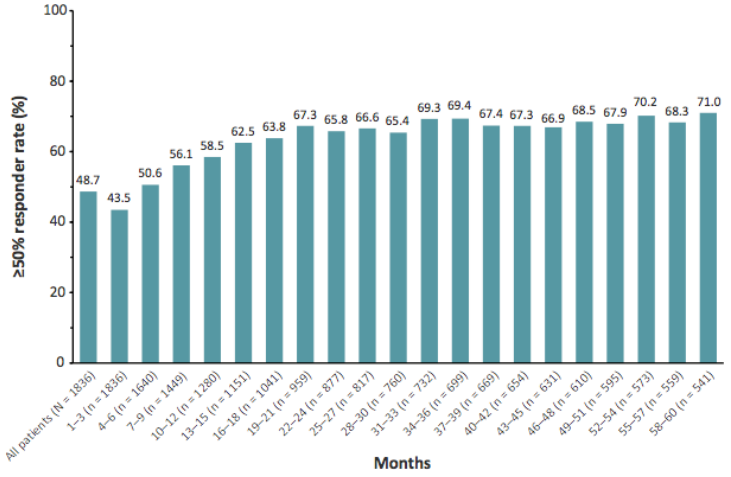
- Available in:
  - Tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets
    - Swallow whole. Not to be chewed/crushed
  - **Oral solution:** 10 mg/mL (3)
  - **Injection:** 50 mg/5 mL single-dose vial
    - 2-min bolus or a 15-min infusion
    - Bioequivalent with oral BRV tablets

- Dosage (Recommended)
  - Dose escalation not required
  - Start: 50 BID
  - Max: 100 BID

BRIVARACETAM: Efficacy Data

- FDA approval based on 3 RCTs
  - Study 1: Compared 50 mg/day and 100mg/day with placebo
  - Study 2: Compared 50mg/day to placebo
  - Study 3: Compared 100 mg/day and 200mg/day with placebo
- Pooled data: Complete Sz freedom: 3-5% patients





Epilepsia, 57(7):1139–1151, 2016; https://www.briviact.com/briviact-PI.pdf

BRIVARACETAM: Adverse Effects

- Not dose dependent.

Patients, n (%)	BRV overall (N = 2,186)	BRV modal dose (mg/day)			
		50 (n = 319)	100 (n = 544)	150 (n = 869)	200 (n = 454)
≥1 TEAE	1,848 (84.5)	277 (86.8)	469 (86.2)	750 (86.3)	352 (77.5)
TEAEs leading to discontinuation of study drug	264 (12.1)	70 (21.9)	79 (14.5)	73 (8.4)	42 (9.3)
Treatment-related TEAEs	1,184 (54.2)	205 (64.3)	317 (58.3)	475 (54.7)	187 (41.2)
Severe TEAEs	431 (19.7)	70 (21.9)	98 (18.0)	193 (22.2)	70 (15.4)
SAEs	401 (18.3)	66 (20.7)	106 (19.5)	168 (19.3)	61 (13.4)
Treatment-related SAEs	95 (4.3)	19 (6.0)	29 (5.3)	35 (4.0)	12 (2.6)
Deaths	28 (1.3)	7 (2.2)	10 (1.8)	9 (1.0)	2 (0.4)
TEAEs reported by ≥5% patients in the overall BRV group					
Headache	457 (20.9)	79 (24.8)	119 (21.9)	196 (22.6)	63 (13.9)
Dizziness	382 (17.5)	63 (19.7)	90 (16.5)	159 (18.3)	70 (15.4)
Somnolence	333 (15.2)	53 (16.6)	98 (18.0)	120 (13.8)	62 (13.7)
Nasopharyngitis	288 (13.2)	32 (10.0)	79 (14.5)	143 (16.5)	34 (7.5)
Fatigue	274 (11.3)	37 (11.6)	58 (10.7)	101 (11.6)	51 (11.2)
Convulsion	231 (10.6)	47 (14.7)	56 (10.3)	102 (11.7)	26 (5.7)
Influenza	170 (7.8)	35 (11.0)	45 (8.3)	75 (8.6)	15 (3.3)
Nausea	168 (7.7)	35 (11.0)	40 (7.4)	70 (8.1)	23 (5.1)
Diarrhea	166 (7.6)	27 (8.5)	42 (7.7)	76 (8.7)	21 (4.6)
Depression	156 (7.1)	36 (11.3)	38 (7.0)	61 (7.0)	21 (4.6)
Urinary tract infection	155 (7.1)	24 (7.5)	37 (6.8)	63 (7.2)	31 (6.8)
Back pain	142 (6.5)	26 (8.2)	31 (5.7)	66 (7.6)	19 (4.2)
Upper respiratory tract infection	142 (6.5)	16 (5.0)	37 (6.8)	67 (7.7)	22 (4.8)
Insomnia	135 (6.2)	22 (6.9)	39 (7.2)	56 (6.4)	18 (4.0)
Vomiting	134 (6.1)	17 (5.3)	39 (7.2)	65 (7.5)	13 (2.9)
Irritability	114 (5.2)	21 (6.6)	29 (5.3)	46 (5.3)	18 (4.0)

BRV, brivaracetam; SAE, serious treatment-emergent adverse event; TEAE, treatment-emergent adverse event.

Epilepsia, 57(7):1139–1151, 2016

BRIVARACETAM: Summary

- Not affected by renal impairement.
- No dose escalation required.
- Concomitant LEV use: 20% of patients in 2 RCTs. No added benefit.
- Switch from LEV to BRV: 27 of 29 (93%) had clinically meaningful reduction in BAEs

Intensity of BAEs at baseline	Intensity of BAEs at end of treatment period, n (%)			
	Resolved	Mild	Moderate	Severe
Mild	1 (3.4)	1 (3.4)	0	0
Moderate	10 (34.5)	3 (10.3)	1 (3.4)	0
Severe	8 (27.6)	2 (6.9)	3 (10.3)	0
Total	19 (65.5)	6 (20.7)	4 (13.8)	0

Epilepsy & Behavior 52 (2015) 165–168

Perampanel

- First of its class ASD.
- **Non-competitive** A*lpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid* **(AMPA) receptor antagonist.**
  - AMPA receptors important in formation of epileptiform discharges and epileptic synchronization in the hippocampus
  - AMPA receptors are not involved in long term potentiation (NMDA mediated)
- FDA indications:
  - adjunctive therapy for FOS in ≥4 yoa patients
  - adjunctive therapy for **primary GTC** in patients ≥ 12 yoa

Perampanel: Pharmacological Properties

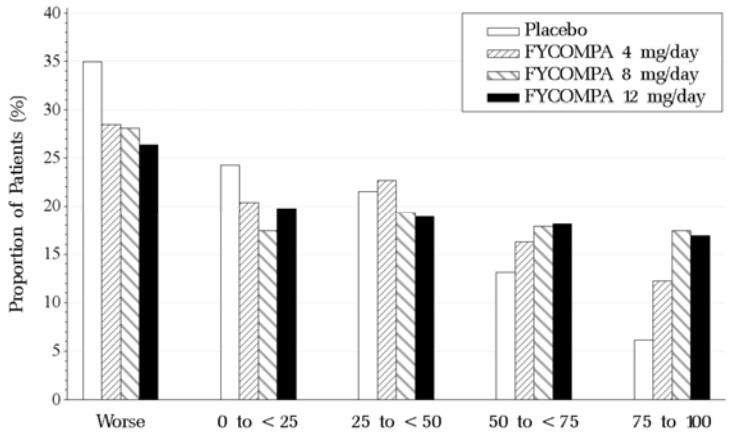
Characteristic	Effect
Protein bindings	High (95%)
T max	30 minutes - 2 hours
Half life ($t_{1/2}$)	105 (53 – 136) hrs. 25 hr in concomitant EIASD. ~2.5x in mild Liver disease
Metabolism	Liver (CYP3A4). Oxidation → Glucronidation
Liver disease	Mild: 6 mg (max), Moderate: 4 mg (max). Not recommended in severe disease
Metabolites	Inactive
Excretion	30% renally excreted
Renal disease	Not recommended in mod-severe disease

Characteristic	Effect
Effect <u>of</u> other ASDs	EIASD (except PB) ↓ concentration by ≥ 50%
Effect <u>on</u> other ASDs	33% ↑ in level of OXC. Not clinically meaningful
Interaction w/ other drugs	None
On OCPs	Progesterone (levonorgestrel) ↓ by 40% (12mg/D). *Alternate contraception needed.*
Cardiac effect	No effect on QT interval
Time to steady state	14 days
EtOH	Worsened mood + anger. Avoid EtOH
Other	Controlled substance (Class III)

Drugs (2015) 75:1657–1668, https://fycompa.com/sites/all/themes/fycompa/pdf/Fycompa_Prescribing_Information.pdf

Perampanel: Efficacy Data

- FDA approval as adjunctive therapy in POS based on 3 RCTs:
  - Each study compared placebo to multiple perampanel doses.
  - Primary endpoint: percent change in sz frequency per 28 days

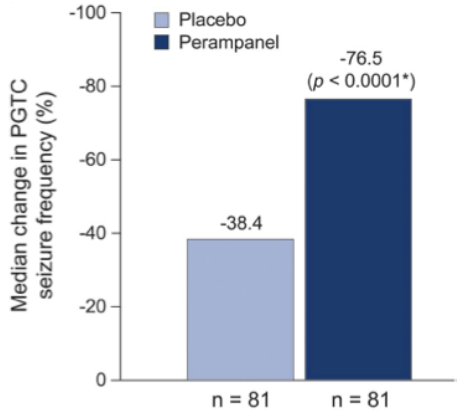


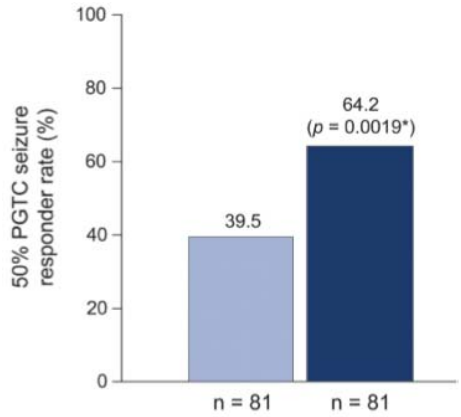
	Without Enzyme-Inducing AEDs		With Enzyme-Inducing AEDs	
	Placebo %	FYCOMPA %	Placebo %	FYCOMPA %
2 mg/day	19	26	18	20
4 mg/day	19	35	18	26
8 mg/day	17	45	19	32
12 mg/day	15	54	21	33

https://fycompa.com/sites/all/themes/fycompa/pdf/Fycompa_Prescribing_Information.pdf

Perampanel
Efficacy Data

- FDA approval as adjunctive therapy in primary GTC based on 1 RCT:
  - Patients titrated to 8 mg daily/highest tolerated dose
  - Primary endpoint: percent change in SZ frequency per 28 days





Neurology® 2015;85:950–957

Perampanel

- Available as:
  - Tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
  - Oral suspension: 0.5 mg/ml
- Dosage:
  - Recommended initial dose: 2 mg daily, preferably at night time
    - 4 mg for patients on EIASDs
  - Dose escalation: 2 mg every week.
  - Maintenance dose: 8 - 12 mg daily

Perampanel: Adverse effects

Adverse event, n (%)	Placebo (n = 442)	Perampanel			
		2 mg (n = 180)	4 mg (n = 172)	8 mg (n = 431)	12 mg (n = 255)
Any TEAE	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

- Dose-dependent. Early withdrawal also dose dependent.
- **Falls much higher (25% vs 9%) in elderly**
- **Hostility and aggression: 12 – 20% (dose dependent).**
- Clinically significant weight gain (>7 %) occurred in 14.6 % vs 7.1%
- Rates of TEAEs similar in patients receiving 1, 2 or 3 ASDs.

Epilepsia, 54(8):1481–1489, 2013

Eslicarbazepine

- Third generation CBZ, which aimed to
  - improves on “second” generation OXC:
    - Reduce side-effects
    - Avoid enzyme induction
- FDA approved for:
  - monotherapy /adjunctive therapy for treatment of FOS.

Eslicarbazepine Acetate: Pharmacological Properties

Characteristic	Effect
MOA	Selectively binds to inactive VGSC + T Ca channel
Protein bindings	Low (<40%)
T max	2 - 3 hours
Half life ($t_{1/2}$)	13 – 20 hours
Metabolization	Prodrug. Hydrolysed in Liver
Liver disease	No change in mild/moderate disease. Not recommended in severe disease
Metabolites	S-licarbazepine (91%- Active), R- licarbazepine, Oxcarbazepine
Excretion	Renal, >90%
Renal disease	Dose reduction by 50% if Cr Cl <50mL/min

Characteristic	Effect
Effect of other ASDs	↑ dose with EI-ASDs
Effect on other ASDs	PHT/CBZ dose may need to be ↓ Not to be taken with OXC.
Interaction w/ other drugs	Simva- and Rosuva-statins dose may need to be ↑ Closely monitor INR during titration.
On OCPs	Decreases ethinylestradiol and levonorgestrel. Alternate contraception needed.
Cardiac effect	No effect on QT interval
Autoinduction	None
Reference range	Not established yet

Drugs (2016) 76:707–71; http://www.aptiom.com/Aptiom-Prescribing-Information.pdf

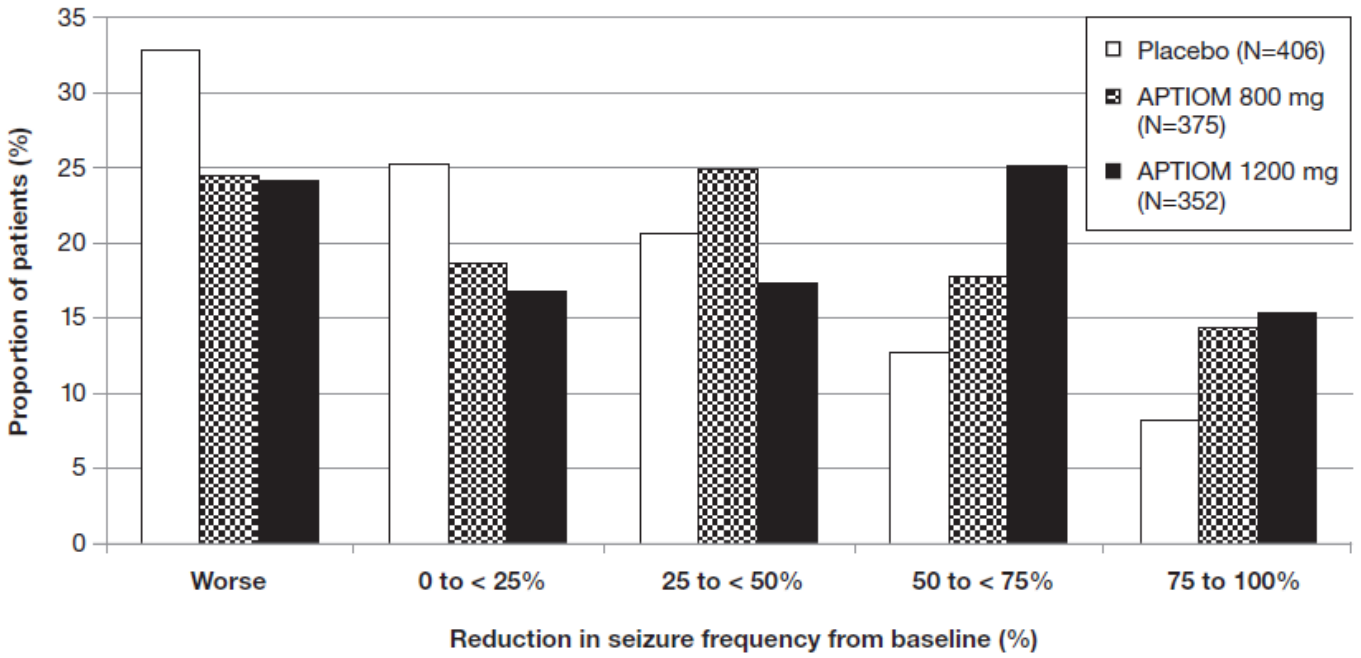
Eslicarbazepine Acetate

- Available forms:
  - Tablets: 200 mg, 400 mg, 600 mg, 800 mg.

- Dosage:
  - Recommended initial dose: 400 mg daily (If benefit>risks, may start 800 mg daily).
  - Maximum dose: 1600 mg daily
  - Dose escalation: 400-600 mg per week.

Eslicarbazepine Acetate: Efficacy Data

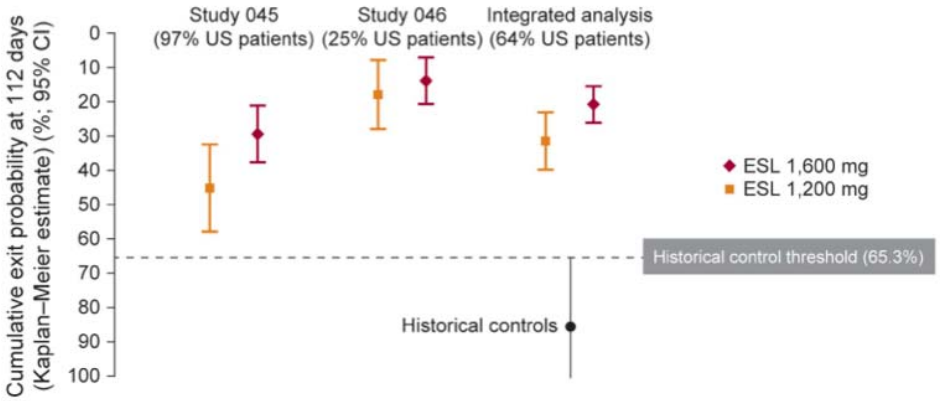
- FDA approval as adjunctive ASD based on 3 RCTs.
  - Two studies: Compared 400, 800, 1200 mg with placebo
  - Third study compared 800 and 1200 mg with placebo

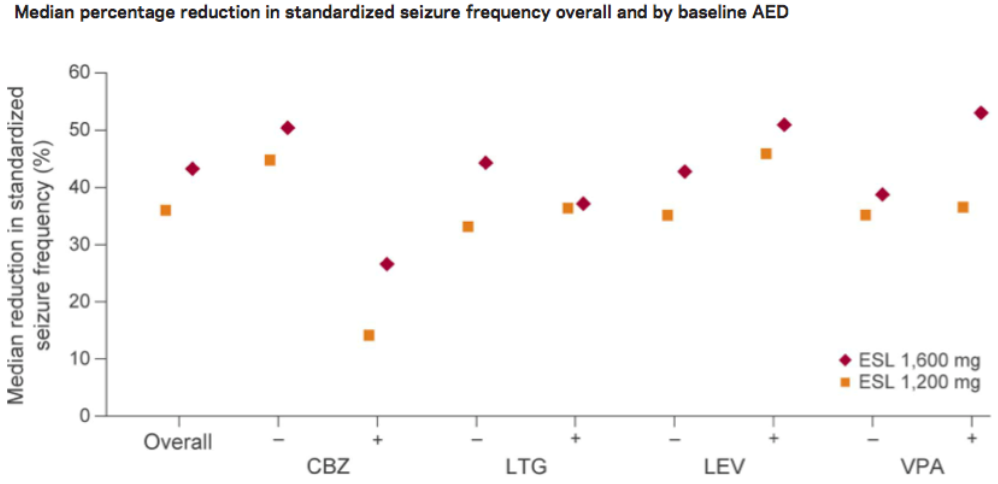


http://www.aptiom.com/Aptiom-Prescribing-information.pdf

Eslicarbazepine Acetate: Efficacy Data

- FDA approval as monotherapy based on 2 identical, dose blinded, historical control trials.
  - Randomized 2:1 to receive 1600 mg or 1200 mg daily
  - Primary end point was 112-day exit rate



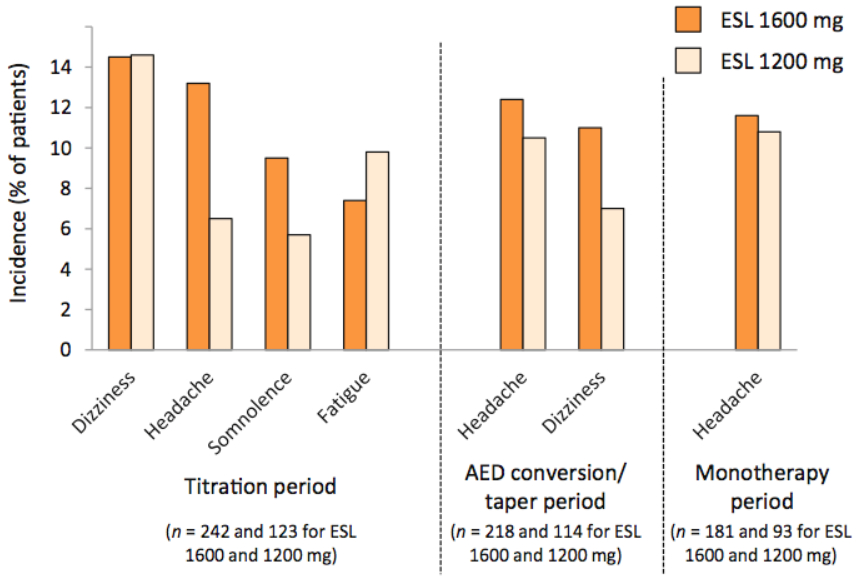


Neurology. 2016 Feb 24;86:1095–1102.

Eslicarbazepine Acetate: Adverse Effects

- Most adverse events are dose related
- Hyponatremia: 5.1% vs 0.7% with decrease in Na >10 mEq/L
  - Appears in first 8 weeks, *dose related*
  - At high doses, risk similar in all 3 gen of drugs
- Rash incidence was 1 – 3%. Case report of TEN.

	Number (%) of patients			
	Integrated phase 3 studies, Double-blind phase			
AE preferred term (MedDRA dictionary)	Placebo (*n* = 289)	ESL 400 mg (*n* = 196)	ESL 800 mg (*n* = 284)	ESL 1200 mg (*n* = 280)
Total patients with AEs	*134 (46.4)*	*119 (60.7)*	*178 (62.7)*	*189 (67.5)*
Dizziness	21 (7.3)	26 (13.3)	60 (21.1)	81 (28.9)
Somnolence	27 (9.3)	21 (10.7)	37 (13.0)	42 (15.0)
Headache	25 (8.7)	17 (8.7)	29 (10.2)	38 (13.6)
Nausea	6 (2.1)	10 (5.1)	21 (7.4)	28 (10.0)
Diplopia	5 (1.7)	10 (5.1)	23 (8.1)	24 (8.6)
Vomiting	7 (2.4)	4 (2.0)	19 (6.7)	20 (7.1)
Coordination abnormal	6 (2.1)	6 (3.1)	15 (5.3)	17 (6.1)
Vision blurred	3 (1.0)	8 (4.1)	11 (3.9)	11 (3.9)
Influenza	6 (2.1)	7 (3.6)	6 (2.1)	8 (2.9)
Vertigo	1 (0.3)	4 (2.0)	5 (1.8)	11 (3.9)
Diarrhoea	3 (1.0)	2 (1.0)	12 (4.2)	6 (2.1)
Fatigue	8 (2.8)	4 (2.0)	5 (1.8)	9 (3.2)
Constipation	3 (1.0)	6 (3.1)	3 (1.1)	6 (2.1)
Rash	1 (0.3)	1 (0.5)	3 (1.1)	9 (3.2)
Depression	1 (0.3)	6 (3.1)	2 (0.7)	5 (1.8)
Nasopharyngitis	8 (2.8)	6 (3.1)	2 (0.7)	4 (1.4)
Abdominal pain upper	9 (3.1)	3 (1.5)	3 (1.1)	4 (1.4)



CONCLUSIONS

- Newer ASDs expand therapeutic options
- Unique MOAs
- Overall, less drug interaction
- Better side effect profile
- One “miracle” drug not likely.
- Choose the drug that best fits your patient.

QUESTIONS?

Lacosamide

- FDA approved for:
  - **Monotherapy** or adjunctive therapy for POS in ≥17 years
- Effective in Diabetic Neuropathy up to dose of 400 mg/day in 3 RCT.
- Available as:
  - Tablets: 50, 100, 150, 200 mg
  - Oral solution: 10 mg/ml
  - Injection: 200 mg/20 ml

Lacosamide:Pharmacological Properties

Characteristic	Effect
MOA	Enhances slow inactivation of VGSC
Protein bindings	<15%
T max	0.5-4 hours
Metabolization	Liver by demethylation (CYP2C19)
Liver disease	Mild/mod Disease: max dose of 300 mg/D. Not recommended in severe.
Metabolites	Not active
Excretion	Renal (40%)
Renal disease	Severe disease: Max dose of 300 mg/D
Half life (t1/2)	13 hours

Characteristic	Effect
Effect of ASDs	EIASDs can increase clearance
Effect on AEDs	Not clinically significant
Interaction w/ other drugs	None reported. Pharmacodynamic: With VGSC blockers- worse AEs
On OCPs	No effect
Cardiac effect	Increases PR interval. No QT prolongation
Time to steady state	2 – 3 days
Reference range	10 – 20 mg/L
Hemodialysis	Removes 50% of dose over 4 hours
Other	Controlled- Schedule V

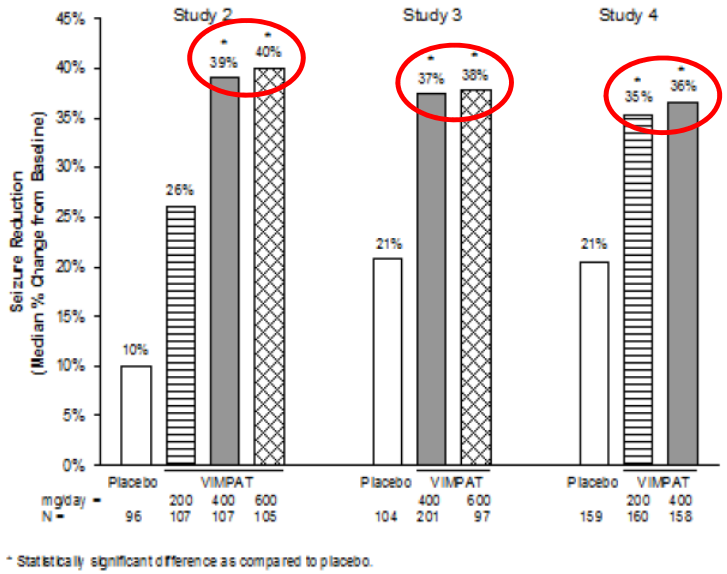
Drugs (2015) 75:1657–1668

Lacosamide

- Dosage:
  - Recommended initial dose: 100 mg BID, preferably at night time
    - May load with 200 mg under medical supervision
  - Maintenance dose: 400 mg daily
  - Dose escalation: 50 mg BID every week
  - IV form: Bioequivalence. Infused over 15-60 minutes

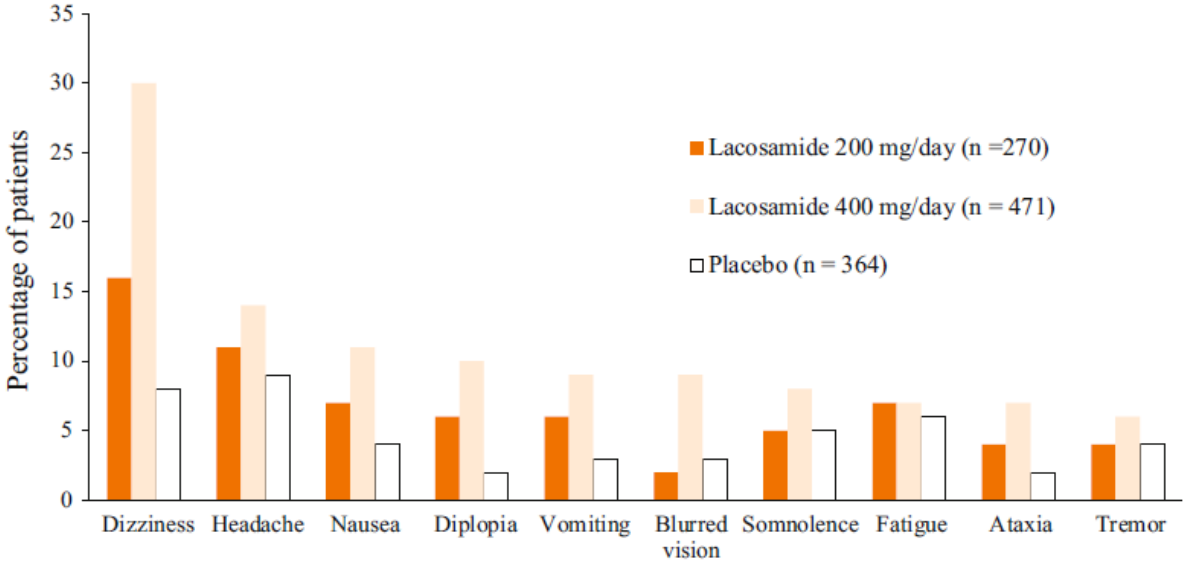
Lacosamide: Pharmacological Properties

- FDA approval as adjunctive AED based on 3 RCTs.
  - One study compared 200, 400, 600 mg with placebo
  - One study compared 400, 600 mg with placebo
  - One study compared 200, 400 mg with placebo



http://www.vimpat.com/pdf/vimpat_PI.pdf

Lacosamide: Adverse Events

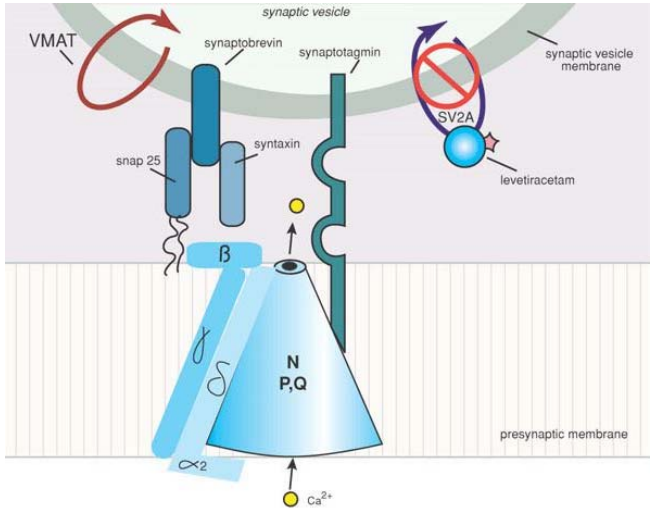


- Asymptomatic PR prolongation observed
- EKG recommended: before beginning and after steady dose
- Caution – careful consideration and monitoring use of LCMin:
  - Patients with known cardiac conduction problems, cardiac disease, heart failure
  - Concomitant use of drugs known to induce PR interval prolongation

Drugs (2015) 75:2143–2154; http://www.vimpat.com/pdf/vimpat_PI.pdf

Levetiracetam: Mechanism of Action

- Binds to SV2A protein
- Moderately inhibits N-type calcium channels
- Recently, a PET agent for human SV2A, 18F-UCB-H, identified.



EJNMMI Res 2013; **3**: 35.

Levetiracetam: Indications

- FDA approved for:
  - Adjunctive treatment of:
    - Partial onset seizures (≥ 1 month of age)
    - Myoclonic seizures in JME (≥12 years of age)
    - Primary GTC seizures in IGE (≥ 6 years of age)

Levetiracetam: Pharmacological Properties

Characteristic	Effect
Oral Bioavailability	**~100%**
Protein bindings	**Weak (≤10%)**
T_{max}	1 – 2 hours (+3 hrs for XR tabs)
Metabolism	Two third unmetabolized
Liver disease	No dose modifications
Metabolites	Hydrolysis to a deaminate metabolite
Excretion	Renal
Renal disease	Dose modification required
Half-life (t1/2)	6 – 8 hours (10 – 11 hrs in elderly)

Characteristic	Effect
With food	Slow but complete absorption. IR tabs: Can be crushed + mixed
Effect on AEDs	No effects
Effect by other drugs	Clearance increased ~20% by EIAEDs. No dose adjustment req.
On OCPs	No interaction
During pregnancy	Decrease up to 70% by 3rd trimester compared to baseline
Cardiac effect	Not clinically significant
Interaction with EtOH	None
Serum level monitoring	12–46 µg/mL

Levetiracetam: Dosing and Titration

- Formulations:
  - Scored tablets: 250 mg, 500 mg, 750 mg, 1000 mg.
  - Solution: 100 mg/ml (Recommended for pediatric pts ≤20 kg)
  - XR tabs: 500 mg, 750 mg
  - Intravenous formulation: 500 mg/5mL
- Dosing:

	1 mo to <6mo	6 mo to <4 y	4y to 16y	Adults/ peds >40 kg
Start	7 mg/kg BID	10 mg/kg BID	10mg/kg BID	500 mg BID
Up-titration (q2wks)	14 mg/kg daily	20 mg/kg daily	20 mg/kg daily	1000 mg/day
Max dose	35 mg/kg/day	50 mg/kg/day	60 mg/kg/day	3000 mg/day

- Note: One of 3 second line options for benzo-resistant convulsive SE at 60 mg/kg loading dose (level U)[2].

Levetiracetam: Renal Dosing

- Patients with Renal Impairment:
  - Adjustments according to patient's renal function.
  - Creatinine Clearance (CLcr) adjusted for BSA must be calculated.
    - (140-age) * (Wt in kg) * (0.85 if female) / (72 * Serum Cr)

Group	CLcr (ml/min/1.73m$^{2)}$	Dosage (mg)	Frequency
Normal	>80	500 – 1500	q 12 hrs
Mild	50 - 80	500 – 1000	q 12 hrs
Moderate	30 - 50	250 – 750	q 12 hrs
Severe	<30	250 – 500	q 12 hrs
ESRD on Dialysis	-	500 – 1000	q 24 hrs

  - Following dialysis, a 250 to 500 mg supplemental dose is recommended

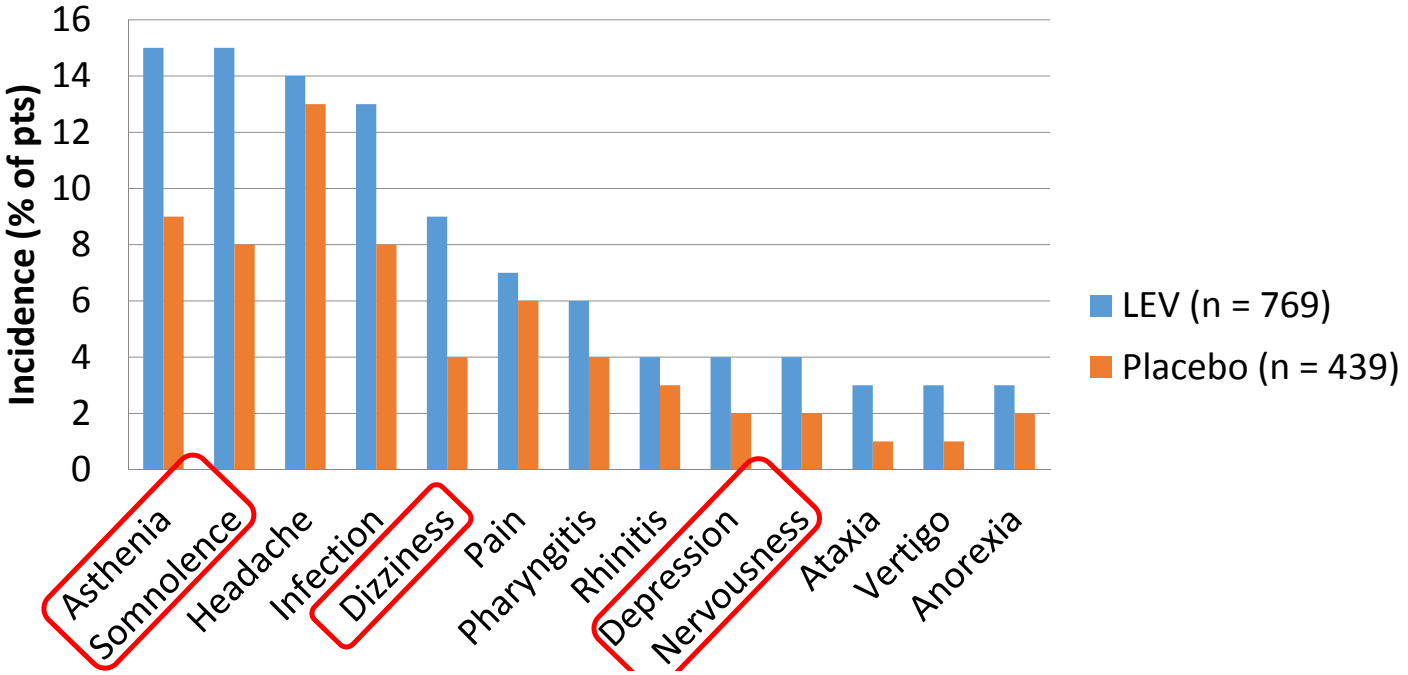
Levetiracetam: Pivotal Studies

Study	n	Inclusion criteria	Doses (mg)	T/t duration	% responders (p ≤0.01)	% seizure free
Shorvon et al	324	Refractory focal seizures ≥4 seizures/4 weeks 1 or 2 concomitant AEDs	1000, 2000	12 weeks	Placebo: 10.4% 1000 mg: 22.8%, 2000 mg: 31.6%	Placebo: 9% 1000 mg: 5% 2000 mg: 2%
Ben-Menachem and Falter	286	Focal seizures ≥2 seizures/4 weeks 1 concomitant AED	3000	18 weeks	Placebo: 16.7% 3000 mg: 42.1%	Placebo: 1% 3000 mg: 8.2%
Cereghino et al.	294	Refractory focal seizures ≥12 seizures/12 weeks 1 or 2 concomitant AEDs	1000, 3000	18 weeks	Placebo: 10.8% 1000 mg: 33%, 3000 mg: 39.8%	Placebo: 0.0% All LEV doses: 5.5%
Betts et al.*	119	Refractory focal seizures ≥4 seizures/24 weeks 1 – 3 concomitant AEDs	2000, 4000	24 weeks	Placebo: 16.1% 2000 mg: 28.6%, 4000 mg: 48.1%#	Placebo: 2.5% 2000 mg: 9.5% 4000 mg: 5.2%

- Combined analysis:
  - $3/4^{th}$ of patients on LEV exhibited seizure reduction
  - Significant dose-seizure reduction relations
  - ED_{50} = 1408 mg/D
  - Retention rate ranged 60 – 75%

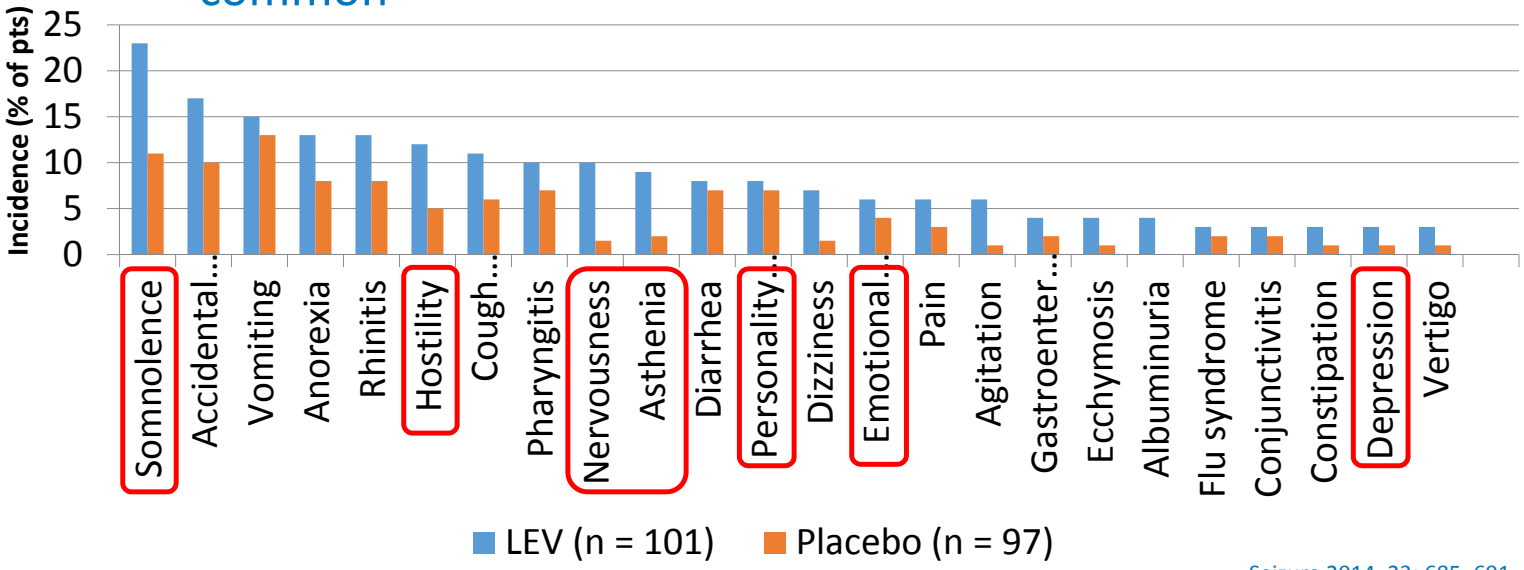
Levetiracetam: Side Effects

- Overall adverse events for 1000-3000 mg/day dosage (55 – 89.1%) comparable to placebo (53 – 88.4%).
- Incidence higher without up-titration.



Levetiracetam: Side Effects

- **Pediatrics**
  - Hostility, nervousness and aggression related to LEV.
  - A RR of 2.18 (1.42–3.37) for all behavioral side-effects.
  - In infants and children ≤ 4yrs, somnolence (LEV 13.3% vs placebo 1.8%) and irritability (LEV 11.7% vs placebo 0%) common



Seizure 2014; 23: 685–691

Levetiracetam: Side Effects

- Behavioral adverse effects
  - Premarketing studies: In 12.9% LEV compared to 6.2% placebo patients[1].
  - Cochrane review[2]: 11 RCTs in adults and pediatric population
    - 22.64% of children (RR 1.90; 99% CI 1.16–3.11)
    - 1.04% of adults were affected (RR 1.79; 99% CI 0.59–5.41)
  - General population[3]:
    - 12–15% of patients
    - Risk factors:
      - Learning disability
      - prior psychiatric history
      - Symptomatic generalized epilepsy.

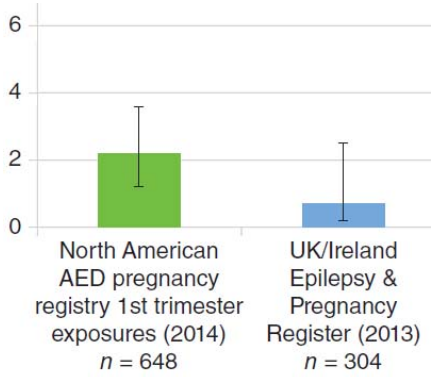
[1]Epilepsy Behav 2003; 4: 124–132. [2]Cochrane Database Syst Rev 2012; 9: CD001901, [3]Drug Saf 2005; 28: 871–890

Levetiracetam: Side Effects

- XR form side effect profile similar to IR form.
- No negative impact on cognitive function.
  - Monotherapy in drug-naïve epilepsy patients: significant in verbal + visual attention, executive functioning and word generation.
  - Open label study in epilepsy patients with Alzheimer's: improved attention and oral fluency.
  - A randomized, DB, placebo-controlled crossover study of 20 healthy elderly:
    - No impact on cognition or balance while on LEV compared to Placebo phase.
    - Trend towards increased fatigue and irritability/anger during LEV phase.

Levetiracetam: Salient Features

- Rare hypersensitivity and skin rashes
- Low teratogenic risk in registries.
- Cognitive and language development comparable to control in kids ≥3 yrs post *in utero* LEV exposure[1].
- Significant reduction in sperm counts and concentrations:
  - 26 male with newly diagnosed epilepsy[3]
  - Pre and post-LEV therapy
  - 10 – 15% reduction in sperm counts and concenteration
  - Moderate correlation in daily dose and ↓in functional sperm count (r: 0.41, p: 0.034)
  - Similar results in a Chinese study[4].



[1]Neurology 2014; 82: 213–221, [2]Epilepsy Currents, Vol. 16, No. 1 (January/February)2016, 48–61, [3]Seizure 41 (2016) 70–74, [4]J Clin Neurosci. 2013 Nov;20(11):1492-7

Lamotrigine: Mechanism of Action

- In animal models, LTG similar but more potent to PHT and CBZ.
- Blocks Na^+ channels (preferential to α unit) in voltage, use and frequency-dependent manner.
- At clinically relevant concentrations, LTG inhibits VD Ca^{2+} channels cortical and striatal neurons.
- LTG also appears to affect K^+ conductance.
- In limbic circuits:
  - Inhibits presynaptic N-type Ca^{2+} channel
  - Inhibits post-synaptic AMPA receptors and Glutamate release

Drug Des Devel Ther 2010; 4: 337–342

Lamotrigine: FDA Indications

- Conversion to monotherapy:
  - In adults (≥ 16 years) with focal szs on CBZm PHT, PHB, VPA, Primidone
- Adjunctive therapy:
  - In patients ≥2 years of age with:
    - Focal onset seizure
    - Primary GTC seizures
    - Generalized seizures of Lennox-Gastaut syndrome
- Safety and effectiveness not established for initial monotherapy.

Lamotrigine: Pharmacological Properties

Characteristic	Effect
Protein bindings	~50%
Tmax	1 – 3 hours (4 – 11 hrs with XR)
Metabolism	Extensively in Liver (Glucronidation – UGT1A4)
Liver disease	Moderate to Severe w/o ascites: ↓25% Severe with ascites: ↓50%
Metabolites	Not active
Excretion	Renal (90% as metabolite)
Renal disease	t1/2 doubled in CKD patients
Half-life (t1/2)	- EIAEDs: 15 – 35 hours + EIAEDs: 8 – 20 hours + VPA: 30 – 90 hours
Serum level monitoring	12.5 - 15 µg/mL

Lamotrigine: Formulations, Doses, Titration

- Scored tabs: 25 mg, 100 mg, 150 mg, 200 mg.
- Chewable dispersible tabs: 2 mg, 5 mg, 25 mg
- Orally disintegrating tabs: 25 mg, 50 mg, 100 mg, 200 mg
- LTG starter kits and titration kits available
- XR tabs: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg

	Patient not on EIAEDs	Patients on VPA	Patients on EIAEDs but NOT VPA
Weeks 1 and 2	25 mg q daily	25 mg q ***other*** daily	50 mg q daily
Weeks 3 and 4	50 mg/day (as BID)	25 mg every day	100 mg/day (as BID)
Weeks 5 onward to maintenance	Increase 50 mg/day q 1 - 2 weeks.	Increase 25 to 50 mg/day q 1- 2 weeks	Increase 100 mg/day q 1 - 2 weeks.
Usual maintenance dose	225 - 375 mg/day (as BID)	100 - 200 mg/day with VPA 100 to 400 mg/day with VPA + other drugs that induce glucuronidation (daily or BID)	300 to 500 mg/day (as BID)

- Even slower up-titration in children

Lamotrigine: Drug Interactions

- VPA increases LTG concentration by ≥ 2 times
  - Maximal inhibition already noted by 500 mg/day VPA dose
- EIAEDs reduce LTG concentration by ~40 - 50%
  - EIAED withdrawal →marked LTG level increase
- Estrogen containing OCPs reduce LTG by ~50%
  - Gradual return to baseline during 7-day pill-free period
- LTG may reduce serum progesterone by ~20%.
- Other drugs that can reduce LTG concenteration
  - Olanzapine by ~25%
  - Rifampicin
  - Lopinavir/ritonavir (50%), Atanazavir/ritonavir (30%)

Drug Des Devel Ther 2010; 4: 337–342

Lamotrigine: Pivotal Studies

Study	n	Inclusion criteria	Doses (mg)	T/t duration	% responders (p ≤0.01)	Median reduction in Sz frequency
Matsuo et al	216	Refractory focal seizures ≥4 seizures/4 weeks 1 or 2 concomitant AEDs – not VPA	300, 500	24 weeks	Placebo: 18% 300 mg: 20%, 500 mg: 34%	Placebo: 9% 300 mg: 20%, 500 mg: 36%
Messenheimer et al. (Cross over trial)	98	Focal seizures ≥3 seizures/4 weeks 1 or 2 concomitant AEDs – not VPA	400	28 weeks	20%	25%
Schapel et al.	41	Refractory focal seizures 1 or 2 concomitant AEDs including VPA	150 - 300	28 weeks	22%	24%
Duchowny et al. (Age 2 – 16 years)	199	Refractory focal seizures ≥4 seizures/4 weeks 1 or 2 concomitant AEDs including VPA	**5mg/kg/D 15mg/kg/D**	18 weeks	Placebo: 16% LTG: 42%	Placebo: 6.7% LTG: 36.1%

- Also shown efficacy in LGS and primary GTC as adjunct therapy

Lamotrigine: Conversion to Monotherapy

- With EIAEDs:
  - Achieve LTG 500 mg/day as routine initial up-titration
  - Reduce EIAED by 20% q week over 4 weeks
- With Valproate
  - Four step process

	LAMICTAL	Valproate
Step 1	Achieve a dose of 200 mg/day	Maintain established stable dose.
Step 2	Maintain at 200 mg/day.	Decrease dose by decrements no greater than 500 mg/day/week to 500 mg/day and then maintain for 1 week.
Step 3	Increase to 300 mg/day and maintain for 1 week.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day.	Discontinue.

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Lamictal/pdf/LAMICTAL-PI-MG.PDF

Lamotrigine
Side Effects

- **BLACK BOX Warning**: Serious Skin Rash
  - 0.3% – 0.8% in pediatrics (2 – 17 y/o)
  - 0.08% – 0.3% in adults
  - Age only factor known to predict risk of rash
  - Possible factors:
    - co-admin with VPA
    - Exceeding initial dose
    - Exceeding recommending escalation
  - Nearly all life-threatening rashes with in 2 – 8 weeks of treatment initiation
  - Recommended to discontinue LTG at first sign of rash

Lamotrigine: Side Effects

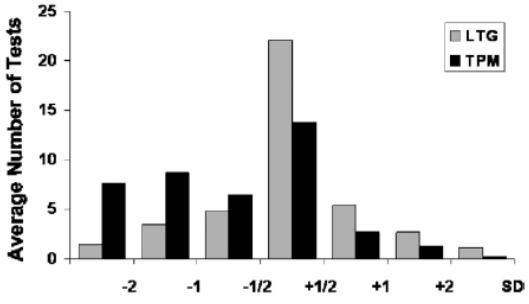
- DRESS may present w/o rash.
- AEs led to d/c in 10.2% pts in pre-marketing trials.
  - Skin rash most common: 3.8%
- Dose related AEs:
  - Dizziness
  - Ataxia
  - Diplopia
  - blurred vision
  - Nausea
  - Vomiting

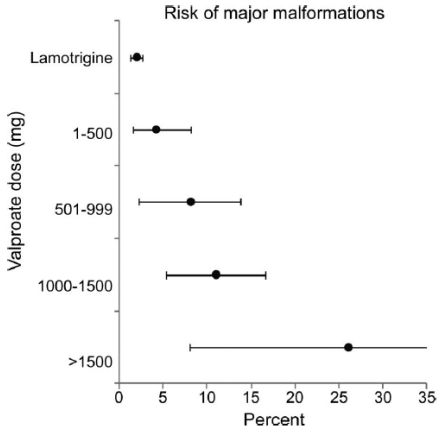
Adverse event	LTG add-on controlled studies [n = 962] (%)	Placebo add-on [n = 593] (%)
Dizziness	35	15
Headache	26	21
Diplopia	25	6
Nausea	19	9
Ataxia	20	6
Somnolence	13	7
Blurred vision	14	4
All Rash	10	5
Vomiting	10	5
Abnormal coordination	6	2
Rhinitis	11	8
Tremor	5	1
Insomnia	6	3

Drug Safety 1998 Apr; 18 (4)

Lamotrigine: Salient Features

- False-positive reading of U-Tox - PCP.
- 2% risk of major malformations with LTG[1].
- FDA approved for Bipolar treatment
- Cognitive profile good.
  - A db RCT cross over study of 47 patients compared LTG and TPM on 41 variables of cognitive function[2].





[1]Neurology® 2012;78:1692–1699, [2]NEUROLOGY 2005;64:2108–2114

Topiramate: Mechanism of Action

- Multiple modes of action – broad spectrum.

Site	Action
Calcium channels	Mild reduction of high-voltage activated calcium current amplitude
Voltage-activated sodium channel	Limits sustained repetitive firing via state dependent blockade of sodium channels
GABA receptor	Potentiates GABA-mediated neuroinhibition at a $GABA_A$ receptor site not modulated by benzodiazepines or barbiturates
Glutamate receptor subtypes (kainate/AMPA)	Blocks glutamate-mediated neuroexcitation with no apparent effect on NMDA receptor activity
Carbonic anhydrase (CA)	Antagonizes isoenzymes, types II and IV

- Relatively weak (CA) inhibitor (ACTZ 10-100 times potent)

Topiramate: Pharmacological Properties

Characteristic	Effect
Oral Bioavailability	**~100%**
Protein bindings	**Weak (13 - 17 %)**
T_{max}	2 – 4 hours (+3 hrs for XR tabs)
Metabolization	Two third unmetabolized
Liver disease	No dose modifications
Metabolites	No active metabolite
Elimination	Partly renal and oxidative met
Renal disease	Half the dose in moderate to severe CKD Dialysis: Supplement dose
Half-life (t1/2)	20 – 30 hrs (10-15 hrs with EIAED)

Characteristic	Effect
With food	Slow (by 2 hr) but complete absorption. w/o regards to meals
Effect on AEDs	Not clinically significant. Do not use other CA inhibitors
Effect by other drugs	Clearance increased ~50% by EIAEDs. Dose adjustment req.
On OCPs	Reduces ethinylestradiol levels with dose >200 mg
Drug interactions	↓Lithium levels; ↑ Metformin
Elderly	Clearance reduced by ~20%
Serum level monitoring	5 - 20 µg/mL

Topiramate: FDA Indications

- Monotherapy:
  - Initial monotherapy in patients ≥2 y/o with POS or primary GTC seizures.

- Adjunctive:
  - patients ≥2 y/o with POS or primary GTCs
  - patients ≥2 y/o with seizure assoc with LGS.

https://www.topamax.com/files/topamax.pdf

Topiramate: Formulations, Doses, Titration

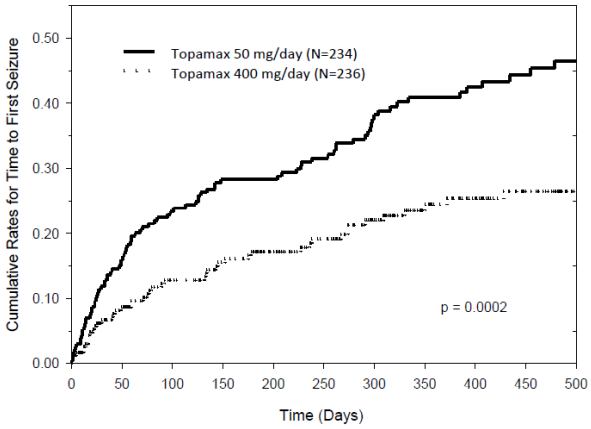
- Tablets: 25 mg, 50 mg, 100 mg, 200 mg.
- Sprinkle capsules: 15 mg, 25 mg
- XR capsules: 25 mg, 50 mg, 100 mg, and 200 mg
- Dosing in patients ≥10 yoa:
  - Initial dose: 25 mg BID.
  - Increments: 25 mg BID q week
  - Max dose: 200 mg BID
- Weight based dosing for pediatric patients 2-9 yoa.
  - Initial dose: 25 mg at bedtime for week

Weight (kg)	Max daily dose (mg/day)
<11	250
12 - 22	300
23 - 38	350
>38	400

https://www.topamax.com/files/topamax.pdf

Topiramate: Pivotal Studies

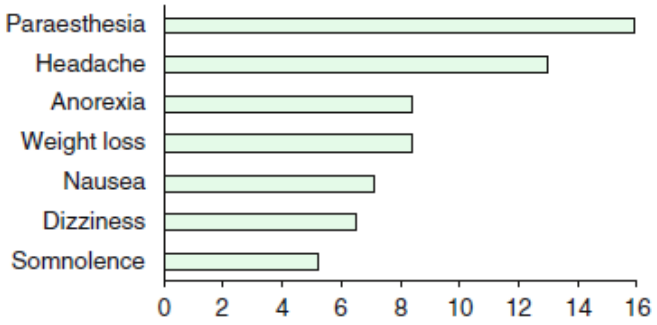
- Six pivotal adjunctive therapy trials for focal epilepsy: responder rates of 35 – 50%.
- Initial monotherapy trial:
  - Parallel group trial
  - 470 patients ≥10 y/o randomized to 50mg/d or 400 mg/d
  - Primary end-point: b/w group comparison of time to first seizure during
- Adjunctive for primary GTC: One placebo control trial comparing single dose TPM
- Adjunctive for LGS: One placebo control trial comparing single dose TPM



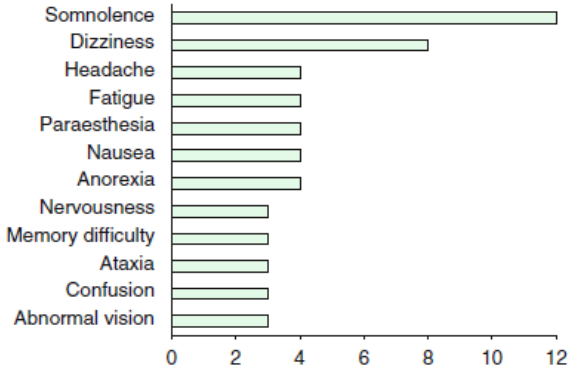
https://www.topamax.com/files/topamax.pdf

Topiramate: Adverse Effects

- Slower up-titration improves tolerance.
- Somnolence and dizziness most common AEs among adjunctive therapy patients.
- In monotherapy trials:



Monotherapy trials



Adjunctive trials

Drugs 2007; 67 (15)

Topiramate: Other considerations

- Metabolic acidosis:
  - Hyperchloremic, non-anion gap metabolic acidosis
  - Typically early, but may appear anytime!
  - Mild to moderate ↓ in HCO_3^- (4mEq)
  - HCO_3^- <17mEq/L: 11% v/s ≤2% in placebo arm

- Renal Stones:
  - Due to ↓ citrate excretion + ↑ urine pH
  - In 1.5% patients: 2-4 times untreated pts
  - In 7% of pts of 1- 24 mo
  - Risk reduced by:
    - Increased hydration
    - Avoiding Ketogenic diet

Drugs 2007; 67 (15)

Topiramate: Other considerations

- Angle closure glaucoma:
  - Idiosyncratic reaction due to ciliochondral effusion
  - Presents with in 1 mo of starting TPM
  - Reversible
- Oligohydrosis + Hyperthermia:
  - Majority reported in pediatric patients
  - 9 of 14 patients had reduced sweating: 8 were <16y/o – 3 had symptoms of heat intolerance[1]
- Hypothermia when used in combination with VPA

Drugs 2007; 67 (15); [1]Pediatr Neurol 2007 Jun; 36 (6): 353-60

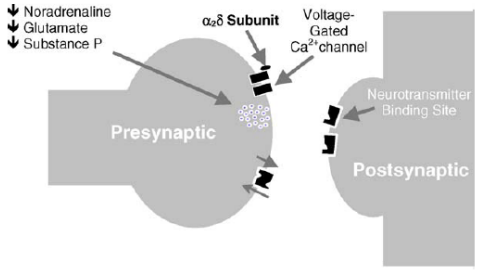
Topiramate: Salient Features

- Cognitive effects:
  - Affects cognitive language and working memory.
    - Psychomotor slowing/Verbal fluency
  - May appear at ≤100 mg/D - Dose dependent
  - Post-marketing: ~41% of 701 pts[2]
- Hyperammonemia ±Encephalopathy
  - Dose dependent.
  - Worse in combination with VPA
- Weight Loss:
  - Pooled controlled trials: 85% (TPM) v/s 39% (placebo)
  - Starts early; peaks by 15 – 18 mos[3]
  - Avg weight loss at 1 year: ~6 kgs (7.3% of baseline). More in Obese
- Cleft lip ± palate in 4 - 5% and SGA in 19.7% of pregnancies.

Drugs 2007; 67 (15); Epilepsia 2001 Sep; 42 (9): 1134-40, [2]Epilepsia 2003; 44 (3): 339-47; [3]Epilepsia 2000; 41 (4 Suppl. 1): S66-71

Gabapentinoids: Mechanism of Action

- Selective inhibitor of calcium channels containing the α2-δ-1
- Subtly reduce the release of a wide variety of neurotransmitters:
  - Noradrenaline
  - Glutamate
  - Acetylcholine
  - Substance P
  - Calcitonin gene-related peptide
- PGB: 3 – 6 times more potent than GBP



Gabapentinoids: Pharmacological Properties

Characteristic	Effect
Protein bindings	None
T_{max}	1 – 2 hrs (PGB); 2 – 3 hrs (GBP)
Metabolization	
Liver disease	
Metabolites	None active
Elimination	Kidney, unchanged
Renal disease	
Half-life (t1/2)	5 – 7 hrs (PGB); 5 – 9 hrs (GBP)
Interactions	None significant
Elderly	**Clearance reduced by 30 – 50%**
Miscellaneous	Bioavailability reduced from 60% with 300 mg to 35% with 600 mg TID

Gabapentinoids: FDA Indications

- Adjunctive therapy for adult patients with partial onset seizures
- GBP for patients ≥3 years
- Other indications:
  - Post-herpetic neuralgia
  - Diabetic Neuropathic pain (PGB only)
  - Fibromyalgia (PGB only)
  - Neuropathic pain in spinal cord injury (PGB only)

Gabapentinoids: Formulations, Doses, Titration

		Gabapentin	Pregabalin
Capsules (mg)		100, 300, 400	25, 50, 75, 100, 150, 200, 225, 300
Tablets (mg)		600, 800	-
Oral Solution		50 mg/ml	20 mg/ml
Starting dose		300 mg TID	150 mg/D (BID/TID)
Max dose		1200 mg TID	600 mg/D
Renal Dosing (based on CLcr)	≥ 60	900 – 3600	600 mg/D (BID/TID)
	30 – 60	400 – 1400	300 mg/D (BID/TID)
	15 – 30	200 – 700	150 mg/D (QD/BID)
	<15	100 – 300	75 mg/D (QD)
	On HD	Supplement 135 – 300 mg	Supplement QD dose

- Add-on PGB on GBP not evaluated in controlled trials.

Gabapentinoids: Pharmacological Properties

Characteristic	Effect
Protein bindings	None
T_{max}	1 – 2 hrs (PGB); 2 – 3 hrs (GBP)
Metabolism	None
Liver disease	No changes
Metabolites	None active
Elimination	Kidney, unchanged
Renal disease	Significant dose reductions
Half-life (t1/2)	5 – 7 hrs (PGB); 5 – 9 hrs (GBP)
Interactions	None significant
Elderly	Clearance reduced by 30 – 50%
Miscellaneous	Bioavailability reduced from 60% with 300 mg to 35% with 600 mg TID

Gabapentinoids: Salient Features

- GBP shown to have lower efficacy than LTG, CBZ.
- A comparative efficacy and safety study of PGB and GBP:
  - randomized, flexible dose, double blind, and parallel group
  - 242 patients each arm
  - No significant difference in primary end point: % reduction from baseline 28 days seizure rate
- Anaphylaxis and angioedema: at first dose or any time during t/t.
- PGB weight gain: ~9% v/s 2% in placebo group.
  - Dose and duration related
- PGB and peripheral edema: 6% v/s 2%

Gabapentinoids: Salient Features

- Abuse potential: Recent systematic review found
  - 59 studies
  - 1.6% prevalence of Gabapentinoids
  - Prevalence 3% to 68% among opioid abusers
  - During 2004 – 2015: 11,940 reports of abuse (>75% since 2012)
  - Risk factors:
    - Hx of abuse, specially opioids
    - Psychiatric co-morbidites

Drugs (2017) 77:403–426