

NEWER PHARMACOLOGICAL TREATMENTS IN ADULTS WITH EPILEPSY: COST-EFFECTIVENESS AND COMORBIDITY CONSIDERATIONS

Focused Milestones in the Sciences and Practice of Pharmacy

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LEARNING OBJECTIVES

1. Review current pharmacological treatments for Adults with Epilepsy
2. Identify barriers to medication compliance for Adult patients with Epilepsy
3. Discuss future treatment landscape for Epilepsy

EPILEPSY

50
million

3x↑

70%

NEW ANTI-SEIZURE MEDICATIONS *PAST DECADE*

2016

Brivaracetam

2018

Cannabidiol
Stripentol

2019

Cenobamate

2020

Fenfluramine

2022

Ganaxolone

BRIVARACETAM

- FDA approval: February 2016
- Co-morbidity considerations: hepatic metabolism
- Counseling pearls: do not crush tablets
- Drug interactions: Substrate of CYP2C19 (major)
- Overall, well tolerated with minimal side effects

CANNABIDIOL

- FDA approval: June 2018
- Counseling pearls: administration with food can increase absorption
- Adverse Drug Reactions: decreased appetite, anemia, diarrhea
- Drug interactions: Substrate of CYP2C19 (minor), CYP3A4 (major), UGT1A7, UGT1A9, UGT2B7; Inhibits BSEP/ABCB11, CYP1A2 (weak), CYP2C19 (moderate), CYP2C9 (weak), CYP3A4 (weak), P-glycoprotein/ABCB1

STRIPENTOL

- FDA approval: August 2018
- Mechanism of action: May enhance GABAergic inhibitory neurotransmission by weak partial agonism and/or positive allosteric modulation of gamma-aminobutyric acid (GABA)-A receptors
- Drug interactions: Substrate of CYP1A2 (minor), CYP2C19 (minor), CYP3A4 (minor); Inhibits CYP1A2 (moderate), CYP2C19 (moderate), CYP3A4 (weak)
- Place in therapy: FDA approved to be used in **combination with clobazam**
- Adverse Drug Reactions: Drowsiness, weight loss
- Counseling pearls: Administer with meals, do not crush; systemic exposure is slightly higher with the powder for suspension than that observed with capsules (caution when switching products)

CENOBAAMATE

- FDA approval: November 2019
- Mechanism of action: inhibits voltage-gated sodium channels, reducing repetitive neuronal firing and is a positive allosteric modulator of GABA_A ion channels
- Co-morbidity considerations: extensive hepatic metabolism, not well studied in impaired renal function
- Adverse Drug Reactions: QT shortening, diplopia
- Counseling pearls: titration pack for new starts

FENFLURAMINE

- FDA approval: June 2020
- Mechanism of action: increase extracellular levels of serotonin through interaction with serotonin transporter proteins, and exhibit agonist activity at serotonin 5HT-2 receptor
- Co-morbidity considerations: valvular heart disease and pulmonary arterial hypertension black box warning

GANALOXONE

- FDA approval: March 2022
- Mechanism of action: positive allosteric modulation of the gamma-aminobutyric acid type A (GABAA) receptor in the CNS
- Drug interactions: Substrate of CYP2B6 (minor), CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (major)
- Counseling pearls: administer with food, allow suspension to sit after shaking before measuring dose

SUMMARY OF NEW AGENTS

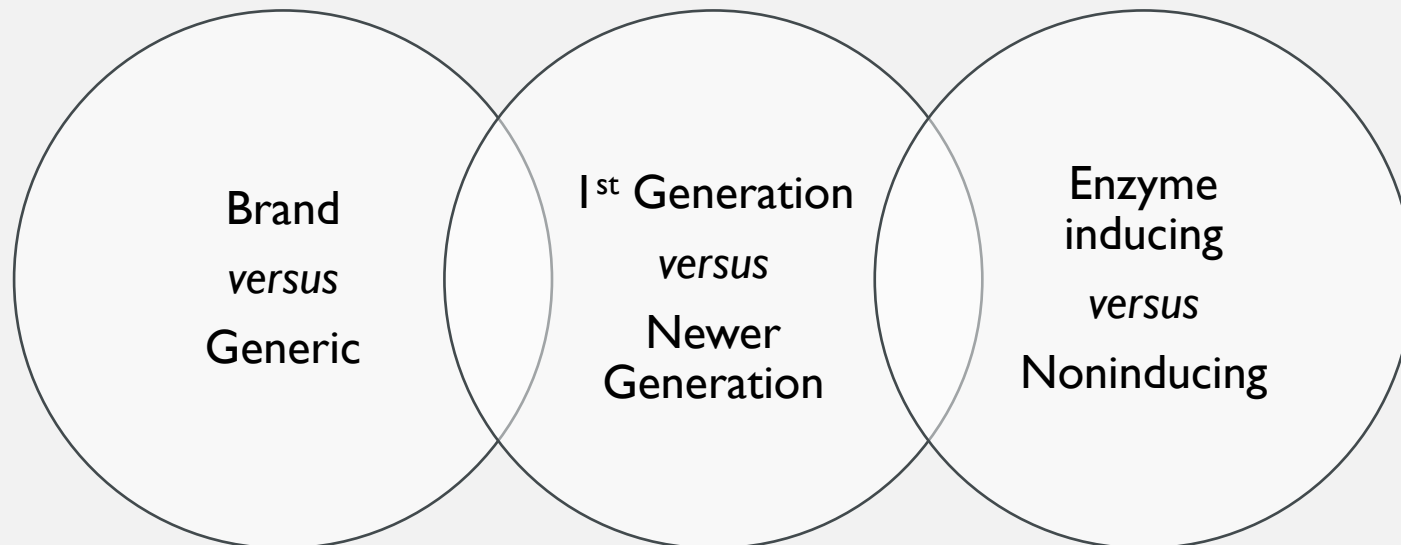
Medication	Place in Therapy
Brivaracetam	Partial-onset seizures
Cannabidiol	Seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex
Stripentol	Combination with clobazam
Cenobamate	Focal (partial) onset seizures
Fenfluramine	Seizures associated with Lennox-Gastaut syndrome or Dravet syndrome
Ganaxolone	Seizures associated with cyclin-dependent kinase-like 5 deficiency disorder

BARRIERS TO COMPLIANCE

- Cost
- Schedule
- Lack of symptoms
- Adverse drug reactions

Changes in the Use of Brand Name and Generic Medications and Total Prescription Cost Among Medicare Beneficiaries With Epilepsy

- Medicare Part D data retrospective cohort study
- Beneficiaries with epilepsy



RESEARCH ARTICLE

Changes in the Use of Brand Name and Generic Medications and Total Prescription Cost Among Medicare Beneficiaries With Epilepsy

- Brand name pill supply
 - Lacosamide and Pregabalin
- Cost increase from \$360 million → \$1.3 billion
- Brand name drugs have demonstrated poorer cost-related adherence



RESEARCH ARTICLE

Changes in the Use of Brand Name and Generic Medications and Total Prescription Cost Among Medicare Beneficiaries With Epilepsy

- Levetiracetam most commonly prescribed
- Decreased use of first-generation and enzyme-inducing medications
- Data reported does not fully reflect current patent expirations and newer agents

AMERICAN EPILEPSY SOCIETY GUIDELINES 2018

- Updates to the 2004 American Academy of Neurology guidelines
- Literature review spanned from January 2003-November 2015
- New-onset epilepsy & treatment-resistant epilepsy



GUIDELINE UPDATE TREATMENT-RESISTANT EPILEPSY

- Pregabalin (2004) – effective as add-on therapy for TRAFE
- Perampanel (2012) – effective as add-on therapy in TRAFE
- Lacosamide (2008) – probably effective in TRAFE
- Eslicarbazepine (2013) – probably effective in TRAFE (doses of 800 and 1200 mg/day); may be considered to decrease seizure frequency as monotherapy for TRAFE
- Clobazam (2011) – possibly effective as add on therapy for TRAFE
- Rufinamide (2008) – effective as add-on therapy for LGS, benefits are modest
- Ezogabine – discontinued by manufacturer secondary to low use in 2017

Medication	Clinical Pearls
Pregabalin	Adjunctive therapy
Perampanel	Half-life elimination ~100 hours Box warning for psychiatric and behavioral adverse reactions
Lacosamide	Caution with prolonged PR interval
Eslicarbazepine	Drug interactions
Clobazam	Long half-life, active metabolite
Rufinamide	Contraindicated in patients with familial short QT syndrome

FUTURE DRUG TARGETS

- Lactate Dehydrogenase Inhibitor
- c-Jun N-Terminal Kinases
- High Mobility Group Box-I Antibody
- Astrocyte Reactivity
- Cholesterol 24-Hydroxylase Inhibitor
- Glycogen Synthase Kinase-3 Beta and Tau Protein
- Glycolytic Inhibition
- Inhibition of mTOR Pathway
- G Protein-Coupled Estrogen Receptor I
- The Endocannabinoid System

Questions?

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