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Drug Class Update: Antiepileptics, outpatient

Date of Review: April 2025

Date of Last Review: October 2022

January 2019 (drugs for fibromyalgia)

June 2024 (off-label uses of gabapentinoids)

Dates of Literature Search: 01/01/2019 – 12/27/2024

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Review recently published evidence for the antiepileptic drug (AED) class. Establish medical necessity criteria for the use of AEDs in fibromyalgia, which will be funded with the 2027 Health Evidence Review Commission (HERC) Benefit Update Plan.

Plain Language Summary:

- Is there new evidence that would change the current policy for medicines used to manage seizures?
- National Institute for Health and Care Excellence (NICE) recommend many different medicines to treat seizures.
 - Guidelines from NICE recommend medicines based on the type of seizure and the person's specific situation.
 - Most recommendations include use of one medicine at a time. But if seizures are not controlled, then more than one medicine may be prescribed by a provider.
- Some medicines used to manage epilepsy are used to treat other conditions such as fibromyalgia, nerve pain caused by diabetes or after shingles infection, mental health conditions, and migraine headaches.
- Medicaid Open Card will pay for medicines that are most often used as the first seizure treatment or for mental health conditions when prescribed by a provider. Providers must explain to the Oregon Health Authority why someone needs other medicines for seizures. This process is called prior authorization.
- We recommend removing prior authorization from clobazam, a drug that is commonly approved for resistant seizures, and revising criteria for fibromyalgia medicines.

Research Questions:

1. Is there new comparative evidence that AEDs differ in efficacy or harms for management of seizures?
2. Is there new comparative evidence that AEDs differ in efficacy or harms for management of chronic pain syndromes or bipolar disorders?
3. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which AEDs may be beneficial or cause more harm?

Conclusions:

- Since the previous AED reviews, 4 high-quality systematic reviews evaluated the clinical guidelines for management of chronic pain with non-opioids; safety of cannabidiol in treating epilepsy; safety of gabapentinoids (gabapentin and pregabalin) in managing neuropathic pain; and the safety and efficacy of lamotrigine in treating bipolar disorder.¹⁻⁴ Five clinical guidelines have been published to recommend utilization of specific AEDs in people of childbearing potential, bipolar disorder, trigeminal neuralgia, and migraine headache.⁵⁻¹⁰

Pain Conditions:

- A rapid review of treatment alternatives for opioids in chronic pain syndromes was published by the Drug Effectiveness Review Project (DERP) in 2023.¹ High-quality clinical guidelines that included recommendations supporting or discouraging the use of AEDs for chronic pain treatment are presented in **Table 3**.
 - The 2020 National Institute for Health and Care Excellence (NICE) guidelines recommend gabapentinoids (gabapentin, pregabalin) for management of neuropathic pain in adults (moderate- to high-quality evidence) and carbamazepine as initial treatment for trigeminal neuralgia (expert opinion).¹¹
 - The 2019 Scottish Intercollegiate Guidelines Network (SIGN) guidance on managing adults with chronic pain recommends gabapentin titrated up to 1200 mg per day for pain associated with postherpetic neuralgia, diabetic peripheral neuropathy (DPN), or mixed neuropathic pain (high-quality evidence).¹² Pregabalin is recommended as third-line therapy for fibromyalgia and neuropathic pain if first and second-line therapies (amitriptyline, gabapentin) are ineffective (high-quality evidence).¹² Carbamazepine should be offered for neuropathic pain with a discussion of risks for adverse events (moderate-quality evidence).¹²
 - The 2022 Veterans Affairs/Department of Defense (VA/DoD) guidance for managing adults with chronic low back pain recommends gabapentin or pregabalin for treatment of low back pain with or without radicular symptoms (low-quality evidence).¹³
 - The 2022 American Academy of Neurology (AAN) guidance recommends for patients with diabetic peripheral neuropathy (DPN), clinicians should offer gabapentinoids to reduce pain (moderate-quality evidence).⁶
- A 2023 systematic assessed the safety of gabapentinoids in the management of neuropathic pain.³ The majority of adverse events pertained to nervous system and psychiatric disorders.³ The highest risk with pregabalin versus placebo was incoordination (RR 7.21; 95% CI 1.36, 38.25), followed by abnormal gait (RR 6.71; 95% CI 1.57, 28.71), ataxia (RR 6.02; 95% CI 2.31, 31.15), euphoria (RR 6.01; 95% CI 3.02, 11.97), and weight gain (RR 4.97; 95% CI 3.08, 8.00).³ In contrast, gabapentin treatment had the highest risk of weight gain (RR 5.61; 95% CI 1.04, 30.22), followed by dizziness (RR 3.33; 95% CI 2.39, 4.65), peripheral edema (RR 3.06; 95% CI 1.25, 7.48), and somnolence (RR 2.91; 95% CI 2.10, 4.03) compared with placebo.³
- In 2021 the European Academy of Neurology (EAN) published guidance for management of people with trigeminal neuralgia.⁷ Recommendations for AEDs in for managing trigeminal neuralgia include:
 - Carbamazepine and oxcarbazepine are recommended for long-term treatment of trigeminal neuralgia (strong recommendation; based on moderate-quality and low-quality evidence, respectively).⁷
 - Lamotrigine or gabapentin can be used either as monotherapy or as add-on therapy for long-term treatment of trigeminal neuralgia (weak recommendation; low-quality evidence).⁷
- In 2023 the Department of Veterans Affairs and Department of Defense (VA/DoD) updated guidance for headaches.⁹ Four AEDs were included in the recommendations.
 - Topiramate is suggested for the prevention of episodic and chronic migraine (weak recommendation).⁹
 - Valproate is suggested for the prevention of episodic migraine (weak recommendation).⁹
 - Gabapentin is not recommended for the prevention of episodic migraine (weak recommendation).⁹
 - There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.⁹
- The 2024 International Headache Society guidelines for migraine prophylaxis included recommendations for 2 AEDs (valproic acid and topiramate).¹⁰

- Valproate may be preferred in patients with comorbid epilepsy, mania, anxiety, and depression.¹⁰ However, valproate should be avoided or prescribed with caution in patients with hepatic disease, bleeding disorders, alcoholism, obesity or people of childbearing potential.¹⁰
- Topiramate may be preferred in patients with epilepsy, obesity, mania, anxiety, essential tremor, or alcohol dependence.¹⁰ Topiramate should be avoided or used with caution in patients with kidney stones, renal failure, angle closure glaucoma, depression, cognitive concerns or people of childbearing potential.¹⁰
- In children and adolescents with migraine who need pharmacologic migraine prevention, beta-blockers, at doses adapted to body weight, can be used, although evidence of efficacy is very limited. In case of ineffectiveness, low dose topiramate or amitriptyline represent possible alternatives.¹⁰ Topiramate is FDA-approved for migraine prevention in children aged 12 years and older.¹⁴

Epilepsy:

- A 2023 systematic review evaluated the risk of adverse events in patients with epilepsy who were prescribed cannabidiol.² In the cannabidiol-treated group, the most common adverse events of any grade were somnolence (22.0%), decreased appetite (19.5%) and pyrexia (15.3%).² Compared with the placebo group, the cannabidiol group had a greater risk for occurrence of serious adverse events (relative risk [RR], 2.67; 95% confidence interval [CI], 1.83 to 3.88), adverse events resulting in discontinuation (RR, 3.95; 95% CI, 1.86 to 8.37), and adverse events resulting in dose reduction (RR, 9.87; 95% CI, 5.34 to 14.40).²
- A 2024 practice guideline From the American Academy of Neurology (AAN), American Epilepsy Society (AES), and Society For Maternal-Fetal Medicine (SMFM) provides recommendations regarding the maternal and fetal effects of AEDs in people with epilepsy of childbearing potential.⁵ The recommendations are summarized below.
 - Once a person with epilepsy is already pregnant, clinicians should exercise caution in attempting to remove or replace an AED that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures (strong recommendation).⁵
 - Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in people with epilepsy of childbearing potential when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of major congenital malformations (MCMs) (very strong recommendation).⁵
 - Clinicians must avoid the use of valproic acid in people with epilepsy of childbearing potential to minimize the risk of MCMs, neural tube defects (NTDs), poor neurodevelopmental outcomes, including autism spectrum disorder and lower intelligence quotient (IQ), in children born to people with epilepsy if clinically feasible (very strong recommendation).⁵
 - Clinicians should avoid the use of valproic acid or topiramate in people with epilepsy of childbearing potential to minimize the risk of offspring being born small for gestational age, if clinically feasible (strong recommendation).⁵

Bipolar Disorder:

- A 2021 Cochrane review examined evidence for the efficacy and safety of lamotrigine in the maintenance treatment of bipolar disorder.⁴ The estimated risk ratio for recurrence of manic symptom at one year was 0.67, (95% CI 0.51 to 0.87; 3 studies, 663 participants; low-quality evidence) in favor of lamotrigine compared with placebo.⁴ The risk of clinical worsening with the need for additional psychotropic treatment favored lamotrigine over placebo (RR 0.82, 95% CI 0.70 to 0.98; 4 studies, 756 participants; moderate-quality evidence).⁴ In the comparison between lamotrigine and lithium, efficacy was similar between groups except recurrence of manic symptoms at one year was more common in the lamotrigine group than that of the lithium group (RR 2.13, 95% CI 1.32 to 3.44; 3 studies, 602 participants; moderate-quality evidence).⁴ Analysis of adverse effects over 6 to 12 months showed that a lower proportion of participants experienced at least one adverse effect when treated with lamotrigine compared to lithium (RR 0.70, 95% CI 0.51 to 0.96; 4 studies, 691 participants; moderate-quality evidence).⁴
- In 2019 the Oregon Health Authority (OHA) Mental Health Clinical Advisory Group (MHCAG) developed clinical practice recommendations for bipolar disorder.⁸ Two AEDs, lamotrigine and divalproex, are included in the treatment algorithms.
 - For bipolar depression, first line medications include lamotrigine, lithium, and quetiapine in addition to psychosocial treatment.⁸

- Second-line monotherapy recommendations for treatment of bipolar depression include cariprazine, divalproex, or lurasidone.⁸
- If combination therapy is warranted for treatment of bipolar depression, lamotrigine with another bipolar treatment medication; lurasidone and lithium or divalproex; olanzapine and fluoxetine; a selective serotonin reuptake inhibitor (SSRI); or bupropion and another bipolar treatment medication are recommended.⁸
- For treatment of acute bipolar mania, MHCAG recommends first-line combination therapy of quetiapine and lithium or quetiapine and divalproex with concurrent psychosocial treatment.⁸
- Lamotrigine should be avoided in patients that only need treatment for acute mania.⁸
- There was no comparative evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one AED is more effective or associated with fewer adverse events.

Expanded Indications and New Formulations

- February 2020: SABRIL (vigabatrin) oral tablets and oral powder received expanded approval for use as adjunctive therapy in refractory complex partial seizures for patients 2 years of age and older who have responded inadequately to several alternative treatments.¹⁵ Previous approval included treatment of refractory partial seizures in patients 10 years of age and older.
- August 2021: BRIVIACT (brivaracetam) oral tablets, oral solution, and intravenous injection received expanded approval for use in pediatric patients 1 month of age and older for treatment of partial-onset seizures.¹⁶ Prior to this approval, brivaracetam was approved for use in patients 4 years of age and older.
- October 2021: VIMPAT (lacosamide) oral tablets, oral solution, and intravenous injection received expanded approval for treatment of partial seizures in patients 1 month of age and older.¹⁷ Previous approval included for treatment of partial seizures in patients 4 years of age and older.
- March 2022: FINTEPLA (fenfluramine) oral solution received an expanded indication for treatment of seizures associated with LGS in patients 2 years of age and older.¹⁸ Previous approval included treatment of seizures associated with DS in patients 2 years of age and older.
- May 2023/June 2024: MOTPOLY XR (lacosamide) extended-release capsules, a new formulation of lacosamide, received FDA-approval for treatment of partial-onset seizures and tonic-clonic seizures in adults and pediatric patients weighing at least 50 kg.¹⁹
- June 2024: VIGAFYDE (vigabatrin) concentrated oral solution 100 mg/mL, a new formulation of vigabatrin, received FDA-approval for use as monotherapy treatment of infantile spasms in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential for vision loss.²⁰ The new formulation is not approved for use in adults.²⁰ This product also carries a black-boxed warning regarding the risk of permanent vision loss and is only available through the restricted Vigabatrin REMS program.²⁰

Recommendations:

- Retire clobazam PA criteria based on compendia support for treatment resistant seizures and make at least one formulation of clobazam preferred.
- Revise pregabalin PA criteria to include medically appropriate use for fibromyalgia for patients with the Early Periodic Screening Diagnostic and Treatment Benefit.
- After review of costs in executive session, make generic clobazam tablets and oral suspension preferred; make pregabalin capsules and generic levetiracetam ER 24H tablets preferred; and make carbamazepine oral suspension non-preferred.

Summary of Prior Reviews and Current Policy:

- At the June 2024 Pharmacy and Therapeutics (P & T) Committee meeting, off-label uses of gabapentinoids were reviewed. In February 2022, the Mental Health Clinical Advisory Group (MHCAG) developed treatment algorithms for GAD. Pregabalin is recommended as first-line adjunct treatment for patients with GAD in conjunction with a SSRI/SNRI.

- Prior authorization (PA) criteria were modified to allow use of pregabalin for generalized anxiety disorder in people who have tried or have a contraindication to first line treatment with a selective serotonin reuptake inhibitor (SSRI) or SNRI and a trial of gabapentin.
- At the January 2019 meeting, the safety and efficacy of pharmacologic treatments for fibromyalgia were reviewed. There was no moderate or high strength evidence for any pharmacological treatment compared to placebo or other therapy.²¹ Like many other conditions for chronic pain, evidence supporting benefit of long-term pharmacological treatment for fibromyalgia is limited, efficacy of pharmacotherapy is relatively modest, and clinical trials often document a large placebo response upon evaluation of symptom improvement.²¹ Pharmacological interventions with the most evidence of benefit include duloxetine, milnacipran, and pregabalin. Fibromyalgia is not currently funded on the Prioritized List of Services.
- Evidence for alternatives to opioids for management of chronic pain were reviewed at the March 2017 P & T Committee meeting. After review, PA criteria were revised as outlined in **Appendix 4** to restrict use of non-analgesics to funded pain conditions. Separate PA criteria for pregabalin and topiramate extended release (non-preferred products) were approved by the Committee.
- The preferred, non-preferred, and voluntary oral and rectal AEDs on the Oregon Medicaid Fee-For-Service (FFS) Preferred Drug List (PDL) are listed in **Appendix 1**. Products which are generally recommended for initial treatment of seizures are typically available without prior authorization (e.g., carbamazepine, diazepam, levetiracetam, midazolam, phenobarbital, topiramate). Divalproex, and lamotrigine, which have indications for bipolar disorder, and gaxanolone are carved-out of Coordinated Care Organizations and generally paid for by fee-for-service (FFS).
- Individual agents which have specific prior authorization (PA) criteria include cannabidiol, clobazam, fenfluramine, ganaxolone, pregabalin, stiripentol and topiramate (**Appendix 4**). PA criteria generally limit treatment to funded and FDA-approved indications. Compendia-supported diagnoses (such as pregabalin for treatment of generalized anxiety disorder or topiramate in people with bipolar or schizoaffective disorder when alternative therapies have failed to improve symptoms) are also covered.
- A review of pharmacy AED claims paid in the fourth quarter of 2024 (September 1, 2024 to December 31, 2024) provides an overview of Medicaid Fee for Service (FFS) utilization. Ninety-two percent of the claims were for preferred or voluntary agents in the AED class. The most frequently requested preferred agent was lamotrigine with over 77% of claims, followed by divalproex (18%) and gabapentin (4%). The most requested non-preferred AED was pregabalin followed by clobazam. Of 87 patients who had a PA request for clobazam from 1/1/2024 to 12/31/2024, 71 (82%) were approved upon initial review, 12 (14%) were approved after appeal or submission of additional information, and only 4 (5%) patients had denied PAs.

Background:

Epilepsy

An epileptic seizure is defined as a sudden occurrence of transient signs and symptoms caused by abnormal and excessive or synchronous neuronal activity in the brain.²² Worldwide, an estimated 65 million people have epilepsy.²² In the United States (US), approximately 150,000 adults present annually with an unprovoked first seizure.²³ The incidence of epilepsy has a bimodal distribution with the highest risk in infants and older age groups.²⁴ The causes of epilepsy vary and are identified in only about 30% of people with the condition.²⁵ Common risk factors include premature birth, complicated febrile seizures, infections such as meningitis or encephalitis, head trauma, or family history of epilepsy.²⁵ Causes of epilepsy may include structural brain lesions, abnormalities of neuronal migration, and fetal intracranial hemorrhage.²⁵ Other acquired lesions can serve as seizure foci, including benign and malignant intracranial or extra-axial tumors, abscesses, cysts, hemorrhagic lesions, or strokes.²⁵ Systemic illnesses, such as HIV infection and malaria, can also lead to epilepsy.²⁵ Antiepileptic drugs work by stabilizing cellular mechanisms that prevent spontaneous neuronal depolarization.²⁵ The exact mechanisms by which various medications influence this function include interaction through sodium, calcium, or potassium channels or effects on neurotransmitters such as gamma-aminobutyric acid (GABA) or glutamate.²⁵ Drug selection is based on seizure type, side effect, childbearing potential of the patient, co-prescribed medications, and patient preference. About half of newly diagnosed patients with epilepsy are successfully treated with the first AED; however, treatment failure and drug

intolerance can occur. Monotherapy is more likely to promote adherence, reduce potential for drug interactions, and is less costly but may not keep a patient seizure-free. There are no controlled trials comparing different combinations of AEDs.

In 2017, the International League Against Epilepsy (ILAE) updated the classification of seizure types as generalized, focal, or unknown (if seizure onset is either missed or obscured), based upon clinical and electroencephalographic criteria.²⁶ Focal seizures involve only a portion of the brain, while generalized seizures arise from both sides of the brain simultaneously.²⁶ Seizures can be further classified depending on the symptoms that occur during the seizure either as motor (tonic-clonic) or non-motor (absence). According to the 2022 NICE guidelines, first-line monotherapy options for treatment of focal seizures are lamotrigine or levetiracetam.²⁷ Second-line agents for focal seizures include carbamazepine, oxcarbazepine, or zonisamide, and the recommended third-line monotherapy agent is lacosamide.²⁷ Add on treatment agents for focal seizures include carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide.²⁷ For generalized motor seizures, the NICE recommendation for first-line monotherapy is valproate and second-line monotherapies are lamotrigine or levetiracetam.²⁷ Add-on treatments for generalized seizures include lamotrigine, levetiracetam, perampanel, or topiramate.²⁷ Ethosuximide or valproate are recommended to treat absence seizures.²⁷

Treatment-resistant epilepsy arises from a failure to achieve sustained seizure remission after trials of at least two AED regimens that are tolerated at therapeutic dosages.²⁸ Two types of severe seizure syndromes associated with epileptic encephalopathies, LGS and DS, are often refractory to pharmacotherapy. Both syndromes are associated with higher rates of mortality than the general epilepsy population, primarily due to status epilepticus and sudden unexpected death due to epilepsy.²⁹ Six antiepileptic medications are FDA-approved for the treatment of LGS, including lamotrigine, topiramate, felbamate, rufinamide, clobazam and clonazepam.³⁰ Direct comparative drug trials in patients with LGS have not been performed. Valproic acid is considered first-line therapy for LGS because it has efficacy in all types of seizures associated with LGS; however, it does not have a specific FDA indication for LGS.³¹ The most commonly used AEDs in patients with seizures associated with DS include valproate, clobazam, fenfluramine, stiripentol, cannabidiol, and topiramate.³² Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut. However, there is compendia support for clobazam as adjunctive therapy for generalized tonic-clonic therapy if monotherapy treatment is ineffective or not tolerated OR as second-line monotherapy.¹⁴ Adjunctive clobazam plus stiripentol may be added to valproate sodium for treatment of Dravet syndrome if valproate monotherapy is unsuccessful.¹⁴ If triple therapy is unsuccessful, clobazam plus cannabidiol may be added to valproate for treatment of Dravet syndrome in children 2 years and older.¹⁴ A summary of AEDs, their mechanism of action, and Food and Drug Administration (FDA)-approved indications is provided in **Table 1**.

Table 1. Mechanism of Action and FDA-Approved Indications for Antiepileptic Drugs^{14,22}

Generic (BRAND) Name	FDA-Approved Indications	Mechanism of Action
Treatment of Focal and Generalized Seizures		
Brivaracetam (BRIVIACT)	<ul style="list-style-type: none"> Focal Seizures 	Binding to SV2A Protein
Cenobamate (XCOPRI)	<ul style="list-style-type: none"> Focal Seizures 	Sodium Channel Blockade
Eslicarbazepine (APTIOM)	<ul style="list-style-type: none"> Focal Seizures 	Sodium Channel Blockade
Lacosamide (VIMPAT)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	Slow Sodium Channel Inactivation
Levetiracetam (KEPPRA)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	Binding to SV2A Protein
Oxcarbazepine (TRILEPTAL)	<ul style="list-style-type: none"> Focal Seizures 	Sodium Channel Blockade
Perampanel (FYCOMA)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	Blocks AMPA glutamate receptor
Phenobarbital	<ul style="list-style-type: none"> Focal and Generalized Seizures 	GABA agonist
Phenytoin (DILANTIN)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	Sodium Channel Blockade

Primidone (MYSOLINE)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	GABA agonist
Tiagabine (GABITRIL)	<ul style="list-style-type: none"> Focal Seizures 	GABA agonist
Valproic Acid (DEPAKENE) Divalproex Sodium (DEPAKOTE)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	Sodium Channel and Calcium Channel Blockade, Potentiates GABA levels
Zonisamide (ZONISADE)	<ul style="list-style-type: none"> Focal and Generalized Seizures 	Sodium and Calcium Channel Blockade
Treatment of Absence Seizures		
Ethosuximide (ZARONTIN)	<ul style="list-style-type: none"> Absence Seizures 	Calcium Channel Blockade
Methsuximide (CELONTIN)	<ul style="list-style-type: none"> Refractory Absence Seizures 	Calcium Channel Blockade
Treatment of Lennox-Gastaut and Dravet Syndrome		
Cannabidiol (EPIDIOLEX)	<ul style="list-style-type: none"> Lennox-Gastaut Syndrome Tuberous Complex Syndrome Dravet Syndrome 	Calcium Channel Blockade
Clobazam (ONFI)	<ul style="list-style-type: none"> Lennox-Gastaut Syndrome 	GABA agonist
Clonazepam (KLONOPIN)	<ul style="list-style-type: none"> Focal and Generalized Seizures Lennox-Gastaut Syndrome 	GABA agonist
Felbamate (FELBATOL)	<ul style="list-style-type: none"> Focal and Generalized Seizures Lennox-Gastaut Syndrome 	Sodium Channel Blockade, NMDA Receptor Blockade, Potentiates GABA levels
Fenfluramine (FINTEPLA)	<ul style="list-style-type: none"> Dravet Syndrome Lennox-Gastaut Syndrome 	Modulation of NMDA receptors and serotonin receptors
Rufinamide (BANZEL)	<ul style="list-style-type: none"> Lennox-Gastaut Syndrome 	Sodium Channel Blockade
Stiripentol (DIACOMIT)	<ul style="list-style-type: none"> Adjunctive Treatment for Dravet Syndrome with Clobazam 	GABA agonist
Treatment of Other Seizure Types		
Ganaxolone (ZTALMY)	<ul style="list-style-type: none"> Cyclin-Dependent Kinase-Like 5 Deficiency Seizure 	GABA agonist
Vigabatrin (SABRIL)	<ul style="list-style-type: none"> Refractory Focal Seizures Infantile Spasms 	GABA agonist
Treatment of Seizures, Chronic Pain Syndromes, or Mental Health Conditions		
Carbamazepine (TEGRETOL, EQUETRO)	<ul style="list-style-type: none"> Focal and Generalized Seizures Trigeminal Neuralgia Bipolar I Disorder 	Sodium Channel Blockade
Gabapentin (NEURONTION)	<ul style="list-style-type: none"> Focal Seizures Postherpetic Neuralgia 	Calcium Channel Blockade
Lamotrigine (LAMICTAL)	<ul style="list-style-type: none"> Focal and Generalized Seizures Lennox-Gastaut Syndrome Maintenance Treatment of Bipolar I Disorder 	Sodium Channel Blockade
Pregabalin (LYRICA)	<ul style="list-style-type: none"> Focal Seizures Postherpetic Neuralgia Fibromyalgia Neuropathic Pain Associated with Spinal Cord Injury 	Calcium Channel Blockade

	<ul style="list-style-type: none"> • Diabetic Neuropathy 	
Topiramate (TOPAMAX)	<ul style="list-style-type: none"> • Focal and Generalized Seizures • Lennox-Gastaut Syndrome • Migraine Prevention in patients 12 years of age and older 	Sodium Channel Blockade, Augments GABA levels, NMDA Receptor Blockade
Abbreviations: AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; FDA = Food and Drug Administration; GABA = gamma-aminobutyric acid; NMDA = N-methyl-D-aspartate; SV2A = synaptic vesicle protein 2A		

Neuropathic Pain

Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain that typically last greater than 3 months or past the time of normal tissue healing.¹⁴ The IASP defines neuropathic pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system.¹⁶ Neuropathic pain can be caused by injury, medical interventions (e.g., chemotherapy, surgery), or different diseases (e.g., diabetes, herpes zoster, or human immunodeficiency virus).¹⁷ The first antiepileptic used in clinical trials to treat a neuropathic pain disorder was carbamazepine. Prior to approval for seizures, carbamazepine was approved by the FDA for trigeminal neuralgia.¹⁴ Carbamazepine and its derivative oxcarbazepine have continued to be used for the treatment of trigeminal neuralgia, but have not been shown to be as effective in treating other neuropathic pain disorders.³³ The gabapentinoid drugs, gabapentin and pregabalin, were originally developed as AEDs but are mostly prescribed for treatment of neuropathic pain.³³ The only pain-related indication approved by the Food and Drug Administration (FDA) for gabapentin is postherpetic neuralgia. For pregabalin, FDA-approved indications related to pain include postherpetic neuralgia, DPN, neuropathic pain associated with spinal cord injury, and fibromyalgia.³⁴ Other AEDs including topiramate, valproic acid, levetiracetam, zonisamide, tiagabine and lamotrigine have been studied for various neuropathic pain disorders; however, evidence of their effectiveness is lacking.³³ A 2007 systematic review of lamotrigine for acute and chronic pain concluded it does not have a place in the treatment of pain, given other more effective therapies.³⁵

Fibromyalgia

Fibromyalgia is a syndrome characterized by chronic widespread musculoskeletal pain accompanied by other symptoms such as fatigue, sleep disturbances, anxiety, and depression.³⁶ Comorbid conditions, such as functional somatic syndromes, psychiatric diagnoses, and rheumatologic conditions may be present.³⁷ Fibromyalgia is diagnosed more frequently in women and affects about 2% of people in the United States.³⁷ The diagnosis and assessment of fibromyalgia remain controversial.³⁶ The main challenge in diagnosing this condition is the scarcity of biomarkers.³⁶ In general, most researchers agree on the need to assess multiple domains of fibromyalgia, including pain, sleep, fatigue, concentration problems, anxiety, overall functional status, sensitivity, and stiffness.³⁶ Diagnosis is based primarily on history, physical exam, and absence of other disorders which would explain the chronic pain.³⁸ In 2013, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) partnership with the FDA and American Pain Society (APS) initiated the ACTTION-APS Pain Taxonomy (AAPT) in an attempt to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders, including fibromyalgia.³⁹ In 2019, the fibromyalgia working group suggested new AAPT diagnostic criteria for fibromyalgia.³⁹ The core diagnostic fibromyalgia criteria are: 1) multisite pain defined as six or more pain sites from a total of 9 possible sites for at least 3 months and 2) moderate to severe sleep problems or fatigue that have been present for at least 3 months.³⁹ According to the AAPT fibromyalgia diagnostic criteria, the presence of another pain disorder or related symptoms does not exclude the diagnosis of fibromyalgia, but a clinical assessment must fully evaluate any condition that could account for the patient's symptoms.³⁹

The antidepressants, duloxetine and milnacipran, and the AED, pregabalin are FDA-approved for fibromyalgia treatment.³⁷ A 2016 Cochrane review evaluated 8 placebo-controlled randomized clinical trials (RCTs) and found pregabalin at doses of 300 mg to 600 mg reduced pain intensity by 30% for a small proportion of people (about 10% more than placebo).⁴⁰ There was no pronounced dose response for efficacy, though the improvements in pain tended to come from 450 mg

daily.⁴⁰ The pain relief was accompanied by improvement in other fibromyalgia symptoms including sleep, quality of life and functional ability.⁴⁰ These results were similar to effects observed with milnacipran and duloxetine.⁴⁰ Withdrawals because of adverse events were more common with higher doses of pregabalin, and were 6% to 17% higher than placebo over the range 300 to 600 mg daily.⁴⁰ Nonsteroidal anti-inflammatory drugs and opioids have not demonstrated benefits for fibromyalgia and have significant adverse effects.³⁷ Fibromyalgia management typically requires a multimodal approach, extending beyond medication use alone.⁴¹

Guidelines from the 2017 European League Against Rheumatism (EULAR) focus on patient education and graded exercise as recommended first-line fibromyalgia treatments to improve pain, sleep, function, and mood (strong recommendation).⁴² Second-line therapies included both pharmacological and non-pharmacological management and were based on weak recommendations.⁴² Second-line non-pharmacological therapies included cognitive behavioral therapy, multicomponent therapy, acupuncture, hydrotherapy, meditative movement, and mindfulness-based stress reduction which may be considered upon inadequate improvement to exercise.⁴² Recommendations for second-line pharmacological management included low-dose amitriptyline, duloxetine, milnacipran, pregabalin, and cyclobenzaprine.⁴² Gabapentin is recommended to be used in research only, not as treatment modality, due to limited evidence in treatment of fibromyalgia.⁴² Evidence supporting off-label use of gabapentin for fibromyalgia is limited to a small (n=150) double-blind, placebo-controlled RCT.^{14,43} The study enrolled adults aged 18 years and older with fibromyalgia. The mean age of participants was 48 years and 90% of the patients were female.⁴³ The median gabapentin dose was 1,800 mg per day (range: 1,200 to 2,400 mg per day).⁴³ Response to treatment was defined as a reduction of 30% or more in the Brief Pain Inventory (BPI) score (range 0 to 10, where 0 = no pain and 10 = severe pain).⁴³ At 12 weeks, 51% of gabapentin-treated patients responded to treatment versus 31% of placebo-treated patients (95% CI not reported; p=0.014).⁴³ Brief Pain Inventory (BPI) scores were decreased more often with gabapentin than with placebo over 12 weeks (gabapentin, 5.7 to 3.2; placebo, 6 to 4.6; difference, 0.92; 95% CI -1.75 to -0.71; p=0.015).⁴³

Bipolar Disorder

Bipolar disorder is a severe chronic mood disorder characterized by episodes of mania, hypomania, and alternating episodes of depression, with a worldwide prevalence of approximately 1%.⁴⁴ The diagnosis of bipolar disorder is made by a comprehensive clinical assessment, and supplemented, when possible, with third-party information (e.g., from family members).⁴⁴ There is no biomarker that informs the diagnosis, prognosis, or treatment outcome of bipolar disorders.⁴⁴ Therapeutic objectives in bipolar disorders include prevention and treatment of syndromal hypomania, mania, and depression; normalization of sleep patterns; improvement and preservation of cognitive function; treatment and prevention of psychiatric and medical comorbidity; improvement of patient-reported outcomes (e.g., quality of life); and reduction of suicidality.⁴⁴ Lithium is the gold standard mood-stabilizing agent for bipolar disorder, and has antimanic, antidepressant, and anti-suicide effects.⁴⁴ Divalproex and carbamazepine are effective in the treatment of acute bipolar mania and lamotrigine is effective at treating and preventing bipolar depression.⁴⁴

Although divalproex is efficacious in managing mania symptoms, efficacy in depression and long-term prevention of symptom recurrence has not been well established.⁴⁴ In addition, divalproex has many tolerability and safety concerns, including menstrual irregularities in women of reproductive age, an association with the development of polycystic ovarian syndrome, hepatotoxicity, pancreatitis, and teratogenicity.⁴⁴ Additional treatment-emergent adverse events with divalproex include tremor, weight gain, sedation, cognitive impairment, and metabolic disruption.⁴⁴ Like divalproex, carbamazepine is effective in acute mania, but there is insufficient evidence showing the acute or long-term effects of carbamazepine in preventing recurrence of bipolar disorders.⁴⁴ Additional limitations of carbamazepine are drug–drug interactions, and concerns over tolerability and safety (e.g., cognitive impairments, rash, tremors, teratogenicity, Stevens-Johnson syndrome).⁴⁴ Pre-treatment pharmacogenetic testing for allelic variants of HLA-B has been shown to mitigate risk for Stevens-Johnson Syndrome in patients who are prescribed carbamazepine.⁴⁴

The Young Mania Rating Scale (YMRS) is one of the most frequently utilized rating scales to assess manic symptoms. The YMRS comprises 11 items, each focusing on a different aspect of mania such as elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, and speech patterns.⁴⁵ The score is based on the patient's subjective report of his or her clinical condition over the previous 48 hours.⁴⁵ There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale.⁴⁵ These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients.⁴⁵ The total score can range from 0 to 60, with higher scores indicating more severe manic symptoms.⁴⁵

Migraine Headache

Migraine is a chronic debilitating and incurable disorder.⁴⁶ It is estimated to affect about 36 million Americans.⁴⁷ The American Academy of Neurology (AAN) and American Headache Society (AHS) 2012 guidelines recommend providers offer topiramate and divalproex sodium for migraine prevention.⁴⁶ Their action as sodium channel blockers may affect the neural component of migraine pain.⁴⁶ Divalproex tends not to be prescribed as first-line therapy due to its potential for weight gain and hepatotoxicity.⁴⁶ Topiramate is generally first choice, but has several contraindications.⁴⁶ Both medications require education on teratogenesis in people of childbearing potential. Carbamazepine is recommended as a Level-C therapeutic option (i.e., may be considered) based on one small study (n=48) conducted over 50 years ago.⁴⁶

There is insufficient data to support or refute the use of gabapentin for migraine prophylaxis.⁴⁶ Lamotrigine and oxcarbazepine should not be considered as they are ineffective in migraine prophylaxis.⁴⁶ Specifically, 2 randomized controlled trials (RCTs) demonstrated that lamotrigine is not more effective than placebo, and significantly less effective than topiramate in reducing migraine frequency.⁴⁶ With respect to oxcarbazepine, the evidence from a single trial showed no difference in number of migraine attacks for patients treated with oxcarbazepine compared to placebo.⁴⁶ A 2013 Cochrane review concluded there is no robust evidence on the efficacy of clonazepam, levetiracetam, oxcarbazepine, vigabatrin, and zonisamide in reducing headache frequency.⁴⁸

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Drug Effectiveness Review Project: Treatment Alternatives for Opioids in Common Chronic Pain Syndromes

A rapid review of treatment alternatives for opioids in chronic pain syndromes was published by the DERP in 2023.¹ The report focused on non-opioid treatments for adults with chronic (i.e., pain duration of ≥ 3 months), noncancer-related pain (e.g., low back pain, neuropathic pain).¹ Eligible non-opioid pharmacologic agents included analgesics (oral acetaminophen, topical capsaicin), nonsteroidal anti-inflammatory drugs (NSAIDs; topical and oral),

antidepressants, AEDs, muscle relaxants, topical anesthetics, topical corticosteroids, botulinum toxin, and corticosteroid injections.¹ Literature was searched from January 1, 2017 through November 22, 2022 with an emphasis on identifying clinical practice guidelines and RCTs that addressed treatment of common pain conditions.¹ High-quality clinical guidelines that included recommendations supporting or discouraging the use of AEDs for chronic pain treatment are summarized in **Table 3**.

Table 3. CPG Recommendations for Treatment of Chronic Pain with Antiepileptic Drugs¹

Organization, Year, Population, Methodological Quality of Guideline	Pharmacological Interventions	Nonpharmacological Interventions
Nonspecific Chronic Pain		
NICE, 2021 ⁴⁹ Adults with Chronic Pain <i>Good</i>	<ul style="list-style-type: none"> • Anticonvulsants, including Gabapentinoids, are Not Recommended (high- to very low-quality RCT data) 	<ul style="list-style-type: none"> • Supervised Group Exercise (high- to very low-quality RCT data) • Acupuncture (moderate- to low-quality RCT)
SIGN, 2019 ¹² Adults with Chronic Pain <i>Good</i>	<ul style="list-style-type: none"> • Gabapentin titrated up to 1200 mg per day: Offer for postherpetic neuralgia, diabetic peripheral neuropathy, or mixed neuropathic pain (high-quality evidence) • Pregabalin titrated up to 300 mg per day: Offer for fibromyalgia (high-quality evidence) and for neuropathic pain if first- and second-line pharmacologic therapies (amitriptyline, gabapentin) fail (high-quality evidence) • Carbamazepine: Offer for neuropathic pain with discussion of risk of adverse effects (moderate-quality evidence) • Anticonvulsants that are Not Recommended: Lacosamide, Lamotrigine, Levetiracetam, Phenytoin, Topiramate, Sodium Valproate 	<ul style="list-style-type: none"> • Mindfulness meditation (weak recommendation; low-quality evidence) • Massage and manual therapy (moderate recommendation; moderate-quality evidence) • Exercise (moderate recommendation; moderate-quality evidence) • Acupuncture (strong recommendation; high-quality evidence)
Chronic Neuropathic Pain		
NICE, 2020 ¹¹ Adults with Chronic Neuropathic Pain <i>Good</i>	<ul style="list-style-type: none"> • Gabapentin or Pregabalin: Offer for neuropathic pain (except trigeminal neuralgia) (moderate- to low-quality RCT data) • Carbamazepine: Offer as initial treatment for trigeminal neuralgia (consensus opinion of the guideline development group) • Anticonvulsants that are Not Recommended: Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Topiramate, Sodium Valproate 	

<p>AAN, 2022⁶ Adults with Diabetic Polyneuropathy <i>Good</i></p>	<ul style="list-style-type: none"> • Should offer gabapentinoids (moderate-quality evidence) • Should offer valproic acid with 2 exceptions: 1) Should not offer for patients with childbearing potential due to teratogenic effects and 2) Should not prescribe unless multiple effective medications have failed due to risk of serious adverse events with valproic acid (moderate-quality evidence). 	<ul style="list-style-type: none"> • CBT (low-quality evidence) • Exercise (low-quality evidence) • Tai chi (low-quality evidence) • Mindfulness (low-quality evidence)
<p>Chronic Musculoskeletal Pain</p>		
<p>Veterans Affairs/Department of Defense, 2022¹³ Adults with Chronic Low Back Pain <i>Good</i></p>	<ul style="list-style-type: none"> • Gabapentin or Pregabalin: Offer for low back pain with or without radicular symptoms (low-quality evidence). 	<ul style="list-style-type: none"> • CBT (weak recommendation; moderate- to low-quality evidence) • Exercise (weak recommendation; low-quality evidence) • Yoga (no recommendation; very low-quality evidence) • Massage and manual therapy (weak recommendation; very-low quality evidence) • MBSR (no recommendation; low-quality evidence) • Acupuncture (weak recommendation; low-quality evidence)
<p>Abbreviations: AAN = American Academy of Neurology; CBT = cognitive behavioral therapy; CPG = clinical practice guideline; MBSR = mindfulness-based stress reduction; NICE = National Institute for Health and Care Excellence; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network</p>		

Adverse Events of Cannabidiol Use in Patients with Epilepsy

A 2023 systematic review and meta-analysis evaluated the risk of adverse events in patients with epilepsy who were prescribed cannabidiol.² Literature was searched through August 2022 for RCTs that investigated at least one adverse event from the use of cannabidiol.² Nine RCTs met inclusion criteria.² The included trials involved patients with various forms of epilepsy (i.e., DS, LGS, and tuberous sclerosis–associated epilepsy).² One study applied 390- and 195-mg transdermal cannabidiol gels twice a day, while all the other studies used oral solutions twice daily.² The daily oral dose of cannabidiol ranged from 5 to 50 mg/kg, and the duration of treatment ranged from 3 to 16 weeks.² The manufacturer’s label recommends an initial dose of cannabidiol oral solution 2.5 mg/kg twice daily by mouth. The dose can be increased after one week to the suggested maintenance dose of 5 mg/kg twice daily, and may be increased, if needed for further seizure control, up to a maximum of 10 mg/kg twice daily (20mg/kg/day).⁵⁰ Most of the studies were multicenter, and the age of participants ranged from 1 to 57 years.² The number of previous and concomitant AEDs was similar between the experimental and placebo arms.² Trials had low risk for bias due to randomization and missing data.² However, risk of bias due to assessment of outcomes and the selection and reporting of results was high in several studies.² Overall, 3 trials had a low risk of bias, 3 had moderate risk of bias, and 3 had a high risk of bias.²

In people who received cannabidiol, the most common adverse events of any grade were somnolence (22.0%), decreased appetite (19.5%) and pyrexia (15.3%).² In the placebo groups, upper respiratory tract infection (11.8%), diarrhea (10.9%), and pyrexia (10.2%) were the most common adverse events.² Overall adverse events were more common in the cannabidiol group than in the placebo group (9.7% vs 4.0%).² The overall risk ratios for any grade and severe grade adverse events were 1.12 (95% CI, 1.02-1.23) and 3.39 (95% CI, 1.42-8.09), respectively, for the cannabidiol group compared with the placebo group.² Compared with the

placebo group, the cannabidiol group had a greater risk for serious adverse events (RR, 2.67; 95% CI, 1.83 to 3.88), discontinuation due to adverse events (RR, 3.95; 95% CI, 1.86 to 8.37), and adverse events resulting in dose reduction (RR, 9.87; 95% CI, 5.34 to 14.40).² Because most of the included studies had some risk of bias, these findings should be interpreted with caution.²

The Safety and Efficacy of Gabapentinoids in the Management of Neuropathic Pain

A 2023 systematic review and meta-analysis evaluated the safety and efficacy of gabapentinoids in the management of neuropathic pain.³ Literature was searched through June 2022 for eligible RCTs.³ Out of the selected 50 placebo-controlled trials, 29 investigated pregabalin, 16 investigated gabapentin and 5 studies assessed pregabalin and gabapentin.³ Pregabalin doses ranged from 150 to 600 mg daily and were titrated from 75 mg daily up to the maximum dose of 300 or 600 mg daily, with titration periods between 1 and 4 weeks.³ Gabapentin was dosed at 1200, 1800, 2400, or 3600 mg daily, with titration periods from 1 to 8 weeks.³

Half of the included studies were conducted in the US. Fewer studies were conducted in India (n=3), China (n=3), the United Kingdom (n=2), Turkey (n=2) and Japan (n=2).³ The report also included one international study from Canada, Netherlands, Iran, Europe, Germany, Australia and Pakistan. In total, these studies included 12,398 patients randomized to receive gabapentinoids, placebo or a combination of active drugs comparators.³ Study sizes ranged from 14 to 804 participants, and lasted 4 to 20 weeks.³ Twenty-seven studies had an unclear risk of bias, while the remaining 23 studies had a high risk of bias.³

Most adverse events were related to a nervous system (dizziness, somnolence, ataxia, amnesia, abnormal gait, incoordination) or psychiatric disorder (confusion, euphoria, abnormal thinking).³ Adverse events associated with pregabalin treatment compared with placebo included incoordination (RR 7.21; 95% CI 1.36 to 38.25), followed by abnormal gait (RR 6.71; 95% CI 1.57 to 28.71), ataxia (RR 6.02; 95% CI 2.31 to 31.15), euphoria (RR 6.01; 95% CI 3.02 to 11.97), and weight gain (RR 4.97; 95% CI 3.08 to 8.00).³ Compared with placebo, gabapentin treatment was associated with weight gain (RR 5.61; 95% CI 1.04 to 30.22), followed by dizziness (RR 3.33; 95% CI 2.39 to 4.65), peripheral edema (RR 3.06; 95% CI 1.25 to 7.48), and somnolence (RR 2.91; 95% CI 2.10 to 4.03).³ Analysis of adverse event data showed no evidence of heterogeneity across the studies.³ The majority of AEs were mild to moderate in severity.³ None of the studies assessed abuse or gabapentinoid misuse.³

Eighteen pregabalin studies and 10 gabapentin studies provided data for treatment discontinuation due to AEs.³ Adverse event withdrawals were more common with pregabalin (10%) compared to placebo (6%) (RR 1.71; 95% CI 1.28 to 2.29; $I^2 = 41\%$; $P=0.0003$; number needed to harm [NNH] = 23).³ Similarly, patients taking gabapentin had more withdrawals due to AEs (12%) compared to placebo (8%) (RR 1.47; 95% CI 1.08 to 2.00; $I^2 = 21\%$; $P=0.01$; NNH = 24).³

The proportion of participants who achieved at least 50% pain reduction for neuropathic pain (i.e., DPN, postherpetic neuralgia, human immunodeficiency virus [HIV] neuropathy, fibromyalgia, neuropathic pain associated with spinal injury) was reported in 15 pregabalin and 6 gabapentin studies. Most of the studies were conducted in people with DPN. The 2 RCTs that were conducted in people with fibromyalgia used pregabalin as the active comparator versus placebo. The pooled results showed pregabalin and gabapentin were statistically significantly better than placebo for pain reduction (RR, 1.72; 95% CI 1.37 to 2.16; number needed to treat [NNT] = 8 and RR, 1.76; 95% CI 1.34 to 2.32; NNT = 7, respectively).³ The proportion of participants who achieved at least 30% pain reduction for neuropathic pain was reported in 12 pregabalin and 7 gabapentin studies. Pregabalin and gabapentin both improved pain reduction of at least 30% from baseline compared to placebo (RR, 1.56; 95% CI 1.29 to 1.88; NNT = 10 and RR, 1.53; 95% CI 1.25 to 1.88; NNT = 8, respectively).³

Cochrane: Lamotrigine In the Maintenance Treatment of Bipolar Disorder

A 2021 Cochrane review assessed the efficacy and safety of lamotrigine in the maintenance treatment of bipolar disorder.⁴ Literature was searched through May 2021 for RCTs conducted in adults with bipolar disorder who were treated with lamotrigine, placebo or lithium.⁴ Eleven RCTs (n=2,214) met inclusion criteria; 1146 participants were randomized to lamotrigine, 869 were randomized to placebo, and 299 to lithium.⁴ Seven RCTs compared lamotrigine with placebo, 2 RCTs compared lamotrigine with lithium, and 2 RCTs compared lamotrigine to lithium and placebo.⁴ All studies had unclear risk of bias in multiple categories including selection bias.⁴ Five studies had a high risk of detection bias.⁴

Compared to placebo, lamotrigine reduced risk for recurrence of manic symptom at one year as measured by the Young Mania Rating Scale (total score ≥ 15) (RR 0.67, 95% CI 0.51 to 0.87; 3 studies, 663 participants; low-certainty evidence).⁴ Lamotrigine decreased incidence of clinical worsening with the need for additional psychotropic treatment (RR 0.82, 95% CI 0.70 to 0.98; 4 studies, 756 participants; moderate-certainty evidence) and withdrawal due to any reason at 6 to 12 months after treatment (RR 0.88, 95% CI 0.78 to 0.99; 4 studies, 700 participants; moderate-certainty evidence).⁴

The rate of adverse events was similar between the lamotrigine and the placebo groups (short-term effect: RR 1.07, 95% CI 0.81 to 1.42; 5 studies, 1138 participants; very low-certainty evidence; long-term effect: RR 0.97, 95% CI 0.77 to 1.23; 4 studies, 756 participants; moderate-certainty evidence).⁴ Only one RCT provided data on treatment withdrawal for any reason and found no difference between lamotrigine and placebo (RR 1.10, 95% CI 0.70 to 1.74; P = 0.67; very low-certainty evidence).⁴

In the comparison between lamotrigine and lithium, efficacy was similar between groups except for recurrence of mania episode at one year which was higher in the lamotrigine group (RR 2.13, 95% CI 1.32 to 3.44; 3 studies, 602 participants; moderate-certainty evidence).⁴ Analysis of AEs at 6 to 12 months showed that fewer participants experienced at least one adverse event when treated with lamotrigine compared to lithium (RR 0.70, 95% CI 0.51 to 0.96; 4 studies, 691 participants; moderate-certainty evidence).⁴

In conclusion, low- to moderate-certainty evidence suggests that lamotrigine may be superior to placebo as a therapeutic option for bipolar disorder.⁴ In comparison to lithium, people with bipolar disorder seem to tolerate lamotrigine better at 12 months; however, the demonstrated efficacy in the maintenance of bipolar disorder was similar between the two groups.⁴

After review, 81 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

American Academy of Neurology, American Epilepsy Society and Society for Maternal-Fetal Medicine: Teratogenesis, Perinatal, And Neurodevelopmental Outcomes After in Utero Exposure To Antiseizure Medication

A 2024 practice guideline From the AAN, AES, and SMFM provides recommendations regarding the effects of AEDs in children born to people with epilepsy.⁵ The odds of maternal mortality during pregnancy is 5 to 12 times greater among people with epilepsy compared to people who are pregnant without epilepsy.⁵ Among 202 pregnancy-related deaths in the United Kingdom from 2013 to 2015, most of the 13 epilepsy-related deaths were from sudden unexpected death in during a seizure.⁵ All participants with pre-pregnancy data had uncontrolled seizures.⁵ Five of the participants who died had stopped taking AEDs during pregnancy.⁵

Infants born to people with epilepsy are at increased risk of major congenital malformations (MCMs), adverse perinatal outcomes, and adverse neurodevelopmental outcomes.⁵ The unadjusted birth prevalence of any MCM among children born to people without epilepsy is approximately 2.4% to 2.9%.⁵ There are limited data available on epilepsy-related outcomes during pregnancy for numerous AEDs, including but not limited to eslicarbazepine, ethosuximide, lacosamide, perampanel, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin.⁵ Of the AEDs with sufficient numbers of exposures to draw reliable conclusions (greater than 1,000 exposures in people with epilepsy), lamotrigine, levetiracetam, and oxcarbazepine are associated with the lowest unadjusted birth prevalence of any MCM in monotherapy (3.1%, 3.5%, and 3.1%, respectively).⁵ Valproic acid is associated with the highest unadjusted birth prevalence (9.7%) of any MCM among children born to people with epilepsy as compared with other AEDs.⁵

Rates for specific MCMs compared with other AEDs are as follows:

- Valproic acid is associated with the highest unadjusted birth prevalence of neural tube defects (1.4%).⁵
- Phenobarbital is associated with the highest unadjusted birth prevalence of cardiac malformations (4.4%).⁵
- Phenobarbital and topiramate are associated with the highest unadjusted birth prevalence of oral and cleft palate (2.2% and 1.4% respectively).⁵
- Valproic acid is associated with the highest unadjusted birth prevalence of urogenital (1.2%) and renal (1.4%) malformations.⁵

Recommendations for people of childbearing potential taking AEDs to manage epilepsy include:

- Clinicians should engage in joint decision-making with their patients, taking individual preferences into account when selecting AEDs and monitoring their dosing (strong recommendation).⁵
- Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures) during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (very strong recommendation).⁵
- Once a person with epilepsy is already pregnant, clinicians should exercise caution in attempting to remove or replace an AED that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (strong recommendation).⁵
- Clinicians should adjust the dose of AEDs at their clinical discretion during the pregnancy in response to (1) decreasing serum AED levels or (2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of AEDs in the pregnant state) (strong recommendation).⁵
- Clinicians treating their patients with epilepsy of childbearing potential using eslicarbazepine, ethosuximide, lacosamide, perampanel, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (strong recommendation).⁵
- Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in people with epilepsy of childbearing potential when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (very strong recommendation).⁵
- Clinicians must avoid the use of valproic acid in people of childbearing potential to minimize the risk of MCMs or neural tube defects, if clinically feasible (very strong recommendation).⁵
- Clinicians must counsel their patients who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared with other studied AEDs (very strong recommendation).⁵
- To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital, if clinically feasible (very strong recommendation).⁵
- To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate, if clinically feasible (strong recommendation).⁵
- To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid, if clinically feasible (strong recommendation).⁵

- Clinicians should avoid the use of valproic acid or topiramate in people of childbearing potential to minimize the risk of offspring being born small for gestational age, if clinically feasible (strong recommendation).⁵
- To reduce the risk of poor neurodevelopmental outcomes in children born to people with epilepsy, including autism spectrum disorder and lower IQ, clinicians should avoid the use of valproic acid, if clinically feasible (strong recommendation).⁵

European Academy of Neurology Guideline on Trigeminal Neuralgia

In 2021 the EAN published guidance for management of people with trigeminal neuralgia (TN).⁷ For long-term treatment, carbamazepine (200–1200 mg/day) or oxcarbazepine (300–1800mg/day) are the most effective medications especially in the early stages of TN.⁷ Slow release preparations are available but there are no studies to compare them with the conventional forms.⁷ However, if these drugs become ineffective or result in poor tolerability, then other drugs need to be considered.⁷ Based on low- to very low-quality evidence, lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen and phenytoin may be used either as monotherapy or combined with carbamazepine or oxcarbazepine when first-line drugs fail due to either efficacy or tolerability.⁷ The following recommendations include an AED:

- Based on a moderate quality of evidence, carbamazepine is strongly recommended for long-term treatment of TN.⁷
- Based on a very low quality of evidence but high confidence from clinical experience, oxcarbazepine is strongly recommended for long-term treatment of TN.⁷
- Based on a very low quality of evidence, lamotrigine is weakly recommended as either monotherapy or add-on therapy for long-term treatment of TN.⁷
- Based on low quality of evidence, a gabapentin is weakly recommended as either monotherapy or add-on therapy for long-term treatment of TN.⁷

Oregon Health Authority Mental Health Clinical Advisory Group: Bipolar Disorder Management

In 2019 the MHCAG developed clinical practice recommendations for bipolar disorder.⁸ Algorithms were developed for management of acute bipolar depression and acute bipolar mania. For bipolar depression, first line medications include lamotrigine, lithium, and quetiapine in addition to psychosocial treatment.⁸ The advantages of lamotrigine compared with lithium and quetiapine are: safety in pregnancy; lowest overall adverse effect profile; and lowest risk of weight gain.⁸ Disadvantages of lamotrigine therapy include: slow titration over 6 or more weeks; necessity of consistent adherence; and rare risk of Stevens-Johnson syndrome.⁸ Second-line monotherapy recommendations include cariprazine, divalproex, or lurasidone.⁸ If combination therapy is warranted, the following combinations are recommended:

- lamotrigine with another bipolar treatment medication;
- lurasidone with either lithium or divalproex;
- olanzapine and fluoxetine, and
- a SSRI or bupropion with another bipolar treatment medication.

For treatment of acute bipolar mania, MHCAG recommends first-line combination therapy of quetiapine and lithium or quetiapine and divalproex with concurrent psychosocial treatment.⁸ Advantages of divalproex compared with lithium include rapid loading and onset, simple dose titration, and safety in renal or thyroid disease.⁸ Disadvantages of divalproex include risk of teratogenicity and monitoring required in hepatic or bleeding disorders.⁸ If symptoms persist, changing to monotherapy treatment with an antipsychotic (aripiprazole, asenapine, cariprazine, risperidone, ziprasidone) is recommended.⁸ Lamotrigine should be avoided in patients who only need treatment for acute mania.⁸

Department of Veterans Affairs and Department of Defense: Clinical Practice Guideline for Headache Management

In 2023 the VA/DoD convened a workgroup to update guidance for management of headaches.⁹ Literature was reviewed through August 16, 2022 to support the revised recommendations.⁹ Tension-type, cluster and migraine headaches were included in the clinical practice guideline. Four AEDs were discussed in the guideline: topiramate, valproate, gabapentin, and levetiracetam. These recommendations include an AED:

- Topiramate is suggested for the prevention of episodic and chronic migraine (weak recommendation).⁹
- Valproate is suggested for the prevention of episodic migraine (weak recommendation).⁹
- Gabapentin is not recommended for the prevention of episodic migraine (weak recommendation).⁹
- There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.⁹

International Headache Society Global Practice Recommendations for Preventive Pharmacological Treatment of Migraine

The International Headache Society updated treatment recommendations for migraine prophylaxis in 2024.¹⁰ Two AEDs are included in the practice guideline: valproic acid and topiramate.¹⁰ Other medication classes recommended for preventative migraine therapy include beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, antidepressants, CGRP monoclonal antibodies, botulinum toxin, and the atogepant.¹⁰ Valproate may be preferred in patients with epilepsy, mania, anxiety, and comorbid depression.¹⁰ However, valproate should be avoided or prescribed with caution in patients with hepatic disease, bleeding disorders, alcoholism, obesity or of childbearing potential.¹⁰ Topiramate may be preferred in patients with epilepsy, obesity, mania, anxiety, essential tremor, or alcohol dependence.¹⁰ Topiramate should be avoided or used with caution in patients with kidney stones, renal failure, closed angle glaucoma, depression, cognitive concerns or patients of childbearing potential.¹⁰ The following recommendations include an AED:

- Preventative medications suggested for people with chronic migraine include: atogepant, erenumab, eptinezumab, fremanezumab, galcanezumab, onabotulinumtoxin A and topiramate.¹⁰
- In children and adolescents with migraine who need pharmacological migraine prevention, beta-blockers at doses adapted to body weight can be used, although evidence of efficacy is very limited. In case of ineffectiveness, low dose topiramate or amitriptyline represent possible alternatives.¹⁰
- In people with migraine and medication overuse, monoclonal antibodies targeting the CGRP pathway, topiramate and onabotulinumtoxin A have proven effective regardless of the presence of medication overuse. Therefore, the immediate withdrawal or reduction of the overused drug might not be necessary in subjects who are initiating such a treatment.¹⁰

New Formulations and Indications:

- New Indication - February 2020: SABRIL (vigabatrin) oral tablets and oral powder received expanded approval for use as adjunctive therapy in refractory complex partial seizures for patients 2 years of age and older who have responded inadequately to several alternative treatments.¹⁵ Vigabatrin is not indicated as a first-line agent for treatment of complex partial seizures.¹⁵ Prior to this expanded indication, vigabatrin was FDA-approved for treatment of refractory partial seizures in patients 10 years of age and older.¹⁵
- New Indication - August 2021: BRIVIACT (brivaracetam) oral tablets, oral solution, and intravenous injection received expanded approval for use in pediatric patients 1 month of age and older for treatment of partial-onset seizures.¹⁶ Prior to this approval, brivaracetam was approved for use in patients 4 years of age and older. Use of brivaracetam in pediatrics is supported by evidence from RCTs of brivaracetam in adults with partial-onset seizures, pharmacokinetic data from adult and pediatric patients, and open-label RCTs to assess safety in pediatric patients 2 months to less than 16 years of age.¹⁶

- New Indication - October 2021: VIMPAT (lacosamide) oral tablets, oral solution, and intravenous injection received expanded approval for treatment of partial seizures in patients 1 month of age and older.¹⁷ Prior to this approval, lacosamide was FDA-approved for treatment of partial seizures in patients 4 years of age and older and as adjunctive therapy in treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older.¹⁷
- New Indication - March 2022: FINTEPLA (fenfluramine) oral solution received an expanded indication for treatment of seizures associated with LGS in patients 2 years of age and older.¹⁸ Prior to this expanded approval, fenfluramine was FDA-approved for treatment of seizures associated with DS in patients 2 years of age and older.¹⁸ The effectiveness of fenfluramine for the treatment of seizures associated with LGS in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients 2 to 35 years of age.¹⁸ In this RCT, fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day doses were compared with placebo.¹⁸ Patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet.¹⁸ The study had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures while on stable AED therapy. Drop seizures were generalized tonic-clonic, secondarily generalized tonic-clonic, tonic, atonic, or tonic-atonic seizures that were confirmed to result in drops. The baseline period was followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of fenfluramine remained stable.¹⁸ In this trial, 99% of patients were taking between 1 and 4 concomitant AEDs.¹⁸ The most frequently used concomitant AEDs (in at least 25% of patients) were clobazam (45%), lamotrigine (34%), and valproate (56%).¹⁸ The primary efficacy endpoint was the median percent change from baseline in the frequency of drop seizures per 28 days during the combined 14-week titration and maintenance periods (i.e., treatment period).¹⁸ The median percent change from baseline (reduction) in the frequency of drop seizures per 28 days was significantly greater for the 0.7 mg/kg/day dose group of fenfluramine compared with placebo (-23.7 vs. -8.7; difference: 15; 95% CI NR; p=0.0037).¹⁸ The median percent reduction from baseline in drop seizure frequency per 28 days for the lower dose of fenfluramine (0.2 mg/kg/day) did not reach statistical significance compared to placebo.¹⁸
- New Formulation – May 2023: MOTPOLY XR (lacosamide) extended-release capsules received FDA-approval for treatment of partial-onset seizures in adults and pediatric patients weighing at least 50 kg.¹⁹
- New Indication - June 2024: MOTPOLY XR (lacosamide) extended release capsules received expanded approval as adjunctive therapy for treatment of primary tonic-clonic seizures in adults and patients weighing at least 50 kg.⁵¹
- New Formulation - June 2024: VIGAFYDE (vigabatrin) concentrated oral solution 100 mg/mL received FDA-approval for use as monotherapy treatment of infantile spasms in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential for vision loss.²⁰ The new formulation is not approved for use in adults.²⁰ This product also carries a black-boxed warning regarding the risk of permanent vision loss and is only available through the restricted Vigabatrin REMS program.²⁰

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts⁵²

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Topiramate	TROKENDI XR EPRONTIA QUDEXY XR TOPAMAX	2/22	Warnings/Precautions	<p>Acute Myopia and Secondary Angle Closure Glaucoma Syndrome: A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular hyperemia (redness), choroidal detachments, retinal pigment epithelial detachments, macular striae, and increased intraocular pressure.</p>
Topiramate	TROKENDI XR EPRONTIA QUDEXY XR TOPAMAX	10/22	Warnings/Precautions	<p>Metabolic Acidosis: A one-year, active-controlled study of pediatric patients treated with immediate-release topiramate demonstrated decreased lumbar spine bone mineral density (BMD) and that the lumbar spine BMD decrease was correlated (using change from baseline for lumbar spine Z score at final visit versus lowest post-treatment serum bicarbonate) with decreased serum bicarbonate, a reflection of metabolic acidosis.</p> <p>Decrease in Bone Mineral Density: Results of a one-year, active-controlled study in pediatric patients (N=63) demonstrated negative effects of immediate-release topiramate monotherapy on bone mineral acquisition via statistically significant decreases in BMD measured in lumbar spine and in total body less head. Twenty-one percent of immediate-release topiramate-treated patients experienced clinically important reductions in BMD (Z score change from baseline of -0.5 or greater) compared to 0 patients in the control group. Although decreases in BMD occurred across all pediatric age subgroups, patients 6 to 9 years of age were most commonly affected. The sample size and study duration were too small to determine if fracture risk is increased. Decreased BMD in the lumbar spine was correlated with decreased serum bicarbonate, which commonly occurs with topiramate treatment and reflects metabolic acidosis, a known cause of increased bone resorption. Although small decreases in some markers of bone metabolism (e.g., serum alkaline phosphatase, calcium, phosphorus, and 1,25-dihydroxyvitamin D) occurred in immediate-release topiramate-treated patients, more significant decreases in serum parathyroid hormone and 25-hydroxyvitamin D, hormones involved in bone metabolism, were observed, along with an increased excretion of urinary calcium.</p> <p>Negative Effects on Growth: Results of a one-year active-controlled study of pediatric patients (N=63) demonstrated negative effects of immediate-release topiramate monotherapy on growth (i.e., height and weight). Although continued growth was observed in both treatment groups, the immediate-release topiramate group showed statistically significant reductions in mean annual change from</p>

				<p>baseline in body weight compared to the control group. A similar trend of attenuation in height velocity and height change from baseline was also observed in the immediate release topiramate group compared to the control group. Negative effects on weight and height were seen across all immediate release topiramate age subgroups. Growth (height and weight) of children receiving prolonged topiramate therapy should be carefully monitored.</p> <p>Kidney Stones: An increase in urinary calcium and a marked decrease in urinary citrate was observed in topiramate-treated pediatric patients in a one-year, active-controlled study. This increased ratio of urinary calcium/citrate increases the risk of kidney stones and/or nephrocalcinosis.</p>
Topiramate	TROKENDI XR EPRONTIA QUDEXY XR TOPAMAX	1/24	Warnings/Precautions	<p>Fetal Toxicity: Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate <i>in utero</i> have an increased risk of major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age.</p>
Carbamazepine	CARBATROL CARNEXIV EQUETRO TEGRETOL	4/23	Warnings/Precautions	<p>Precautions: Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac conduction disturbance, including second- and third-degree atrioventricular (AV) block; cardiac, hepatic, or renal damage; adverse hematologic or hypersensitivity reaction to other drugs including reactions to other anticonvulsants; or interrupted courses of therapy with carbamazepine.</p> <p>AV block, including second- and third-degree block, has been reported following carbamazepine treatment. This occurred generally, but not solely, in patients with underlying EKG abnormalities or risk factors for conduction disturbances.</p> <p>Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure, have been reported. In some cases, hepatic effects may progress despite discontinuation of the drug. In addition, rare instances of vanishing bile duct syndrome have been reported. This syndrome consists of a cholestatic process with a variable clinical course ranging from fulminant to indolent, involving the destruction and disappearance of the intrahepatic bile ducts. Some, but not all, cases are associated with features that overlap with other immunoallergenic syndromes such as multiorgan hypersensitivity and serious dermatologic reactions. As an example, there has been a report of vanishing bile duct syndrome associated with Stevens-Johnson syndrome and in another case an association with fever and eosinophilia.</p> <p>Warnings: Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms.</p>

				<p>HLA-A*3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (e.g., Tamil Nadu) and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American and other Indian ancestry; and up to about 5% in African Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry.</p> <p>Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids have been reported in patients after taking the first or subsequent doses of carbamazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with carbamazepine the drug should be discontinued and an alternative treatment started. These patients should not be rechallenged with the drug.</p>
Levetiracetam	ELEPSIA XR KEPPRA SPRITAM	3/24	Warnings/Precautions	<p>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Multiorgan Hypersensitivity: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including levetiracetam. These events can be fatal or life-threatening, particularly if diagnosis and treatment do not occur as early as possible. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Levetiracetam should be discontinued if an alternative etiology for the signs or symptoms cannot be established.</p>
Clobazam	ONFI SYMPAZAN	3/24	Warnings/Precautions	<p>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Multiorgan Hypersensitivity: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including clobazam. These events can be fatal or life-threatening, particularly if diagnosis and treatment do not occur as early as possible. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Clobazam should be discontinued if an alternative etiology for the signs or symptoms cannot be established.</p>
Fenfluramine	FINTEPLA	9/23	Controlled Substance Designation Removed	The FDA approved the removal of the Drug Enforcement Administration (DEA) designation of fenfluramine as a C-IV controlled substance. ⁵³

Randomized Controlled Trials:

A total of 298 citations were manually reviewed from the initial literature search. After further review, 298 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
carbamazepine	CARBAMAZEPINE	ORAL SUSP	PO	Y
carbamazepine	TEGRETOL	ORAL SUSP	PO	Y
carbamazepine	CARBAMAZEPINE	TAB CHEW	PO	Y
carbamazepine	CARBAMAZEPINE ER	TAB ER 12H	PO	Y
carbamazepine	TEGRETOL XR	TAB ER 12H	PO	Y
carbamazepine	CARBAMAZEPINE	TABLET	PO	Y
carbamazepine	EPITOL	TABLET	PO	Y
carbamazepine	TEGRETOL	TABLET	PO	Y
diazepam	DIAZEPAM	KIT	RC	Y
diazepam	VALTOCO	SPRAY	NS	Y
divalproex sodium	DEPAKOTE SPRINKLE	CAP DR SPR	PO	Y
divalproex sodium	DIVALPROEX SODIUM	CAP DR SPR	PO	Y
divalproex sodium	DEPAKOTE ER	TAB ER 24H	PO	Y
divalproex sodium	DIVALPROEX SODIUM ER	TAB ER 24H	PO	Y
divalproex sodium	DEPAKOTE	TABLET DR	PO	Y
divalproex sodium	DIVALPROEX SODIUM	TABLET DR	PO	Y
ethosuximide	ETHOSUXIMIDE	CAPSULE	PO	Y
ethosuximide	ZARONTIN	CAPSULE	PO	Y
ethosuximide	ETHOSUXIMIDE	SOLUTION	PO	Y
ethosuximide	ZARONTIN	SOLUTION	PO	Y
gabapentin	GABAPENTIN	CAPSULE	PO	Y
gabapentin	NEURONTIN	CAPSULE	PO	Y
gabapentin	GABAPENTIN	TABLET	PO	Y
gabapentin	NEURONTIN	TABLET	PO	Y
lacosamide	LACOSAMIDE	TABLET	PO	Y
lacosamide	VIMPAT	TABLET	PO	Y
lamotrigine	LAMICTAL	TABLET	PO	Y
lamotrigine	LAMOTRIGINE	TABLET	PO	Y
lamotrigine	SUBVENITE	TABLET	PO	Y
levetiracetam	KEPPRA	SOLUTION	PO	Y
levetiracetam	LEVETIRACETAM	SOLUTION	PO	Y
levetiracetam	KEPPRA	TABLET	PO	Y
levetiracetam	LEVETIRACETAM	TABLET	PO	Y
levetiracetam	ROWEEPRA	TABLET	PO	Y
methsuximide	CELONTIN	CAPSULE	PO	Y
methsuximide	METHSUXIMIDE	CAPSULE	PO	Y
midazolam	NAYZILAM	SPRAY	NS	Y

oxcarbazepine	OXCARBAZEPINE	ORAL SUSP	PO	Y
oxcarbazepine	TRILEPTAL	ORAL SUSP	PO	Y
oxcarbazepine	OXCARBAZEPINE	TABLET	PO	Y
oxcarbazepine	TRILEPTAL	TABLET	PO	Y
phenobarbital	PHENOBARBITAL	ELIXIR	PO	Y
phenobarbital	PHENOBARBITAL	TABLET	PO	Y
phenytoin	DILANTIN-125	ORAL SUSP	PO	Y
phenytoin	PHENYTOIN	ORAL SUSP	PO	Y
phenytoin	DILANTIN	TAB CHEW	PO	Y
phenytoin	PHENYTOIN	TAB CHEW	PO	Y
phenytoin sodium extended	DILANTIN	CAPSULE	PO	Y
phenytoin sodium extended	PHENYTEK	CAPSULE	PO	Y
phenytoin sodium extended	PHENYTOIN SODIUM EXTENDED	CAPSULE	PO	Y
primidone	MYSOLINE	TABLET	PO	Y
primidone	PRIMIDONE	TABLET	PO	Y
rufinamide	BANZEL	TABLET	PO	Y
rufinamide	RUFINAMIDE	TABLET	PO	Y
tiagabine HCl	TIAGABINE HCL	TABLET	PO	Y
topiramate	TOPAMAX	TABLET	PO	Y
topiramate	TOPIRAMATE	TABLET	PO	Y
valproic acid	VALPROIC ACID	CAPSULE	PO	Y
valproic acid (as sodium salt)	VALPROIC ACID	SOLUTION	PO	Y
zonisamide	ZONISAMIDE	CAPSULE	PO	Y
carbamazepine	EQUETRO	CPMP 12HR	PO	V
ganaxolone	ZTALMY	ORAL SUSP	PO	V
lamotrigine	LAMICTAL (BLUE)	TAB DS PK	PO	V
lamotrigine	LAMICTAL (GREEN)	TAB DS PK	PO	V
lamotrigine	LAMICTAL (ORANGE)	TAB DS PK	PO	V
lamotrigine	LAMOTRIGINE (BLUE)	TAB DS PK	PO	V
lamotrigine	LAMOTRIGINE (GREEN)	TAB DS PK	PO	V
lamotrigine	LAMOTRIGINE (ORANGE)	TAB DS PK	PO	V
lamotrigine	SUBVENITE (BLUE)	TAB DS PK	PO	V
lamotrigine	SUBVENITE (GREEN)	TAB DS PK	PO	V
lamotrigine	SUBVENITE (ORANGE)	TAB DS PK	PO	V
lamotrigine	LAMICTAL XR	TAB ER 24	PO	V
lamotrigine	LAMOTRIGINE ER	TAB ER 24	PO	V
lamotrigine	LAMICTAL ODT	TAB RAPDIS	PO	V
lamotrigine	LAMOTRIGINE ODT	TAB RAPDIS	PO	V
lamotrigine	LAMICTAL	TB CHW DSP	PO	V
lamotrigine	LAMOTRIGINE	TB CHW DSP	PO	V

lamotrigine	LAMICTAL XR (BLUE)	TB ER DSPK	PO	V
lamotrigine	LAMICTAL XR (GREEN)	TB ER DSPK	PO	V
lamotrigine	LAMICTAL XR (ORANGE)	TB ER DSPK	PO	V
lamotrigine	LAMICTAL ODT (BLUE)	TB RD DSPK	PO	V
lamotrigine	LAMICTAL ODT (GREEN)	TB RD DSPK	PO	V
lamotrigine	LAMICTAL ODT (ORANGE)	TB RD DSPK	PO	V
lamotrigine	LAMOTRIGINE ODT (BLUE)	TB RD DSPK	PO	V
lamotrigine	LAMOTRIGINE ODT (GREEN)	TB RD DSPK	PO	V
lamotrigine	LAMOTRIGINE ODT (ORANGE)	TB RD DSPK	PO	V
brivaracetam	BRIVIACT	SOLUTION	PO	N
brivaracetam	BRIVIACT	TABLET	PO	N
cannabidiol (CBD)	EPIDIOLEX	SOLUTION	PO	N
carbamazepine	CARBAMAZEPINE ER	CPMP 12HR	PO	N
carbamazepine	CARBATROL	CPMP 12HR	PO	N
cenobamate	XCOPRI	TAB DS PK	PO	N
cenobamate	XCOPRI	TABLET	PO	N
clobazam	SYMPAZAN	FILM	PO	N
clobazam	CLOBAZAM	ORAL SUSP	PO	N
clobazam	ONFI	ORAL SUSP	PO	N
clobazam	CLOBAZAM	TABLET	PO	N
clobazam	ONFI	TABLET	PO	N
diazepam	LIBERVANT	FILM	BC	N
eslicarbazepine acetate	APTIOM	TABLET	PO	N
felbamate	FELBAMATE	ORAL SUSP	PO	N
felbamate	FELBATOL	ORAL SUSP	PO	N
felbamate	FELBAMATE	TABLET	PO	N
felbamate	FELBATOL	TABLET	PO	N
fenfluramine HCl	FINTEPLA	SOLUTION	PO	N
gabapentin	GABAPENTIN	SOLUTION	PO	N
gabapentin	NEURONTIN	SOLUTION	PO	N
gabapentin	GABAPENTIN ER	TAB ER 24H	PO	N
gabapentin	GRALISE	TAB ER 24H	PO	N
gabapentin	GRALISE	TAB24HDSPK	PO	N
gabapentin enacarbil	HORIZANT	TABLET ER	PO	N
lacosamide	MOTPOLY XR	CAP ER 24H	PO	N
lacosamide	LACOSAMIDE	SOLUTION	PO	N
lacosamide	VIMPAT	SOLUTION	PO	N
lacosamide	VIMPAT	TAB DS PK	PO	N
levetiracetam	ELEPSIA XR	TAB ER 24H	PO	N
levetiracetam	KEPPRA XR	TAB ER 24H	PO	N

levetiracetam	LEVETIRACETAM ER	TAB ER 24H	PO	N
levetiracetam	SPRITAM	TAB SUSP	PO	N
oxcarbazepine	OXCARBAZEPINE ER	TAB ER 24H	PO	N
oxcarbazepine	OXTELLAR XR	TAB ER 24H	PO	N
perampanel	FYCOMPA	ORAL SUSP	PO	N
perampanel	FYCOMPA	TABLET	PO	N
phenobarbital	PHENOBARBITAL	ELIXIR	PO	N
pregabalin	LYRICA	CAPSULE	PO	N
pregabalin	PREGABALIN	CAPSULE	PO	N
pregabalin	LYRICA	SOLUTION	PO	N
pregabalin	PREGABALIN	SOLUTION	PO	N
pregabalin	LYRICA CR	TAB ER 24H	PO	N
pregabalin	PREGABALIN ER	TAB ER 24H	PO	N
primidone	PRIMIDONE	TABLET	PO	N
rufinamide	BANZEL	ORAL SUSP	PO	N
rufinamide	RUFINAMIDE	ORAL SUSP	PO	N
stiripentol	DIACOMIT	CAPSULE	PO	N
stiripentol	DIACOMIT	POWD PACK	PO	N
topiramate	TOPIRAMATE ER	CAP ER 24H	PO	N
topiramate	TROKENDI XR	CAP ER 24H	PO	N
topiramate	QUDEXY XR	CAP SPR 24	PO	N
topiramate	TOPIRAMATE ER	CAP SPR 24	PO	N
topiramate	TOPAMAX	CAP SPRINK	PO	N
topiramate	TOPIRAMATE	CAP SPRINK	PO	N
topiramate	EPRONTIA	SOLUTION	PO	N
vigabatrin	SABRIL	POWD PACK	PO	N
vigabatrin	VIGABATRIN	POWD PACK	PO	N
vigabatrin	VIGADRONE	POWD PACK	PO	N
vigabatrin	VIGPODER	POWD PACK	PO	N
vigabatrin	VIGAFYDE	SOLUTION	PO	N
vigabatrin	SABRIL	TABLET	PO	N
vigabatrin	VIGABATRIN	TABLET	PO	N
vigabatrin	VIGADRONE	TABLET	PO	N
zonisamide	ZONISADE	ORAL SUSP	PO	N

Appendix 2: Medline Search Strategy

AEDS in Neuropathic Pain

Ovid MEDLINE(R) ALL <1946 to December 27, 2024>

1	Carbamazepine/	12163
2	Diazepam/	18230
3	divalproex.mp. or Valproic Acid/	14826
4	Ethosuximide/	999
5	lacosamide.mp.	1396
6	lamotrigine.mp.	6854
7	levetiracetam.mp.	5899
8	methsuximide.mp.	103
9	oxcarbazepine.mp.	2553
10	Phenobarbital/	18311
11	Phenytoin/	13911
12	Primidone/	1320
13	rufinamide.mp.	372
14	tiagabine.mp.	1048
15	topiramate.mp.	6079
16	Valproic Acid/	14468
17	zonisamide.mp.	1684
18	brivaracetam.mp.	526
19	clobazam.mp.	1288
20	esclicarbazepine.mp.	2
21	felbamate.mp.	783
22	perampanel.mp.	1023
23	Pregabalin/	2635
24	Vigabatrin/	1727
25	Gabapentin/	4615
26	midazolam spray.mp.	15
27	stiripentol.mp.	399
28	Cannabidiol/	4018
29	cenobamate.mp.	188
30	Pregnanolone/ or ganaxolone.mp.	2188
31	Fenfluramine/	3125
32	Anticonvulsants/	57759
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	134401

34	Neuralgia, Postherpetic/ or Neuralgia/ or Diabetic Neuropathies/	36580
35	Trigeminal Neuralgia/	8036
36	34 or 35	43973
37	33 and 36	2746
38	limit 37 to (english language and humans and yr="2019 -Current")	373
39	limit 38 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review")	57

AEDs in Fibromyalgia

Ovid MEDLINE(R) ALL <1946 to December 27, 2024>

1-33 as above

33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	134401
34	Fibromyalgia/	10579
35	33 and 34	301
36	limit 35 to (english language and humans and yr="2019 -Current")	51
37	limit 36 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review")	10

AEDS in Bipolar Disorder

Ovid MEDLINE(R) ALL <1946 to December 27, 2024>

1-33 as above

33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	134401
34	Bipolar Disorder/	46891
35	33 and 34	3584
36	limit 35 to (english language and humans and yr="2019 -Current")	322
37	limit 36 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review")	58

AEDS in Migraine Disorders

Ovid MEDLINE(R) ALL <1946 to December 27, 2024>

1-33 as above

33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	134401
34	Migraine Disorders/	31269
35	33 and 34	1318
36	limit 35 to (english language and humans and yr="2019 -Current")	215
37	limit 36 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review")	44

AEDs in Epilepsy

Ovid MEDLINE(R) ALL <1946 to December 27, 2024>

1-33 as above

33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	134401
34	Epilepsy/	89331
35	33 and 34	23429
36	limit 35 to (english language and humans and yr="2022 -Current")	1421
37	limit 36 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review")	129

Appendix 3: Key Inclusion Criteria

Population	People with neuropathic pain, fibromyalgia, migraine headaches, bipolar disorders, or seizures.
Intervention	Antiepileptic drugs
Comparator	Other antiepileptic drugs
Outcomes	Relief of neuropathic pain, fibromyalgia, or migraine headaches. Reduction of bipolar symptoms or seizure activity per month.
Timing	Maintenance dosing
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is this an FDA approved indication?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication AND is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	Yes: Go to #5 Document current seizure frequency_____	No: Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 25 mg/kg/day?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to # 6

Approval Criteria

6. Are baseline liver function tests (LFTs) on file (serum transaminases and total bilirubin levels)?
AND
If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?

LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver.

Yes: Approve for 12 months

Document results here:

Date of lab work _____

AST _____

ALT _____

Total Bilirubin _____

No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria

1. Are recent LFT's documented in patient records?

AND

If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?

Yes: Go to # 2

Document results here:

Date of lab work _____

AST _____

ALT _____

Total Bilirubin _____

No: Pass to RPh. Deny; medical appropriateness

2. Has seizure frequency decreased since beginning therapy?

Yes: Go to #3

Document baseline & current seizure frequency

No: Pass to RPh. Deny for lack of treatment response.

3. Is the prescribed dose greater than 25mg/kg/day?

Yes: Pass to RPh. Deny; medical appropriateness

No: Go to # 4

Renewal Criteria		
4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment¹

Hepatic Impairment	Starting Dosage	Maintenance Dosage Range in Patients with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS)	Maintenance Dosage in Patients with Tuberous Sclerosis Complex (TSC)
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 to 10 mg/kg twice daily (10 to 20 mg/kg/day)	12.5 mg/kg twice daily (25 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day)	6.25 mg/kg twice daily (12.5 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 to 2 mg/kg twice daily (2 to 4 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. July 2020.

*P&T/DUR Review: 4/25 (DM); 10/22 (SF); 10/21; 10/20; 6/20; 3/19; 1/19
Implementation: 11/1/20; 5/1/19; 3/1/19*

Clobazam - RETIRE

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- 12 months

Requires PA:

- Clobazam

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for renewal of therapy previously approved by the FFS system?	Yes: Go to Renewal Criteria	No: Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	Yes: Go to #4	No: Go to #5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria

1. Has seizure frequency decreased since beginning therapy?	Yes: Approve for 12 months	No: Pass to RPh. Deny for lack of treatment response.
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Limitations of Use:

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.¹

1. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. [nice.org.uk/guidance/cg137](https://www.nice.org.uk/guidance/cg137). Accessed July 30, 2018

P&T Review: 10/22 (SF); 10/21 (DM); 10/20; 6/20; 1/19; 3/18; 7/16; 3/15; 5/12
Implementation: 3/1/19; 8/16, 8/12

Fenfluramine

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Fenfluramine

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is this an FDA approved indication?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Does the patient have uncontrolled seizures on current baseline therapy with at least one other antiepileptic medication AND is fenfluramine intended to be prescribed as adjuvant antiepileptic therapy?	Yes: Go to #5 Document seizure frequency_____	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the prescribed dose greater than 0.7 mg/kg/day or 26 mg/day OR 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to # 6
6. Is baseline echocardiogram on file that was performed within past 6 months?	Yes: Approve for 12 months Document results here: Date of echocardiogram _____ Results _____	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has an echocardiogram been obtained within the past 6 months?	Yes: Go to # 2 Document results here: Date of echocardiogram _____	No: Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	Yes: Go to #3 Document baseline and current seizure frequency _____	No: Pass to RPh. Deny; medical appropriateness
3. Is the prescribed dose greater than 0.7mg/kg/day or 26 mg/day or greater than 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to # 4
4. Is fenfluramine prescribed as adjuvant therapy and is patient adherent to all prescribed seizure medications?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness

P&T Review: 4/25 (DM); 10/22 (SF); 10/21; 10/20
Implementation: 11/1/20

Ganaxolone Safety Edit

Goal:

- To ensure appropriate drug use and restrict to indications supported by medical literature

Length of Authorization:

- Up to 12 months

Requires PA:

- Ganaxolone

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the medication FDA-approved for the requested indication and patient age?	Yes: Go to #3	No: Go to #5
3. What is the patient's current weight?	Record weight: _____ (within past 6 months) Go to #4	
4. Does the requested dosing align with the FDA-approved dosing?	Yes: Approve for up to 12 months	No: Go to #5
5. Has the patient already been taking this medication for longer than 4 weeks AND currently taking at time of this request?	Yes: Approve for 1 month and forward to medical director for review. (Abrupt withdrawal may precipitate increased seizures)	No: Pass to RPh. Deny; medical appropriateness.

P&T / DUR Review: 4/25 (DM); 10/22 (SF)
Implementation: 1/1/23

Pregabalin

Goal(s):

- Provide coverage only for diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	Yes: Go to Renewal Criteria	No: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	Yes: Go to #4	No: Go to #5
4. Does the patient have a diagnosis of epilepsy?	Yes: Approve for lifetime	No: Go to #5
5. Is the request for a diagnosis funded by OHP?	Yes: Go to #6	<p>No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP</p> <p>If eligible for EPSDT review: Go to #6</p>

Approval Criteria		
6. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	Yes: Go to # 7	No: Pass to RPh; Deny; medical necessity.
7. Is the request for an FDA-approved or evidence-supported diagnosis (see Table 1 below for examples)?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness.
8. Is the request for generalized anxiety disorder?	Yes: Go to #9	No: Go to #10
9. Has the patient tried and failed to have benefit from, or have a contraindication to, first line treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI)?	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness.
10. Is the patient concurrently on short- or long-acting opioids? Note: There is insufficient evidence for use of opioid products (e.g., long-acting opioid with short-acting opioid) in neuropathic conditions.	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #11
11. Is there documentation that the patient has inadequate response or contraindication to at least 2 nonpharmacologic treatments for the requested condition? Relevant treatments may include: acupuncture, supervised exercise therapy, yoga, and meditative movement.	Yes: Go to # 12	No: Pass to RPh. Deny; medical appropriateness.
12. Has the patient tried and failed, or have contraindications or intolerance to, a preferred gabapentinoid for 90 days?	Yes: Approve for 90 days	No: Pass to RPh. Deny; medical appropriateness. Recommend trial of gabapentin for 90 days

Renewal Criteria

1. Does the patient have documented improvement from pregabalin?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness
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Table 1. Pregabalin formulations for FDA-approved or evidence-supported indications

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	
Generalized Anxiety Disorder	X	
Nonfunded		
Fibromyalgia	X	

P&T Review: 4/25 (DM); 6/24 (MH); 4/23; 10/22; 10/21; 10/20; 1/19; 7/18; 3/18; 3/17
 Implementation: 5/12/25; 7/1/24; 10/1/18; 8/15/18; 4/1/17

Stiripentol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Stiripentol capsules and powder for oral suspension

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 6 months of age or older, weighing 7 kg or more, and taking clobazam?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is baseline white blood cell (WBC) and platelet counts on file within the past 3 months? <u>Note:</u> Labs should be assessed every six months while receiving stiripentol therapy.	Yes: Approve for 12 months Document results here: Date of lab work _____ WBC _____ Platelets _____	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records? <u>Note:</u> Labs should be assessed every six months while receiving stiripentol therapy.	Yes: Go to #2 Document results here: Date of lab work _____ WBC _____ Platelets _____	No: Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	Yes: Approve for 12 months	No: Pass to RPh. Deny for lack of treatment response.

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	Yes: Approve for lifetime.	No: Go to #3
3. Is the request for treatment of migraine?	Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime.	No: Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	Yes: Go to #5	No: Go to #6

Approval Criteria

<p>5. Has the patient tried or are they contraindicated to at least two of the following drugs?</p> <ul style="list-style-type: none"> • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic <p>Document drugs tried or contraindications.</p>	<p>Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.</p>	<p>No: Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.</p>
<p>6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?</p>	<p>Yes: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP AND weight loss drugs excluded by state plan.</p> <p>If eligible for EPSDT review: Go to #7</p>	<p>No: Pass to RPh. Go to #9</p>
<p>7. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?</p>	<p>Yes: Go to #8</p>	<p>No: Pass to RPh. Deny; medical necessity.</p>
<p>8. Has the patient failed to have benefit with, or have contraindications or intolerance to, preferred topiramate products?</p> <p>Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.</p>	<p>Yes: Approve for 90 days with subsequent approvals up to 12 months dependent on documented positive response</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Inform prescriber of covered alternatives in class and process appropriate PA.</p>

Approval Criteria

9. All other indications need to be evaluated for appropriateness:

- Neuropathic pain
- Post-Traumatic Stress Disorder (PTSD)
- Substance abuse

Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate.

If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal.

MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."

P&T Review: 4/25 (DM);10/22 (SF); 10/21; 10/20; 6/20; 5/19; 1/19; 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07
Implementation: 4/18/15; 5/12, 1/12