



Antiseizure Medication in the Setting of Systemic Illness: A Focused Review

Bindu Menon¹ Medha Menon² Praveen Kumar Yadav³ Mainak Bardhan⁴

¹Department of Neurology, Apollo Speciality Hospitals, Nellore, Andhra Pradesh, India

²Department of Medicine, Kasturba Medical College, Manipal, Karnataka, India

³Sri Ramakrishna Mission Medical College (SRIMS), Durgapur, general Medicine West Bengal, India

⁴Miller School of Medicine, Human Genetics University of Miami, Miami, Florida, United States

Address for correspondence Bindu Menon, MD (Med.), DM (Neuro), DNB (Neuro), FRCP (Edinburgh), FRCP (London), FAAN, PGDCN (Neuro), (London), MNAMS.FICP, FIAN, FWSO, FAMS, Department of Neurology, Apollo Speciality Hospitals, Nellore 524002, Andhra Pradesh, India (e-mail: bindu.epilepsycare@gmail.com).

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Abstract

Epilepsy is a common neurological disorder, and managing seizures can be challenging when other systemic illnesses are present, as these can affect the choice of antiseizure medication (ASM). Various comorbidities, such as cardiovascular disorders, liver and kidney impairment, psychiatric conditions, porphyria, and thyroid dysfunction, can significantly influence the pharmacokinetics and pharmacodynamics of ASMs. This requires careful selection of suitable ASMs based on their safety profiles and potential for drug interactions. Traditional ASMs such as phenytoin, carbamazepine, and valproate should be taken cautiously in individuals with cardiovascular disorders because of the possibility of side effects. Conversely, newer medications like lamotrigine and lacosamide (LCM) may offer safer alternatives. Levetiracetam and LCM are examples of medications with minimal hepatic metabolism, which are recommended since hepatic dysfunction can impact the binding potential of ASMs and result in toxicity. Furthermore, drugs that are mostly eliminated by the kidneys may take longer to be eliminated due to renal impairment, necessitating dose adjustments or the consideration of alternate therapies. ASMs can also affect psychiatric conditions; some medications may provide mood-stabilizing or antidepressant effects, while others may worsen psychiatric symptoms. Certain ASMs can trigger porphyria or disrupt thyroid function, necessitating careful monitoring and appropriate selection of treatments. This review offers a comprehensive overview of considerations and recommendations for the use of ASMs in various systemic illnesses, highlighting the need for a sophisticated strategy to maximize managing seizures while reducing side effects and medication interactions.

Keywords

- ▶ epilepsy
- ▶ antiseizure medications (ASMs)
- ▶ systemic illnesses
- ▶ pharmacokinetics
- ▶ safety profiles

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Introduction

Many people worldwide suffer from epilepsy, a common neurological condition. The Global Burden of Disease Study from 2016 estimates that 39.3 million individuals in India and 45.9 million people worldwide suffer from active epilepsy.¹ The main goal of treating epilepsy using antiseizure medications (ASMs) is to completely control seizures while reducing adverse effects. Many ASMs have been developed over time, and there are currently close to 30 in widespread use.² However, controlling seizures can be challenging, especially when ASM selection is influenced by other comorbid medical disorders. The absorption, distribution, metabolism, and excretion of ASMs are greatly impacted by several comorbidities, including cardiovascular risk factors (such as type 2 diabetes, hypertension, dyslipidemia, and atrial fibrillation) as well as hepatic and renal illnesses. Older ASMs often have high protein binding, which requires careful therapeutic drug monitoring. In contrast, newer ASMs generally have narrower therapeutic indices but offer better safety profiles. As a result, selecting the appropriate ASMs with favorable safety profiles for patients with comorbidities presents a significant challenge for neurologists.³

In this context, we provide an overview of ASMs used to treat epilepsy in people with systemic diseases.

Materials and Methods

We did not perform a systematic literature search because this was a narrative review. However, a search of the PubMed database was conducted using the following search parameters: “anticonvulsant” and “antiepileptic drugs” along with the keywords “cardiovascular disease,” “liver disease,” “kidney disease,” “porphyria,” “psychiatric disorder,” “psychiatric disorder,” “cognitive impairment,” and “comorbid conditions” and the outcomes were evaluated to make sure they were pertinent to the review’s subject. The analysis includes studies that addressed the use of antiseizure drugs in relation to systemic disorders. Studies that did not address systemic illness or focus solely on epilepsy without considering systemic factors were excluded. No date limitations were applied to the searches. Once the articles were identified, a comprehensive review of all the results was undertaken, and the findings and conclusions were aggregated and summarized.

Cardiovascular Disease

Hepatic enzymes are known to be induced by older ASMs, including carbamazepine (CBZ), phenytoin (PHT), and phenobarbital (PB), and this can be linked to vascular hazards.⁴ Even at higher therapeutic concentrations (e.g., 20 µg/mL), PHT is often not linked to the requirement for cardiac monitoring.⁵ It is noteworthy, therefore, that a large prospective cohort study discovered that 24.1% of patients over 60 experienced hypotension when given PHT at a dose of 11 to 25 mg/kg (with an infusion rate of 50 mg/min). Additionally, another study reported that administering 1000 mg of PHT over 2.5 minutes during a seizure caused hypotension in

0 to 18% of patients, arrhythmia in 0 to 5%, and apnea in 0 to 2%.⁶ The cardiovascular effects of PHT are primarily attributed to high infusion rates, which lead to rapid distribution into body tissues. Factors such as metabolic disorders and older age can affect the elimination of PHT from the body. According to studies, people over 50 and those with cardiovascular conditions are thought to be safer with an infusion rate of 25 mg/min.⁷ Nonetheless, the prodrug fosphenytoin is regarded as safer compared with PHT, as it has a lower incidence of hypotension and fewer tissue side effects.⁸

CBZ is known to have negative effects on heart rate and electrical conduction, including causing dysfunction in the sinus node and atrioventricular (AV) node block, particularly in patients with existing cardiac abnormalities.⁹ According to earlier observations, even at therapeutic dosages of CBZ, bradycardia and sinus rhythm tachycardia might occur.¹⁰ In a separate study, it was found that CBZ overdose resulted in tachycardia, while therapeutic or moderate doses were associated with bradycardia.¹¹ Furthermore, a recent study with 5,473 people in a general population found that using CBZ is linked to a higher risk of sudden cardiac arrest, with a modified odds ratio of 1.90.¹²

Valproate (VPA), a broad-spectrum antiepileptic medication, has a 1 to 5% chance of causing hypertension, tachycardia, and palpitations. It is generally well tolerated, even in cases of new-onset status epilepticus, with no significant cardiac side effects reported.^{13,14}

The newer antiepileptic medication, lacosamide (LCM), has demonstrated cardiac effects when administered rapidly via intravenous dosing. It has been associated with first-degree AV block in 22.4% of patients.¹⁵ However, a recent study suggested that administering LCM at an infusion rate of 30 minutes is safer, showing no incidence of atrial fibrillation, bradycardia, or atrial flutter. An isolated case of atrial premature complexes ($n = 1$), hypotension ($n = 1$), and first-degree AV block ($n = 1$) was documented in 38 patients.¹⁶

Lamotrigine (LTG) is generally considered safe compared with other antiepileptic medications. The Food and Drug Administration of the United States (FDA) did, however, issue a warning about its usage in patients with heart problems in 2021. Based on *in vitro* data, this caution was issued because LTG may have poor cardiac sodium inhibitory action, which could result in class IB antiarrhythmic effects.¹⁷ Following the FDA warning, a systematic review indicated that LTG at therapeutic doses is associated with mild QRS widening (not serious),¹⁸ and LTG is not linked to an elevated risk of cardiac conduction abnormalities in people without preexisting cardiac problems, nor does it increase the risk of mortality in patients with such morbidities, according to another study with large cohorts.¹⁹ In conclusion, LTG is regarded as a safe choice for treating epilepsy in those who have cardiac issues. – **Table 1** shows the metabolism of ASM with cardiac medications and precautions to be taken.

Compared with a placebo, using eslicarbazepine acetate (ESL) was linked to a slightly increased incidence of elevated total cholesterol, triglycerides, and low-density lipoprotein levels. It is important for patients taking warfarin to have their international normalized ratio monitored to ensure

Table 1 Medications must be used carefully in those with heart disease

ASM	Cardiac drug	Interaction/Effect	
PHT	Ticlopidine	Increases PHT level	
	Antiarrhythmic	Increases metabolism of antiarrhythmic	
	Amiodarone	Increases PHT levels	
	Beta-blockers	Increases B blocker metabolism	
	Dihydropyridine	Increases dihydropyridine metabolism	
	Losartan	PHT reduces active metabolite by 63%	
	Oral anticoagulants (OAC)		Reduces effects of OAC
			OAC increases PHT levels
	Diuretics	PHT reduces the diuretic response	
Digoxin Statins	PHT reduces digoxin levels. PHT stimulates statin metabolism		
CBZ	Ticlopidine	Increases the level of CB2	
	Antiarrhythmic	Increases antiarrhythmic metabolism. Diltiazem/verapamil increase CB2 levels	
	Antihypertensive	Increases metabolism of beta-blockers	
	OAC	Reduces the effect of OAC	
	Diuretics	Use with caution to avoid hypernatremia	
	Statins	Stimulates the metabolism of statins	
VPA	Salicylates	Increases the VPA's available percentage	
	Antihypertensive	Raises nimodipine levels by 50%	

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; PHT, phenytoin; VPA, valproate.

proper maintenance. As ESL operates as a sodium channel blocker, there is a theoretical risk of arrhythmias in patients who have preexisting heart rhythm disorders.²⁰

Patients using cenobamate may experience over 20 minutes of QT shortening, with 31% affected with a dose of 200 mg and 66% at 500 mg. Cenobamate should not be used to treat people with inherited short QT syndrome. When cenobamate is taken with other drugs that also reduce the QT interval, caution is advised. Additionally, cenobamate is extensively metabolized, and its metabolism can be influenced by other drugs, while it may also affect the metabolism of other medications.²¹

Studies have indicated that rufinamide treatment can lead to QT interval shortening. However, there is currently no evidence linking its use to ventricular rhythm disturbances or drug-induced sudden mortality. There is no known therapeutic danger associated with the degree of QT slowing brought by the drug rufinamide. Rufinamide should not be used to treat patients with familial short QT syndrome since they are more likely to experience sudden cardiac arrest and ventricular arrhythmias, particularly with ventricular fibrillation. Additionally, rufinamide should not be taken with any medications that decrease the QT interval.²²

Liver Disease

Neurologists find ASM especially difficult since sudden symptomatic seizures or seizures might exacerbate the progression of hepatic disorders. ASMs' ability to bind to

plasma proteins can be impacted by several liver conditions, which raises the possibility of toxicity.

Lorazepam is a safer option for patients with liver disease due to fewer drug interactions and is suggested as the primary treatment for seizure control. Since the majority of benzodiazepines are processed in the liver, hepatic illness can significantly impact their metabolism. In particular, midazolam undergoes metabolism by cytochrome P450, and its clearance is compromised during liver pathologies. As a result, these should generally be avoided in patients with liver disease to prevent sedation and reduce the risk of aggravating preexisting encephalopathy.²³

VPA can follow an alternate metabolic pathway in individuals with liver disease, leading to the production of toxic hepatotoxic metabolites and hyperammonemia.²⁴ Because of its unpredictable dynamics, PHT can accumulate to hazardous serum levels in low albumin levels.²⁵ PB has an extended half-life in patients with liver cirrhosis (~130 hours), which can lead to drug accumulation.²⁵

As such, avoid these medications in the treatment of epilepsy in individuals with hepatic pathologies.

Levetiracetam (LEV) is the most important medication for treating epilepsy in individuals with liver disease because only 2% of it is broken down by liver enzymes, resulting in minimal drug interactions. Typically, no modification of the dosage is necessary for mild to moderate liver disease. However, a 50% dosage reduction is advised in situations of severe liver illness that are categorized as Child–Pugh class C.²⁶

LCM is predominantly metabolized through particular pathways, although its byproducts are inert, and currently, there is no evidence of medication interactions. Because of its linear pharmacokinetics and modest protein binding (15%), it is a safer choice for hepatic disease patients.²⁷

Topiramate (TPM) is also considered safe for use in liver disease since only 20% is broken down in the liver. In cases of severe hepatic disease, a 30% reduction in dosage is advised. Additionally, gabapentin (GBP) and pregabalin (PGB) are commonly used in clinical settings due to their negligible to minimal protein binding, which allows for the safe management of seizures in individuals with hepatic disease.^{28,29}

In summary, an appropriate ASM for individuals with hepatic disease should feature less binding with the protein and minimal hepatic metabolism.³⁰

A pharmacokinetic study involving adults with hepatic cirrhosis across grades A, B, and C of Child–Pugh revealed a 50, 57, and 59% increase in brivaracetam (BRV) exposure, respectively, compared with matched healthy controls. Because of this increased exposure, dosage adjustments for BRV are recommended at all stages of liver damage.³¹ No effects were observed in individuals with slight liver dysfunction (Child–Pugh grade A) after administration of one dose of 200 mg cannabidiol. However, individuals with moderate (Child–Pugh grade B) or severe (Child–Pugh grade C) liver disease experienced an increase in the area under the curve of approximately 2.5 to 5.2 times high compared with healthy volunteers with healthy liver. Due to this increased exposure, dose modifications are necessary for individuals with moderate or severe liver disease; no dose modification is required for those with mild liver disease.³²

Cannabidiol causes a dose-dependent elevation in hepatic transaminases. The most pertinent reason behind the discontinuation of cannabidiol in trials was an increase in transaminases. In controlled research studies of Lennox–Gastaut syndrome or Dravet syndrome, the alanine aminotransferase elevation incidence is greater than three times the upper limit of normal (ULN) with 13% in cannabidiol-treated patients to 1% in placebo-treated diseased individuals. Risk factors for elevated transaminases include concomitant use of VPA or clobazam, baseline transaminase levels above the ULN, and high doses of cannabidiol.³¹

Cenobamate is cautiously used in individuals with mild to moderate liver disease, as a low-maintenance drug dose may be required (data are currently missing). The cenobamate use is not suggested for individuals with severe liver dysfunction. Additionally, cenobamate may rarely cause a dose-dependent increase in liver transaminases.³²

Renal Disease

Chronic kidney disease (CKD) or renal impairment can have a major impact on how well medications or their active metabolites are eliminated, which may result in toxicity. A normal glomerular filtration rate (GFR) and some indication of renal impairment are characteristics of CKD stage 1. A slight decline in GFR (60–89 mL/min per 1.73 m²) is indicative of stage 2 CKD. A GFR of 30 to 59 mL/min per 1.73 m² is

considered to be mild renal impairment in CKD stage 3. A GFR of 15 to 29 mL/min per 1.73 m² is referred to as CKD stage 4, which is regarded as significant renal impairment. A GFR of less than 15 mL per minute per 1.73 m² is known as CKD stage 5, and to maintain life at this point, dialysis or a kidney transplant must be considered.³³

LEV, GBP, PGB, LCM, and vigabatrin are among the ASMs that the kidneys partially remove. The elimination half-life of these medications is extended in cases of decreased renal clearance, which causes drug buildup in the body. For instance, GBP can accumulate in individuals with renal impairment, resulting in sedation.³⁴ Additionally, when vigabatrin or LEV is used in individuals with renal issues, there is a possibility of developing encephalopathy.³⁵

LEV is primarily excreted from the body through the renal, with approximately 95% of a given drug excreted while passing urine in healthy individuals. However, in individuals with kidney problems, the elimination of LEV is prolonged, and its clearance depends on the rate of creatinine clearance. The drug's half-life varies: it takes approximately 10 hours in cases of mild kidney failure and up to 24 hours in severe kidney failure.²⁵ Consequently, dosage adjustments are often necessary based on the severity of kidney dysfunction. LEV is effectively taken out through hemodialysis, with roughly 50% of the drug cleared within 4 hours of a dialysis session. Therefore, it is recommended to administer an additional dose of 250 to 500 mg every 4 hours during dialysis.²⁵

In individuals with renal damage, the accumulated uremic acid and hypoalbuminemia decrease the binding of the protein to certain ASMs like PHT and VPA, which are normally more than 90% protein-bound. This reduction in binding of the protein can elevate the pharmacologically active fraction of these drugs, leading to more pronounced therapeutic effects and side effects.³⁶ Renal replacement therapy (RRT) also affects the pharmacokinetics of ASMs. Both hemodialysis and continuous RRT significantly influence the removal of ASMs, necessitating adjustments in dosing or supplementation.³⁷ For patients receiving PHT, oxcarbazepine (OXC), CBZ, VPA, BRV, LTG, and LCM, no dose reduction is required during maintenance hemodialysis. In contrast, PB, GBP, TPM, vigabatrin, LEV, and ethosuximide (ETX) are largely removed during hemodialysis and thus require supplementation.

In renal transplant patients, it is vital to manage drug interactions with immunosuppressant medications to prevent organ rejection. Hepatic enzyme-inducing agents like PHT and CBZ should be avoided to prevent failure of immunosuppressive therapy and to reduce the risk of transplant rejection.

Based on how they are eliminated, ASMs can be divided into three major groups. Medications that are removed by a combination of renal and nonrenal pathways, pharmaceuticals that are primarily eliminated by hepatic metabolism, and drugs that are excreted unchanged by the kidneys or undergo minimal metabolism.²⁵ When used alone or in conjunction with medications that do not induce enzymes, the medications in the first group include TPM, vigabatrin, PGB, and GBP. PHT, VPA, CBZ, tiagabine (TGB), and rufinamide are among the

medications that are primarily removed through biotransformation. LEV, LCM, zonisamide (ZNS), primidone, phenobarbital, ezogabine/retigabine, OXC, eslicarbazine, ETX, and felbamate are among the medications in the intermediate group.²⁵ Patients who have liver or renal disease should use these medications with caution. It is challenging to employ antiepileptic medications when hepatic or renal illness is present, necessitating a thorough understanding of the pharmacokinetics of these drugs. To improve clinical outcomes, more frequent serum concentration monitoring and closer patient follow-up are required.²⁵ In individuals with combined liver and renal impairment, LEV, LTG, LCM, GBP, and PGB can be used with dose adjustments.

CKD or renal impairment can have a major impact on how well medications or their active metabolites are eliminated, which could be harmful. The GFR is used to classify the stages of CKD: stage 1 denotes normal GFR with evidence of kidney damage; stage 2 denotes mild GFR reduction (60–89 mL/min per 1.73 m²); stage 3 denotes moderate impairment (30–59 mL/min per 1.73 m²); stage 4 denotes severe impairment (15–29 mL/min per 1.73 m²); and stage 5 (GFR < 15 mL/min per 1.73 m²) requires RRT, such as dialysis or transplantation, to maintain life.³³

LEV, GBP, PGB, LCM, and vigabatrin are among the ASMs that are partially eliminated by the kidneys. Drug buildup may result from a longer elimination half-life caused by reduced renal clearance. For example, GBP accumulation in renal impairment can lead to sedation,³⁴ while vigabatrin and LEV can cause encephalopathy.³⁵

LEV is primarily excreted through renal, with approximately 95% of the given dose eliminated through the urine in normal individuals.²⁵ Its half-life is prolonged from roughly 10 hours in mild renal failure to 24 hours in severe cases due to the considerable slowdown in its clearance caused by renal impairment. As a result, it is crucial to modify dosage according to creatinine clearance. During hemodialysis, approximately 50% of LEV is removed within 4 hours, and supplemental doses of 250 to 500 mg are recommended every 4 hours.²⁵

Hypoalbuminemia and the accumulation of uremic acid in renal dysfunction reduce the protein binding of highly protein-bound ASMs like PHT and VPA. This reduction leads to increased free drug fractions and enhanced pharmacological effects. Additionally, RRT further affects the pharmacokinetics of ASMs. For example, hemodialysis significantly removes drugs such as GBP, TPM, vigabatrin, and LEV, necessitating supplemental dosing. In contrast, patients

taking PHT, CBZ, OXC, VPA, LTG, BRV, and LCM typically do not require dose reductions during maintenance hemodialysis.³⁷

In renal transplant patients, it is crucial to manage drug interactions with immunosuppressants to prevent organ rejection. ASMs that induce the enzymes, such as PHT and CBZ, can compromise efficacy with immunosuppressants and should be avoided. LTG, which is also an enzyme inducer, requires careful consideration. On the other hand, LCM has the advantage of having minimal impact on immunosuppressants and can be included in treatment regimens.

ASMs can be categorized based on their elimination routes: those excreted unchanged or minimally metabolized by the kidneys (e.g., GBP, PGB, vigabatrin, TPM), those predominantly eliminated by hepatic metabolism, and those removed through both renal and nonrenal routes (e.g., LEV, LCM, ZNS, PB, OXC, ETX).²⁵ Caution is warranted in cases of renal or hepatic impairment, requiring close monitoring and serum concentration checks to optimize outcomes. For individuals with both kidney and liver dysfunction, LEV, LTG, LCM, GBP, and PGB are preferable ensuring appropriate dose adjustments. **Table 2** shows the recommended ASM in renal transplant patients.

Psychiatric Disorders

Psychiatric diseases are most common in individuals with epilepsy. The most frequent include anxiety, depression, psychosis, personality changes, cognitive abnormalities, and attention deficits. ASMs can have both sedative and excitatory effects. For example, LTG acts as a mood stabilizer with antidepressant properties,³⁸ while LEV has been linked to aggressive behavior.³⁹ In contrast, PHT and VPA are associated with lower levels of irritability. Certain antidepressants can also have proconvulsant effects. According to the FDA phase 2 and 3 clinical trials, clomipramine and bupropion are linked with a higher incidence of seizures.⁴⁰ Additionally, amoxapine and maprotiline have been reported to pose an elevated seizure risk at standard doses.⁴¹

The first-line ASMs, including CBZ, PHT, CBZ, and PB, are potent inducers of the enzymes. As a result, they can reduce the serum concentrations of certain antidepressants, such as tricyclic antidepressants as well as selective serotonin reuptake inhibitors such as paroxetine and citalopram. To maintain therapeutic levels of these antidepressants, a dose reduction of approximately 30% may be necessary. In contrast, VPA does not exhibit such interactions with antidepressants.⁴² The newer

Table 2 ASM in renal transplant patients

ASM	Category	Recommendations for renal transplant
PHT, CBZ	Older ASMs	Avoid due to enzyme induction
PHT, CBZ	Older ASMs	Avoid due to enzyme induction
VPA	Older ASM	Safe in renal transplant patients
LCM, LTG, LEV	Newer ASMs	Preferred due to minimal interaction with immunosuppressants

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; VPA, valproate.

Table 3 Psychiatric medications and their level of seizure risk

Risk level	Severe risk	Medium risk	Mild risk
Psychiatric medications	Bupropion, clomipramine, chlorpromazine, clozapine	Tricyclic antidepressants, venlafaxine, thioridazine, olanzapine, quetiapine	Fluoxetine Sertraline Paroxetine Trazodone Haloperidol Risperidone

ASMs, including LTG, TGB, LEV, and ZNS, also do not have this effect.

The relationship between ASMs and suicidal behavior has raised concerns. In 2008, a meta-analysis of 11 ASMs from a multicenter randomized controlled study highlighted a potential link between suicide and these medications.⁴³ However, there is no conclusive evidence of the risk of suicidal behavior associated with ASMs⁴⁴ and epilepsy.⁴⁵

When treating individuals with epilepsy, it is significant to consider the adverse effects of ASMs and antipsychotics. Weight gain is a significant concern with VPA and CBZ. Fluoxetine is a preferred option because it is linked with a relatively smaller increase in weight and has the additional benefit of enhancing alertness. However, it can increase the plasma concentrations of CBZ and PHT, so monitoring serum levels is necessary.

Additionally, hyponatremia should be considered when using serotonin and norepinephrine reuptake inhibitors in combination with CBZ, OXC, and ESL. ASMs that have negative psychotropic effects, such as benzodiazepines, barbiturates, TPM, LEV, and ZNS, should be used with caution. In contrast, LTG, LCM, PGB, and GBP are known to have beneficial effects. Psychiatric drugs and their effect on seizures are listed in ►Table 3.

In addition, ASMs may cause sexual dysfunction, which may lead to psychiatric consequences.

- Enzyme-inducers, in high doses, can increase the sex hormone-binding globulin, lower the free testosterone, and thereby reduce the libido and sexual function impairment.⁴⁶

- Other ASMs, including acetazolamide, benzodiazepines, and PGB, may cause sexual dysfunction as well.
- Sexual dysfunction is not common with ETX, GBP, LTG, LEV, TGB, VPA, and ZNS.⁴⁷

When prescribing an ASM for a patient with epilepsy, preexisting psychiatric problems, or learning disabilities, drug–drug interactions and side effects of ASM should be taken into consideration (►Table 4). The treating physician should consider which ASM might best help the patient maximize seizure control and minimize psychiatric symptoms.

Porphyria

A group of diseases known as porphyria is brought on by an aberrant buildup of porphyrins and impacts the skin and nervous system. A reduction in neuronal activity, which can result in seizures, is one outcome of this metabolic imbalance, which is frequently characterized by hyponatremia, which can be brought on by digestive and kidney losses, high water intake, and the impacts of the hormone antidiuretic. These metabolic abnormalities may also be the cause of common symptoms during porphyric attacks, such as headaches, cramping in the muscles, feeling nauseated, and altered awareness.⁵⁸

Certain isoenzymes of cytochrome, specifically CYP2C9, CYP2C19, and CYP3A4, can be activated by various ASMs such as CBZ, PHT, and PB. However, these medications worsen or trigger attacks of acute intermittent porphyria. They accelerate the breakdown of uroporphyrinogen decarboxylase and hydroxymethylbilane synthetase while altering the feedback mechanism involved in heme biosynthesis.

Table 4 Recommended antiseizure medications in patients with preexisting psychiatric, learning, and behavioral problems

Preexisting psychopathology	Recommended antiseizure medications
Depression	Carbamazepine, lamotrigine
Mania	Valproate, carbamazepine, oxcarbazepine
Bipolar disorder	Valproate, carbamazepine, lamotrigine, oxcarbazepine
Aggression and agitation	Valproate, carbamazepine, phenytoin
Anxiety disorders	Pregabalin (generalized anxiety disorder), gabapentin (social anxiety disorder)
Binge-eating disorder	Topiramate, zonisamide
Learning disability	Lamotrigine, levetiracetam
Attention-deficit hyperactivity disorder	Lamotrigine, carbamazepine, oxcarbazepine

Note: From Nadkarni and Devinsky,⁴⁸ Brodtkorb and Mula,⁴⁹ Schubert,⁵⁰ Schmitz,⁵¹ Mula et al,⁵² Tassone et al,⁵³ Kaufman,⁵⁴ Bialer,⁵⁵ Kimiskidis and Valeta,⁵⁶ and Kanner.⁵⁷

Table 5 ASM recommendations in individuals with epilepsy and other comorbidities²⁴

Safe ASMs		Not recommended/To avoid ASMs
Cardiac disorders	LEV, LTG, TPM, VPA, ZNS. GBP	CBZ, OXC, PGB, PHT
Liver disorders	LEV, PGB, TPM. GBP, ZNS	BZD, CBZ, ESM, LTG PB, PHT, PRM, TGB, VPA,
Kidney disease	BZD, CBZ, ESM, PHT, TGB, VPA	GBP, LEV, LTG, OXC, PB, PGB, PRM, TPM, ZNS
Porphyria	LEV, OXC, PGB. GBP*	BZD, CBZ, LTG, PB, PHT, PRM, TGB, TPM, VPA, ZNS
Renal transplantation	BZD, LTG, VPA	ASM with renal excretion, enzyme-inducing ASM
Cognitive impairment	LTG, LCM, OXC, VPA. GBP	BZD, CBZ, LEV, PB, PHT, PRM, PGB, TPM, ZNS
Psychiatric disorders	LTG, OXC, VPA, GBP, PGB	LEV, PER, TPM, ZNS
Hypothyroidism	BZD, LEV, LTG, PGB, ZNS. GBP	CBZ, OXC, PB, PHT, PRM, TPM, VPA

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; TGB, tiagabine; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

Current research regarding newer ASMs only partially clarifies their potential role in precipitating porphyric attacks.⁵⁸

Most ASMs induce porphyrias, enhancing liver metabolism and raising heme synthesis in the liver.⁵⁹ Safer alternatives include GBP, LEV, and OXC, which have minimal effects on hepatic enzymes and do not induce porphyric crises.^{60,61} Acute porphyric attacks can be treated effectively with benzodiazepines, particularly clonazepam. Intravenous magnesium has also been administered for status epilepticus, although with a less favorable response.⁶² Additionally, propofol has been utilized safely in cases of status epilepticus, along with GBP and LEV for maintenance therapy.⁶³

Epilepsy and Thyroid Disease

According to earlier research, there may not be a direct correlation between a patient's thyroid hormone levels and epilepsy. However, using ASMs may cause certain abnormalities in thyroid function. Numerous biological functions depend on thyroid gland hormones, and insufficiency can exacerbate metabolic syndrome by impacting several body systems. Therefore, it is crucial to thoroughly investigate thyroid hormone levels in epileptic patients undergoing long-term therapy with ASMs.⁶⁴

Prolonged use of ASMs has been linked to several metabolic, endocrine, and hormonal abnormalities, as well as an increase in cardiovascular risks and incidents according to research on epilepsy. Even when ASMs are given within therapeutic parameters, these hazards may still materialize. Lipid abnormalities, hyperhomocysteinemia, being overweight or obese, increased insulin resistance, diabetes type 2, hyperuricemia, and subclinical thyroid dysfunction are a few of the dangers that are linked to this condition. Additionally, long-term ASM users with persistent epilepsy may develop asymptomatic or subclinical atherosclerosis disease, enlarged carotid arterial intima-media thickness, and perhaps serious cerebrovascular and cardiovascular events.⁶⁵

The chronic use of ASMs has notable effects on endocrine functions. Clinical studies have indicated that medications such as CBZ, PHT, and VPA can alter normal thyroid functions.⁶⁶ In one study involving 298 epilepsy patients, it was

found that CBZ, TPM, and LEV led to a significant decrease in free thyroxine levels.⁶⁷

► **Table 5** shows the advised use of ASMs in individuals with epilepsy and other comorbidities.

Many patients with epilepsy also have comorbidities, which should be a significant factor when selecting the most appropriate ASM. Although there is limited scientific evidence regarding the management of epilepsy in individuals with associated diseases, it is essential to evaluate the available data that supports the use of specific ASMs for particular conditions. ► **Table 4** is a summary of the most recommended ASMs in each situation, as well as those that, according to the best-known data, need to be avoided or are not as strongly advised.²⁴

In conclusion, administering ASMs in the context of systemic illness requires a careful and nuanced approach. The effects of ASMs extend beyond just controlling seizures; they also impact various physiological systems. It is crucial to recognize and address potential interactions, particularly when managing comorbid issues like psychiatric, cardiovascular problems, kidney and liver disorders, endocrine disturbances, and porphyrias.

Conflict of Interest

None declared.

References

- Beghi E, Giussani G, Nichols E, et al; GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18(04):357–375
- Gunasekera CL, Sirven JI, Feyissa AM. The evolution of antiseizure medication therapy selection in adults: Is artificial intelligence -assisted antiseizure medication selection ready for prime time? *J Cent Nerv Syst Dis* 2023;15:11795735231209209
- Alsouk BAA, Brodie MJ, Walters M, et al. Tolerability of antiseizure medications in individuals with newly diagnosed epilepsy. *JAMA Neurol* 2020;77(05):574–581
- Yamamoto Y, Terada K, Takahashi Y, Imai K, Kagawa Y, Inoue Y. Influence of antiepileptic drugs on serum lipid levels in adult epilepsy patients. *Epilepsy Res* 2016;127:101–106

- 5 Wyte CD, Berk WA. Severe oral phenytoin overdose does not cause cardiovascular morbidity. *Ann Emerg Med* 1991;20(05):508–512
- 6 Wallis W, Kutt H, McDowell F. Intravenous diphenylhydantoin in treatment of acute repetitive seizures. 1968. *Neurology* 1998;50(06):1525–1525, 13
- 7 Donovan PJ, Cline D. Phenytoin administration by constant intravenous infusion: selective rates of administration. *Ann Emerg Med* 1991;20(02):139–142
- 8 Marchetti A, Magar R, Fischer J, Sloan E, Fischer P. A pharmacoeconomic evaluation of intravenous fosphenytoin (Cerebyx) versus intravenous phenytoin (Dilantin) in hospital emergency departments. *Clin Ther* 1996;18(05):953–966
- 9 Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. *Epilepsia* 2010;51(05):725–737
- 10 Takayanagi K, Yamaguchi H, Hayashi T, Morooka S, Takabatake Y. Carbamazepine-induced bradycardia-tachycardia syndrome with pharmacological analysis and concurrent ECG monitoring. *J Electrocardiol* 1990;23(01):85–88
- 11 Kasarskis EJ, Kuo CS, Berger R, Nelson KR. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. *Arch Intern Med* 1992;152(01):186–191
- 12 Jia L, Eroglu TE, Wilders R, Verkerk AO, Tan HL. Carbamazepine increases the risk of sudden cardiac arrest by a reduction of the cardiac sodium current. *Front Cell Dev Biol* 2022;10:891996
- 13 Gilad R, Izkovitz N, Dabby R, et al. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. *Acta Neurol Scand* 2008;118(05):296–300
- 14 Radgoudarzi M, Vafaee-Shahi M, Naderi F. Effect of sodium valproate treatment on the cardiac index in new cases with status epilepticus. *Open Neurol J* 2021;15:59–64
- 15 Nagendra K, Wilson C, Ravichander B, Sood S, Singh S. Incidence and etiology of respiratory distress in newborn. *Med J Armed Forces India* 1999;55:331–333
- 16 Lu Y-T, Lin C-H, Ho C-J, Hsu C-W, Tsai M-H. Evaluation of cardiovascular concerns of intravenous lacosamide therapy in epilepsy patients. *Front Neurol* 2022;13:891368
- 17 French JA, Perucca E, Sander JW, et al. FDA safety warning on the cardiac effects of lamotrigine: an advisory from the Ad Hoc ILAE/AES Task Force. *Epilepsy Curr* 2021;21(03):1535759721996344
- 18 Restrepo JA, MacLean R, Celano CM, Huffman JC, Januzzi JL, Beach SR. The assessment of cardiac risk in patients taking lamotrigine; a systematic review. *Gen Hosp Psychiatry* 2022;78:14–27
- 19 Christensen J, Trabjerg BB, Dreier JW. Cardiac morbidity and mortality associated with the use of lamotrigine. *Epilepsia* 2022;63(09):2371–2380
- 20 Eslicarbazine acetate (Aptiom). Accessed January 25, 2024 at: <https://www.aptiom.com/>
- 21 Cenobamate (Xcopri). Accessed January 19, 2025 at: <https://reference.medscape.com/drug/xcopricenobamate-1000328/2020>
- 22 Rufinamide (Banzel). Accessed January 25, 2024 at: <https://www.banzel.com/>
- 23 Anderson GD, Hakimian S. Pharmacokinetic of antiepileptic drugs in patients with hepatic or renal impairment. *Clin Pharmacokinet* 2014;53(01):29–49
- 24 Ruiz-Giménez J, Sánchez-Alvarez JC, Cañadillas-Hidalgo F, Serrano-Castro PJ. Andalusian Epilepsy Society. Antiepileptic treatment in patients with epilepsy and other comorbidities. *Seizure* 2010;19(07):375–382
- 25 Asconapé JJ. Use of antiepileptic drugs in hepatic and renal disease. *Handb Clin Neurol* 2014;119:417–432
- 26 Brockmüller J, Thomsen T, Wittstock M, Coupez R, Lochs H, Roots I. Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. *Clin Pharmacol Ther* 2005;77(06):529–541
- 27 Romigi A, Placidi F, Liguori C, et al. Lacosamide as add-on treatment of focal symptomatic epilepsy in a patient with alcoholic liver cirrhosis. *Epilepsy Behav Case Rep* 2014;2:161–163
- 28 Ahmed SN, Siddiqi ZA. Antiepileptic drugs and liver disease. *Seizure* 2006;15(03):156–164
- 29 Ahn S, Hong Y-H, Lee DH, et al. Efficacy and safety of pregabalin for muscle cramps in liver cirrhosis: a double-blind randomized controlled trial. *J Korean Med Sci* 2022;37(07):e56
- 30 Vidaurre J, Gedela S, Yarosz S. Antiepileptic drugs and liver disease. *Pediatr Neurol* 2017;77:23–36
- 31 Brivaracetam (Briviact). Accessed January 25, 2024 at: <https://www.briviact.com/>
- 32 Cannabidiol (Epidiolex). Accessed January 25, 2024 at: <https://www.epidiox.com/>
- 33 Diaz A, Deliz B, Benbadis SR. The use of newer antiepileptic drugs in patients with renal failure. *Expert Rev Neurother* 2012;12(01):99–105
- 34 Dogukan A, Aygen B, Berilgen MS, Dag S, Bektas S, Gunal AI. Gabapentin-induced coma in a patient with renal failure. *Hemodial Int* 2006;10:168–169
- 35 Vulliemoz S, Iwanowski P, Landis T, Jallon P. Levetiracetam accumulation in renal failure causing myoclonic encephalopathy with triphasic waves. *Seizure* 2009;18(05):376–378
- 36 Bansal AD, Hill CE, Berns JS. Use of antiepileptic drugs in patients with chronic kidney disease and end stage renal disease. *Semin Dial* 2015;28(04):404–412
- 37 Mahmoud SH. Antiepileptic drug removal by continuous renal replacement therapy: a review of the literature. *Clin Drug Investig* 2017;37(01):7–23
- 38 Kawai M, Goji H, Kanemoto K. Differences in aggression as psychiatric side effect of levetiracetam and perampanel in patients with epilepsy. *Epilepsy Behav* 2022;126:108493
- 39 Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biol Psychiatry* 2007;62(04):345–354
- 40 Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Crit Rev Neurobiol* 1999;13(04):317–356
- 41 Trimble MR, Mula M. Antiepileptic drug interactions in patients requiring psychiatric drug treatment. In: *Antiepileptic Drugs*. Cambridge University Press; 2005:350–368
- 42 Busko M. FDA advisory members agree antiepileptics pose suicidality risk, nix need for black-box warning. [Internet]. *Medscape*; 2008. Accessed October 21, 2023 at: [medscape.com/viewarticle/577432](https://www.medscape.com/viewarticle/577432)
- 43 Hesdorffer DC, Berg AT, Kanner AM. An update on antiepileptic drugs and suicide: are there definitive answers yet? *Epilepsy Curr* 2010;10(06):137–145
- 44 Wang H, Zhang Y, Tan G, Chen D, Fu Y, Liu L. Suicidality and epilepsy: a systematic review and meta-analysis. *Front Psychiatry* 2023;14:1097516
- 45 Harden CL. Sexuality in men and women with epilepsy. *CNS Spectr* 2006;11(8, suppl 9):13–18
- 46 Facts and Comparisons. Drug Facts and Comparisons. St. Louis: Wolters Kluwer Health/ Facts and Comparisons; 2007
- 47 Nadkarni S, Devinsky O. Psychotropic effects of antiepileptic drugs. *Epilepsy Curr* 2005;5(05):176–181
- 48 Brodtkorb E, Mula M. Optimizing therapy of seizures in adult patients with psychiatric comorbidity. *Neurology* 2006;67(12, suppl 4):S39–S44
- 49 Schubert R. Attention deficit disorder and epilepsy. *Pediatr Neurol* 2005;32(01):1–10
- 50 Smith MC. Optimizing therapy of seizures in children and adolescents with developmental disabilities. *Neurology* 2006;67(12, suppl 4):S52–S55

- 51 Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. *J Clin Psychopharmacol* 2007;27(03):263–272
- 52 Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007;29(01):26–48
- 53 Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav* 2011;21(01):1–11
- 54 Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia* 2012;53(suppl 7):26–33
- 55 Kimiskidis VK, Valeta T. Epilepsy and anxiety: epidemiology, classification, aetiology, and treatment. *Epileptic Disord* 2012;14(03):248–256
- 56 Kanner AM. Management of psychiatric and neurological comorbidities in epilepsy. *Nat Rev Neurol* 2016;12(02):106–116
- 57 Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci* 2004;11(04):356–361
- 58 Hahn M, Gildemeister OS, Krauss GL, et al. Effects of new anticonvulsant medications on porphyrin synthesis in cultured liver cells: potential implications for patients with acute porphyria. *Neurology* 1997;49(01):97–106
- 59 Tatum WO IV, Zachariah SB. Gabapentin treatment of seizures in acute intermittent porphyria. *Neurology* 1995;45(06):1216–1217
- 60 Gaida-Hommernick B, Rieck K, Runge U. Oxcarbazepine in focal epilepsy and hepatic porphyria: a case report. *Epilepsia* 2001;42(06):793–795
- 61 Taylor RL. Magnesium sulfate for AIP seizures. *Neurology* 1981;31(10):1371–1372
- 62 Weir PM, Hodgkinson BP. Is propofol a safe agent in porphyria? *Anaesthesia* 1988;43(12):1022–1023
- 63 Elshorbagy HH, Barseem NF, Suliman HA, et al. the impact of antiepileptic drugs on thyroid function in children with epilepsy: new versus old. *Iran J Child Neurol* 2020;14(01):31–41
- 64 Hamed SA. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. *Expert Rev Clin Pharmacol* 2015;8(06):741–750
- 65 Moshé SL, Perucca E, Ryvlin P, Tomson T. Epilepsy: new advances. *Lancet* 2015;385(9971):884–898
- 66 Shih F-Y, Chuang Y-C, Chuang M-J, et al. Effects of antiepileptic drugs on thyroid hormone function in epilepsy patients. *Seizure* 2017;48:7–10
- 67 Adhimoalam M, Arulmozhi R. Effect of antiepileptic drug therapy on thyroid hormones among adult epileptic patients: an analytical cross-sectional study. *J Res Pharm Pract* 2016;5(03):171–174