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Safe Treatment of Seizures in the Setting of HIV/AIDS

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OPINION STATEMENT

HIV⁺ patients are at increased risk for developing seizures due to the vulnerability of the central nervous system to HIV-associated diseases, immune dysfunction and metabolic disturbances. In patients with acute seizures, standard protocols still apply with urgent seizure cessation being the priority. Management of the person with established epilepsy who contracts HIV is challenging, but the decision to initiate chronic antiepileptic drug (AED) therapy in an HIV⁺ patient is also difficult. Chronic treatment guidelines emphasize the interactions between AEDs and antiretroviral (ARV) medications, but provide no explicit advice regarding when to initiate an AED, what medication to select, and/or the duration of treatment. Epidemiologic data regarding seizure recurrence risk in HIV⁺ individuals is not available. The risk of further seizures likely depends upon the underlying etiology for the seizure(s) and patients' immune status and may be increased by the use of efavirenz (an ARV). The issues for consideration include AED-ARV interactions, organ dysfunction, seizure type, and drug side effects which may worsen or be confused with symptoms of HIV and/or epilepsy. Co-administration of enzyme inducing (EI)-AEDs and ARVs can result in virological failure, breakthrough seizure activity, AED toxicity and/or ARV toxicity. Where available, the AED of choice in HIV⁺ patients is levetiracetam due to its broad spectrum activity, ease of use, minimal drug interactions, and favorable side effect profile. Lacosamide, gabapentin, and pregabalin are also favored choices in patients with partial onset seizures and/or those failing levetiracetam. Where newer AEDs are not available, valproic acid may be the treatment of choice in terms of an AED which will not cause enzyme induction-associated ARV failure, but its side effect profile causes other obvious problems. In resource-limited settings (RLS) where only EI-AEDs are available, there are no good treatment options and further pressure needs to be placed upon policymakers to address this care gap and public health threat.

Keywords

Seizure; Epilepsy; HIV; AIDS; Antiepileptic drugs; Antiretroviral medications; Highly active antiretroviral therapy; Opportunistic infections; Treatment; Safe treatment; Cerebrovascular disease; HIV viremia; Acute management; Chronic management

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Gretchen L. Birbeck has served on a board for Lifting the Burden.

INTRODUCTION

Worldwide there are 34 million people infected with HIV. In 2011, there were 2.5 million new infections and 1.7 million deaths from AIDS related causes.[1] In the United States, the number of people living with HIV is 1.3 million.[2] Since the introduction of highly active antiretroviral therapy (HAART) in the mid 1990's, AIDS related mortality has markedly decreased and where HAART is widely available, HIV has evolved into a chronic disease. Central nervous system (CNS) complications occur in 39–70%[3] of HIV patients and both the etiology and severity correlate with the degree of immunosuppression. CNS opportunistic infections (OIs) are among the most common complications of HIV. The incidence of CNS OIs has decreased with HAART but CNS infections remain a common etiology for seizure among HIV+ patient. Other CNS complications of HIV infection include malignancy, stroke, dementia, and immune reconstitution inflammatory syndrome (IRIS).

The incidence of seizures in the HIV population varies depending on a patient's immune status.[4] In a German study of 831 patients both on and off HAART, 51 (6.1%) had either symptomatic seizures or epilepsy. The most common etiology of seizures in this German population was HIV encephalopathy, progressive multifocal leukoencephalopathy (PML), and toxoplasmosis.[5] Though generalized seizures certainly exist in the HIV+ population, focal onset seizures are more likely due to the vulnerability of the CNS to brain lesions. In HIV+ individuals with an intact immune system, seizure etiologies will be more similar to the HIV- population.

Beyond infections, other etiologies for seizures in people with HIV include metabolic disturbances, medication side effects, and cerebrovascular disease. Evidenced-based guidelines have recently been developed regarding the co-administration of ARVs and AEDs.[6] However, there is limited guidance in the literature on when to initiate chronic treatment, drug selection and duration of treatment. Considerations include risk of seizure recurrence, seizure type, drug metabolism, drug side effects, comorbid conditions and drug-drug interactions.

TREATMENT

Diagnostic Studies Guide Treatment

Since symptomatic seizures are especially common among people with HIV, it is critical to thoroughly evaluate the underlying cause for the seizure. A clinical assessment looking for sources of infection is needed and laboratory investigations should include serum glucose, sodium, calcium, magnesium, liver function tests, and creatinine. Additionally, one should obtain a complete blood count, CD4 count, rapid plasma reagin, blood cultures, urine cultures, a toxicology screen, and a chest x-ray. Although infectious causes are of primary concern, common seizure triggers such as alcohol withdrawal need to remain on the differential. Neuroimaging should ultimately include an MRI with gadolinium, but an initial CT to assess for acute blood and to rule out a mass lesion prior to lumbar puncture should be done acutely. Cerebrospinal fluid (CSF) examination is pivotal in this patient population due to the risk of CNS infection. Lumbar puncture is recommended in all immunocompromised patients with new onset seizure even if they are afebrile.[7] CSF studies should include cell count, differential, glucose, total protein, gram stain, acid fast bacilli stain, India ink stain, bacterial/fungal/TB culture, cryptococcal antigen testing, and cytologic examination. Depending upon the clinical presentation, immune status, and results of the initial evaluation, CSF polymerase chain reaction (PCR) studies can include TB, JC virus (JCV), cytomegalovirus (CMV), varicella zoster virus (VZV), herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and CSF HIV viral load (if peripherally suppressed).

Depending on suspicion for a mass lesion, toxoplasmosis antibody testing may be helpful in determining a patient's prior exposure to toxoplasmosis. Electroencephalography (EEG) may be helpful in evaluating seizure recurrence risk and can distinguish encephalopathy from non-convulsive status epilepticus in patients with persistent obtundation.

Infectious causes of seizure in HIV+ patients—Tuberculous meningitis (TBM) is the most common form of CNS TB and can present at any level of immune suppression.[8–10] TBM can present with seizure as the initial manifestation in 10–16% of adults.[10–13] It is often associated with a chronic headache of several weeks duration. In more severe cases it can present with florid meningismus and cranial nerve palsies. The seizures can be both generalized and partial onset. In the cases of partial onset seizures, one must also consider the presence of a tuberculoma or a TB abscess. CSF studies generally show a pleocytosis, with hypoglycorrachia, and elevated total protein. Imaging findings include basal meningeal enhancement, ring enhancing lesion(s), and hydrocephalus.

Cryptococcal meningitis is the most common CNS fungal infection in HIV and typically occurs at CD4 counts < 100 cells/μl. The clinical presentation can include seizure often associated with headache which can be indicative of a poor prognosis.[14] Diagnosis is typically made by positive India ink stain, cryptococcal antigen test, or culture of CSF. Neuroimaging can appear normal but may show dilated Virchow-Robin spaces as well as a focal lesion representing a cryptococcoma.

Toxoplasmosis is the most common focal brain lesion seen in the HIV typically occurs with CD4 counts < 100 cells/μl. It has been documented to be the etiology of new onset seizure in HIV patients between 15–40% of HIV patients depending upon if patients are on HAART. [15, 16] Seizures are most commonly partial onset due to cortically based lesions. Diagnosis is problematic in toxoplasmosis. Treatment is often initiated empirically and a positive diagnosis is based on response to treatment. Neuroimaging typically shows isolated or multiple ring enhancing lesions at the grey white junction or in the basal ganglia.

Progressive Multifocal Leukoencephalopathy (PML) is a demyelinating disease caused by JC virus infection of oligodendrocytes. PML typically occurs at CD4 counts < 100 cells/μl. Seizures have been documented to occur in 18% of PML cases.[17] Seizures can be both generalized and focal onset. Diagnosis is made by detection of JCV DNA within CSF. Neuroimaging can show patchy and confluent white matter lesions though electron microscopy has also demonstrated cortical involvement in PML.

Other considerations of CNS-associated infections include HIV encephalopathy, EBV-associated primary CNS lymphoma, brain abscess, and immune reconstitution inflammatory syndrome (IRIS) in the setting of recently initiated ART.

Metabolic Perturbation causing seizures in people with hiv—HIV⁺ patients are vulnerable to common electrolyte disturbances including hyponatremia, hypomagnesemia, hypocalcemia, and hypoglycemia. Hyponatremia is of particular concern as it can be symptomatic of serious underlying pathologies. It occurs in 35–55% of hospitalized HIV infected patients.[18–20] HIV⁺ patients may have hyponatremia as a result of syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to pulmonary and/or central nervous system infections including pulmonary or CNS TB. Hyponatremia may also be the result of hypovolemia due to gastrointestinal losses or sepsis thus requiring prompt evaluation.

Cerebrovascular disease—HIV⁺ patients are at risk for unique mechanisms of stroke which may present acutely as a seizure or result in brain injury that presents as post stroke

epilepsy. Infectious etiologies associated with stroke include tuberculous meningitis, meningovascular syphilis, and varicella zoster virus vasculitis. Other considerations are HIV-associated vasculopathy, cardioembolism, coagulopathy, and accelerated atherosclerotic disease.[21] Neuroimaging is essential in any HIV⁺ patient presenting with seizure, particularly those who present with an acute onset focal neurological deficit.

Medication Side Effects Causing Seizures in HIV: As in any other patient population presenting with seizures, medication side effects deserve strong consideration in the HIV population. These patients can be on multiple medications in addition to their ARVs due to co-morbid medical conditions. Clinicians should carefully evaluate for any medications that are known to lower the seizure threshold. Of note, there have been pediatric and adult case reports of seizures due supratherapeutic levels of the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz.[22, 23] Impaired efavirenz clearance is associated with a CYP2B6 genotype variant.[24–27]

HIV viral load in the CSF—Even with exhaustive investigations, up to 28% of HIV⁺ patients with new onset seizure will have no identifiable etiology.[28] It has been speculated that a certain percentage of these cases suffer seizures as a result of HIV's primary effects on the brain.[15, 16] HIV is known to cause inflammation within the brain[29, 30] which is a risk factor for seizure activity.[31, 32] While the association of HIV itself as underlying etiology for seizures is reasonable, this remains unproven.

Newly diagnosed hiv in a person with epilepsy—Although it is more common for an HIV⁺ patient to subsequently develop epilepsy, people with epilepsy can certainly contract HIV. New guidelines now recommend ARV initiation in all HIV-infected individuals[33] thus ARV and AED co-administration is nearly unavoidable in this population. A discussion with the HIV physician initiating ARVs in your patient with epilepsy is warranted. Ideally, an effective ARV regimen which will not interact with the patient's established, effective AED therapy will be selected. When this is not possible, a transition to another AED is needed. Recurrent seizures or increased seizure frequency should be evaluated differently in people with epilepsy and HIV, especially those with advanced HIV disease. One should maintain a low threshold for repeat neuroimaging and a lumbar puncture in a person with HIV and epilepsy to assure no underlying HIV-related pathology is contributing to seizure recurrence.

Diet and lifestyle

- Given the challenges of adhering to multiple medications, counseling and support services may be needed.
- Patients should be aware of the hyperlipidemia which can occur with some AEDs as well as some ARVs and may require dietary modifications and/or lipid lowering agents to decrease long term cardiovascular complications.

Pharmacologic treatment

The goal of treatment in an HIV⁺ patient with seizures or epilepsy is to prevent a recurrent seizure. AED selection is based on maximizing seizure control, minimizing drug side effects, and avoiding exacerbation of any underlying medical conditions. Of particular concern in HIV⁺ patients is to avoid drug-drug interactions that compromise HIV control, seizure control, or both. The decision to initiate treatment, AED selection, and duration of treatment differs based upon whether the clinical presentation is acute or chronic.

Acute Management—When an HIV⁺ patient presents with an acute seizure, controlling the seizure and its associated complications takes precedent over concerns of compromising HIV therapy. In the case of a brief (< 5 min) acute symptomatic seizure with abnormality identified and deemed readily reversible, chronic pharmacological therapy does not need to be initiated. Recurrent seizures between which there is incomplete recovery of consciousness or seizures of duration greater than 5 minutes are at risk for the development of status epilepticus [34, 35] and should be managed with standard status epilepticus protocol. After controlling an acute seizure, an evaluation must commence to assess the underlying etiology, risk of recurrence and the need to start an AED in the short term and long term. In the case of an acute symptomatic seizure due to CNS infection or a metabolic abnormality, if the cause is reversible and there is normal brain imaging and EEG, then it is reasonable to initiate treatment for 3–6 months and reassess. In the presence of an infection, seizure activity may persist for the entire period of activity of the infection.[36] Risk stratification for more chronic recurrence will vary across individual patients. Factors that are associated with a higher risk of recurrence in the general population include an abnormal EEG, and underlying symptomatic cause or an abnormal neurological exam.[37–39] If seizure recurrence, abnormal imaging or abnormal EEG findings support chronic AED therapy, then careful consideration must be given to drug selection. The patient may require transition from the medication used acutely to something for suitable for chronic use (figure 1). It is important to note that the majority of data regarding the risk of recurrence after first seizure and the duration of treatment warranted have been conducted in the general population, not in people with HIV. The extrapolation of this data as it applies to the HIV⁺ population may not be valid.

Chronic Management—Drug selection becomes more complex when initiating AED treatment on an HIV⁺ patient for an extended period of time. In this situation, consideration of drug-drug interactions and compromise of the underlying medical conditions, particularly HIV treatment, are of paramount importance. AEDs and ARVs can interact when co-administered. Depending on the specific drug combinations, the adverse effects may include breakthrough seizures, virologic failure, or drug toxicity. Along with the seizure type and co-morbid medical conditions, the selection of an AED is dictated by a patient's specific ARV regimen.

The American Academy of Neurology has recently developed guidelines for AED selection in people with HIV/AIDS. One of the recommendations is that it may be important to avoid enzyme-inducing AEDs in people on ARV regimens that include protease inhibitors or nonnucleoside reverse transcriptase inhibitors as pharmacokinetic interactions may result in virologic failure.[6] This particularly applies to the older generation AEDs—primidone, phenytoin, phenobarbital, and carbamazepine. Unfortunately, in many RLS EI-AEDs are the only available options making the treatment of seizures in the HIV population problematic. One small pharmacokinetic study demonstrated a reduced half-life of the NNRTI nevirapine in combination with both carbamazepine and phenytoin.[40] Another study demonstrated that carbamazepine reduces the serum concentration of the NNRTI efavirenz.[41] A natural history study of HIV⁺ US military personnel demonstrated a greater risk of virologic failure in patients taking EI-AEDs and HAART compared to patients taking not enzyme-inducing AEDs and HAART.[42]

Past recommendations have suggested avoidance of valproic acid in HIV⁺ patients[43, 44] because of its ability to stimulate HIV replication in vitro.[45, 46] However, in vivo studies have not supported this assertion.[47, 48] The benefits of valproic acid include its broad spectrum activity and cost relative to newer AEDs. When newer AEDs are not available, valproic acid is a reasonable choice as it will not cause a drug-drug interaction that results in ARV failure. It is an enzyme-inhibiting agent and, when co-administered, has demonstrated

increased serum of levels of the protease inhibitor lopinavir/ritonavir and the nucleoside reverse transcriptase inhibitor zidovudine.[49, 50] Thus, it should be used with caution and may require dose adjustments, particularly with the above mentioned ARVs in order to avoid drug toxicity. Coordinating care with the patient's HIV physician is critical.

Another noteworthy pharmacokinetic interaction is with the protease inhibitors and lamotrigine. Lopinavir/ritonavir and atazanovir/ritonavir both resulted in decreased bioavailability of lamotrigine when co-administered with lamotrigine.[51, 52] Oxcarbazepine has not been shown to have any significant pharmacokinetic interaction with ARVs. However, it should be used with caution in any patient with HIV⁺ and hyponatremia as this may be further exacerbated with use of oxcarbazepine.

In general, the ideal AED in the HIV population avoids hepatic metabolism, minimizes drug-drug interaction, is not protein bound, and has a favorable side effect profile (table 1). Rufinamide and Tiagabine are hepatically metabolized and susceptible to increased clearance from enzyme inducing medications. Therefore, they are not first line treatment candidates. Clobazam is similarly hepatically metabolized and there is a case report of neurotoxicity from increased concentrations of clobazam when co-administered with the NNRTI etravirine.[53] Felbamate and vigabatrin are normally reserved for refractory epilepsy cases and the associated adverse side effects of aplastic anemia and liver failure (felbamate) and vision loss (vigabatrin) could be particularly devastating in the HIV population. Zonisamide is an attractive candidate because its once daily dosing is favorable for compliance, particularly in patients with neurocognitive impairment. Its interactions with ARVs have not been thoroughly studied. It is metabolized by the CYP450 isoenzyme 3A4[54] which is induced by protease inhibitors.[55–57] As a result, zonisamide is not first line treatment but, if used, may require a dosage adjustment to maintain a therapeutic level. Topiramate should not be considered first line because it is susceptible to reductions in serum concentration in the presence of CYP450 enzyme inducing agents. Topiramate also induces the CYP450 system at higher doses. In addition, its side effect of anorexia is less favorable in HIV patients who often suffer from weight loss and require nutritional supplementation.

The favored anti-epileptic drugs for use in HIV⁺ patients are levetiracetam, lacosamide, gabapentin, and pregabalin. Though these medications are FDA-approved as adjunctive therapy, it is appropriate to use them as monotherapy in the HIV population. Dosage administration, pharmacokinetics, and special considerations for these medications are discussed below:

Levetiracetam

Standard dosage: Immediate release Levetiracetam can be administered orally or intravenously. Initial dose should be 1000 mg given 500 mg twice daily. Dosage may be increased by 1000 mg every two weeks to a maximum dose of 3000 mg. Extended release tablets are given once daily at an initial dose of 1000 mg. Dosage may also be increased 1000 mg every two weeks to a maximum dose of 3000 mg.

Contraindications: Prior hypersensitivity reaction to levetiracetam.

Main drug interactions: Levetiracetam is renally metabolized and does not demonstrate any significant drug interactions with other anti-epileptic or antiretroviral medications.[58–62]

Main side effects: The most common side effects include somnolence, asthenia, headache, and infection. Behavior abnormalities include depression, irritability, emotional lability, and

suicide. Slower titration should be considered in patients considered high risk of levetiracetam discontinuation for behavioral reasons.[63]

Special points: Levetiracetam is almost entirely renally cleared thus in patients with documented renal disease it may require dosage adjustment for impaired creatinine clearance.

Cost / cost effectiveness: Moderate

Lacosamide

Standard dosage: Lacosamide can be administered either orally or intravenously. The initial dose is 100 mg given 50 mg twice daily. Dosage may be increased by 100 mg every week to a maintenance dose of 200–400 mg daily.

Contraindications: Prior hypersensitivity reaction to lacosamide. Lacosamide should be avoided in patients with second-degree or third-degree atrioventricular block as PR interval prolongation can occur.[64, 65] Lacosamide solution contains aspartame, a source of phenylalanine, and should be avoided in patients with phenylketonuria.

Main drug interactions: Lacosamide is eliminated by renal excretion and biotransformation and does not demonstrate any significant drug interactions with other antiepileptic or antiretroviral medications.[66]

Main side effects: The most common side effects include dizziness, headache, diplopia, fatigue, vomiting, and blurred vision.[67]

Special points: EKG should be performed prior to administration to screen for possible cardiac conduction defects.

Cost / cost effectiveness: Expensive

Gabapentin

Standard dosage: The only route of administration is oral. The initial dose is 300 mg on day one with a titration to 900 mg in three divided doses on day three. It can subsequently be increased by 300 mg every three days to a target dose of between 900 mg to 3600 mg daily in three divided doses based on clinical response.[68]

Contraindications: Prior hypersensitivity reaction to gabapentin.

Main drug interactions: Gabapentin is not metabolized and is eliminated by renal excretion. [69] It does not demonstrate any significant drug interactions with other antiepileptic or antiviral medications.

Main side effects: The most common side effects include somnolence, dizziness, ataxia, fatigue, nystagmus, and tremor.

Special points: Gabapentin is almost entirely renally cleared thus in patients with documented renal disease it may require dosage adjustment for impaired creatinine clearance.

Cost / cost effectiveness: Moderate

Pregabalin

Standard dosage: The only route of administration is oral. The initial dose is 150 mg daily in two or three divided doses. It can be titrated weekly to a target dose of 150mg to 600 mg in two divided doses.

Contraindications: Prior hypersensitivity reaction to pregabalin or any of its components.

Main drug interactions: Pregabalin is minimally metabolized and is eliminated by renal excretion. It does not demonstrate any significant drug interactions with other anti-epileptic or antiviral medications.[70]

Main side effects: The most common side effects include dizziness, somnolence,, diplopia, tremor, dry mouth, and infection.

Special points: Pregabalin is almost entirely renally cleared thus in patients with documented renal disease it may require dosage adjustment for impaired creatinine clearance.

Cost / cost effectiveness: Expensive

Drug Resistant Epilepsy: When a patient has failed to achieve sustained seizure freedom with two or more trials of appropriately selected antiepileptic medications then they are deemed to have drug resistant epilepsy. In this situation, a clinician must consider alternative therapies to AEDs. HIV+ patients may readily be candidates for alternative therapies given that a significant number of the available AEDs may not be appropriate. Refractory seizures are associated with increased morbidity, neurocognitive impairment, and compliance with other medications. If an HIV+ is felt to have drug resistant epilepsy then these alternative therapies should be pursued:

Surgery

Given the predisposition to CNS injury from infection, HIV+ patients commonly have lesional epilepsy. This may be due to residual scar after an infection is successfully treated or lesions that similarly occur in the non-HIV population. If their HIV disease is adequately treated and they have medication resistant epilepsy, these patients are candidates for epilepsy surgery. Although the best surgical outcomes are in patients with mesial temporal sclerosis with anterior temporal lobectomy, any lesion seen on imaging with EEG correlate is a candidate for surgical resection.

Standard procedure—Prior to resective surgery, video/EEG monitoring (with scalp, and if needed, intracranial electrodes) is performed to localize the epileptic focus, and to confirm that it corresponds to the suspected lesion. Wada testing and brain mapping may be indicated to identify cortical areas to be spared during resection of the epileptic focus.

Contraindications—Contraindications to surgery include non-lesional epilepsy or a lesion whose removal would cause unacceptable neurological deficits such as within a language area. Additionally, if the hemisphere contralateral to a hemisphere with mesial temporal sclerosis is deemed not to have adequate memory compensation this is a contraindication to an anterior temporal lobectomy.

Complications—Complications include all the associated risks of surgery as well as the neurological deficits associated with removal of the lesion.

Special points—This option should be pursued at specialized epilepsy surgery centers.

Cost / cost effectiveness—Surgery has high initial costs. It becomes cost effective over an extended period of time if the patient obtains improved seizure control resulting in reduced medications and hospitalizations.[71–73]

Vagal Nerve Stimulator

Usage—Vagus nerve stimulation (VNS) was approved by the US FDA in 1997 as an adjunctive treatment for medically refractory epilepsy. It is considered for use in patients who are poor candidates for resection or those in whom resection has failed. On average, it reduces seizure frequency by 50% or more in approximately 50% of patients.[74] It may also allow patients to reduce the number of AEDs they are taking.

Special points—This is of potential benefit to HIV+ patients who may be more easily able to switch their ARV regimens when an AED with an unfavorable drug interaction is removed.

Cost / cost effectiveness—Initial costs are expensive related to device and implantation. VNS is cost effective if it reduces medications and seizure related hospitalizations.[75, 76]

Pediatric considerations

Ketogenic Diet—The ketogenic diet has been utilized for treatment in epilepsy since the 1920's. It involves restricting dietary intake to high fat and low carbohydrate foods to induce ketosis. The mechanism of action remains unclear though it has been speculated that ketone bodies contribute to hyperpolarization of neurons.[77] It is largely restricted for use to the pediatric population as ketosis is difficult to maintain for adults. An alternative to the ketogenic diet that has been explored in adults is a modified Atkins diet.[78]

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Figure 1. Algorithm for seizure treatment in HIV⁺ patient. Note: AED use for seizure management beyond acute seizure control (i.e. 1 week max) requires consideration of AED-ARV interactions in AED selection and management

Table 1

AED selection in HIV-positive patients

Medication	Indication	Formulation	Maintenance dose	Side effects	Drug interactions	Cost
Levetiracetam	Generalized or partial onset seizures	oral and IV	1000 – 3000 mg/day	Somnolence, asthenia, depression, irritability. Neuropsychiatric symptoms more likely in those with cognitive compromise.	Not significant	Moderate
Lacosamide	Partial onset seizures	oral and IV	200 – 400 mg/day	Dizziness, headache, diplopia, fatigue. Cardiac conduction abnormalities with IV load. Baseline ECG warranted before chronic use.	Not Significant	Expensive
Gabapentin	Partial onset seizures	oral	900 – 3600 mg/day	Somnolence, dizziness, ataxia, fatigue	Not significant	Moderate
Pregabalin	Partial onset seizures	oral	150 – 600 mg/day	Somnolence, dizziness, diplopia, tremor.	Not significant	Expensive
Valproic Acid	Generalized or partial onset seizures	oral and IV	750 – 3000 mg/day	Somnolence, ataxia, tremor, hyperamylasemia, pancreatitis, weight gain, hirsutism. Avoid in woman of childbearing age. Avoid if other hepatotoxic medications are in use.	Significant. Hepatic enzyme inhibition. Highly protein bound.	Inexpensive
Zonisamide	Partial onset seizures	oral	100 – 400 mg/day	Somnolence, dizziness, anorexia, headache Avoid in patients with history of renal calculi.	Moderately significant. Hepatic enzyme induction can increase its metabolism. Modestly protein bound.	Expensive