Table 2: Recommendations

	Commonly Used		Reasonable alternatives		Drugs to avoid
Partial onset (focal) seizures +/- secondarily generalized convulsions	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine	Topiramate Zonisamide Lacosamide (NF)	Felbamate* Gabapentin Phenobarbital Phenytoin Valproate Brivaracetam (NF)	Clobazam* (NF) Eslicarbazepine (NF) Perampanel (NF) Pregablin (NF) Rufinamide* (NF) Vigabatrin* (NF)	
Primary Generalized epilepsy (or unknown classification)	Ethosuximide (absence only) Lamotrigine Levetiracetam	Topiramate Valproate Zonisamide	Carbamazepine Clonazepam Oxcarbazepine Phenytoin	Clobazam* (NF) Felbamate* (NF) Perampanel (NF)	Gabapentin Pregabalin Tiagabine Vigabatrin
Elderly Patients with focal epilepsy	Lamotrigine Levetiracetam		Other drugs may be used if needed*		
Women of child bearing potential* please see Considerations in Women table below	Lamotrigine Levetiracetam Zonisamide		Carbamazepine Other drugs may be used if needed*		Valproate*

NF Non Formulary *Recommend consultation with epilepsy specialist

HOW TO USE TABLE 2: Formulary medications are listed first followed by non-formulary medications in alphabetical order. When selecting from multiple options in the table, consider individual patient characteristics and co-morbidities. Please refer to reference table for additional guidance. Providers may choose a drug from the reasonable alternative list or non-formulary list without necessarily having failed any or all formulary drugs in the commonly used column if the provider determines it is appropriate for the individual patient and submits an NFDR consult.

Table 3: Seizure Medication Considerations in Women

1. Women with epilepsy of childbearing age should be educated early in life, and choices reviewed annually.
2. Epilepsy treatment should be optimized BEFORE family planning since teratogenesis occurs during the first 4 weeks of pregnancy, before most women know they are pregnant.
3. Valproate can cause anovulatory cycles/amenorrhea, sexual dysfunction, and polycystic ovarian like syndrome

Hormonal Contraceptives

- 1 out of 4 pregnancies are unplanned due to contraception failure in women with epilepsy.
- Antiepileptic Drugs (AEDs) have potential drug interactions with hormonal contraceptives (HC) including combined oral/patches/emergent, vaginal rings and progesterone implants.
- AEDs that induce liver enzymes lead to fast metabolism of sex hormones and decreased contraceptive effectiveness

Decreased Effectiveness of HC (Enzyme Inducing AED)		No Effect on HC	
Carbamazepine	Phenytoin	Acetazolamide	Levetiracetam
Clobazam	Primidone	Clonazepam	Pregabalin
Felbamate	Rufinamide	Ethosuximide	Valproate/Divalproex
Oxcarbazepine	Topiramate (doses > 200 mg/day)	Gabapentin	Vigabatrin
Phenobarbital	Eslicarbazepine (not an enzyme inducer)	Lacosamide	Zonisamide
		Lamotrigine	

- Estrogen lowers lamotrigine levels. Adjust lamotrigine dosing accordingly with any start/stop of estrogen-containing therapies or pregnancy.
- Better emergency contraceptive options within 120 hours of unprotected sex include a single 3 mg dose of levonorgestrel OR placement of a copper IUD.

Teratogenicity

- AED teratogenicity is reinforced by polytherapy and/or folate deficiency.
- Valproate/Divalproex is the only AED definitively associated with significantly increased risks of major congenital malformations/autism spectrum disorders. If it cannot be avoided, doses of 500 mg/day or less should be used.
- Topiramate, phenytoin, carbamazepine, and phenobarbital have been associated with malformation at lower rates than Valproate/Divalproex, and appropriate counseling needs to be provided. Early reports suggest pregabalin may be associated with malformations, but the level of risk is not yet clear for women with epilepsy.
- Lamotrigine and levetiracetam carry the lowest risk of overall malformations.

Pregnancy

- Increased drug clearance is common during pregnancy, This fact is especially relevant with lamotrigine (often requires 3x doses divided every 6-8 hours)
- Frequent visits and AED levels are recommended to maintain seizure control during the entire pregnancy. Free and total AED levels are useful for older drugs that are highly protein-bound.
- Lamotrigine and levetiracetam levels may need to be monitored monthly, while other AEDs may be monitored each trimester and 1-2 weeks post-partum

Post-pregnancy

- Increased drug clearance during pregnancy gradually reverts to baseline over 2-4 weeks.
- AED doses should be reduced to prevent toxicity, but with a slightly higher target than pre-pregnancy dose to balance the increased sleep deprivation.

Folate Supplementation

- Folate supplementation is recommended for ALL women who may become pregnant at no less than 1 mg/day.
- Women prescribed valproate/divalproex or enzyme-inducing AED may warrant 2 mg/day.
- Women with prior pregnancy with neural tube malformation may warrant 4 mg/day.

Lactation

- Breastfeeding is generally promoted regardless of AED as the benefits outweigh known risks. Levels in milk do not necessarily correlate with any known clinical significance.
- Premature and term neonates exposed to benzodiazepines and barbiturates throughout pregnancy are at risk of withdrawal, especially if formula-fed. Neonates/infants may need to be monitored for sedation and apneas if breastfed.
- Lamotrigine present in breastmilk may predispose premature neonates to sedation due to immature hepatic function (glucuronidation).

Prepared by the VA Epilepsy Centers of Excellence Pharmacy Workgroup and the Women Veterans with Epilepsy workgroup. Design & Layout by Lesa Hall, Medical Illustrator, Durham VA Health Care System. (Prepared April 2014; **Revised February 2017**).

Epilepsy Centers of Excellence

DEPARTMENT OF VETERANS AFFAIRS

ECoE website: www.epilepsy.va.gov

The proposed recommendations made in this document are based on available medical evidence and suggestions made by the Epilepsy Centers of Excellence (ECoE) and the Pharmacy Benefits Management (PBM) Services, including input from subject matter experts as well as position statements, recommendations and guidelines from the International League Against Epilepsy (ILAE), the American Epilepsy Society (AES) and the American Academy of Neurology (AAN.) The content of this document will be dynamic and revised as new information becomes available. The purpose of the document is to assist practitioners in clinical decision-making and improve the quality of patient care. The clinician will be expected to use and interpret the final version of this guidance in the clinical context of the individual patient. These are general recommendations and suggestions, and should not supersede the clinical judgment of the treating provider. Providers may consult their local neurologist or regional ECoE for additional guidance through referral, e-consult, or SCAN ECHO if desired. (Prepared April 2014; Revised February 2017).

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Table 1: Antiepileptic Drugs (AEDs)

Drug (Class if scheduled) Formulations *Indicates non-formulary	Total daily dose FDA Recommended		Dosing Interval	Preferred in	Avoid in	Special Considerations (interactions, titration tips)	Potentially serious ADRs	Common SE
	Initial	Maintenance						
Brivaracetam Tablet*, Oral solution*, IV solution*	100 mg	100-200 mg	BID	Consider converting well-controlled patients from levetiracetam if intolerable psychiatric SE		Dosage adjustment required in hepatic impairment . May raise carbamazepine epoxide metabolite levels and phenytoin levels.	Bronchospasm, angioedema	Sedation, fatigue, dizziness, ataxia, nausea, vomiting
Carbamazepine Chewable tablet, Tablet, Extended release tablet and Liquid suspension	200 mg	400-1600 mg	TID or Q6h; BID (XR)	Bipolar, neuralgia	Cross-reaction allergic rash to phenytoin, phenobarb, oxcarb, lamotrigine, may worsen absence sz	Check HLA B*1502 in Asian to predict SJS or TEN. p450 inducer-Interacts with warfarin and many drugs. Potential teratogen. Levels of active epoxide metabolite are increased by valproate and brivaracetam.	Liver dysfunction, hyponatremia, Rash, agranulocytosis, Stevens Johnson Syndrome (SJS)	Sedation, dizziness, diplopia/blurry vision, headache, GI upset, sun sensitivity
Clobazam (Schedule IV) Tablet*	10 mg	20-40 mg	QD-BID		Abuse potential,use with etoh and other benzos increases risk of overdose/death	Ideal if dose-limiting SE with other effective chronic benzodiazepines	Rash (SJS), anemia, LFT elevation	Lethargy, sedation, ataxia
Clonazepam (Schedule IV) Tablet	0.5 mg	2-8 mg	TID	Myoclonic seizures and subcortical myoclonus	Elderly, abuse potential, use with etoh and other benzos increases risk of overdose/death	Withdrawal from clonazepam may induce status epilepticus or exacerbation of seizures. Psychiatric withdrawal also may occur, manifested as insomnia, anxiety, psychosis, and tremor.	Nausea, vomiting, aplastic anemia, idiosyncratic rash, cardiovascular or respiratory depression	Sedation, ataxia, hyperactivity, restlessness, irritability, depression
Eslicarbazepine Tablet*	400 mg	800-1600 mg	QD			Active metabolite of oxcarbazepine. modest inducer of CYP3A4, weak inhibitor CYP2C19	Eosinophilia and systemic symptoms (DRESS) reported, hyponatremia	Dizziness, sedation, nausea, headache, diplopia
Ethosuximide Capsule*, liquid solution*	15 mg/kg	15-40 mg/kg	BID-QID	Absence seizures only	Worsens generalized tonic clonic and other sz types; allergic to succinimides	Primarily for children/teens with absence epilepsy	Idiosyncratic rash, hallucinations, depression	GI upset, anorexia, diarrhea, sleep disturbance, sedation, hyperactivity
Felbamate Tablet, liquid suspension	1200 mg	3600 mg	TID, QID	Only for severe refractory epilepsy	Comorbid autoimmune disorders	Consider checking ANA prior to initiation; consult with epilepsy center due to high risk	Liver failure, irreversible fatal aplastic anemia	Insomnia, headache, ataxia, weight loss, anorexia
Fosphenytoin Injectable solution	15-20 mg PE/kg load	4mg-6mg/kg	QD, BID, TID	IV only --preferred over IV phenytoin	Cardiovascular problems	P450 inducer (warfarin interaction); perineal paresthesia with loading doses (side effect)	Rash, liver dysfunction	Confusion, slurred speech, diplopia, ataxia, sedation
Gabapentin Tablet, Capsule	300 mg	900-4800 mg	TID, QID	Chronic pain, neuropathy		Renal excretion--minimal interactions, absorption impaired for doses over 1200 mg	Anaphylaxis, angioedema. Potential for abuse when taken with opiates	Sedation, dizziness, ataxia, weight gain
Lacosamide (V) Tablet*, injectable solution	100mg if add-on; 200 mg if monotherapy	200-400 mg	BID		3rd degree heart block	Renal excretion--minimal interactions	AV conduction abnormalities, DRESS	Ataxia, dizziness, diplopia, headache, nausea, vomiting
Lamotrigine Tablet; chew tablet*; ODT*, XR tablet*	12.5-50 mg	200-600mg	BID, QD (XR)	MDD, bipolar	May exacerbate tremor, myoclonus	Slow titration to avoid rash--rate varies if on concurrent enzyme inducers or inhibitors; levels lowered by inducers; levels raised by inhibitors and valproate	Rash (SJS/TEN) DRESS	Dizziness, tremor, ataxia, headache, vivid dreams, insomnia
Levetiracetam Tablet, XR tablet*, injectable solution	250-500 mg	1000-3000 mg	BID, QD (XR)	Dialysis/renal failure, polypharmacy	May worsen MDD, PTSD, anxiety, thought disorders	Renal excretion--minimal interactions	Rash	Sedation, irritability, agitation, anxiety, depression
Oxcarbazepine Tablet, tablet ER*, liquid suspension*	600 mg	600-2400 mg	BID or QD (XR)	Bipolar		Check HLA B*1502 in Asian to predict SJS or TEN. modest inducers of CYP3A4, and can weak inhibitor CYP2C19	Rash, hyponatremia, SJS TENS	Sedation, vertigo, ataxia, diplopia
Perampanel (III) Tablet*	2 mg, or 4 mg if on concurrent enzyme-inducer	8-12 mg	QD		Active psychosis or unstable recurrent affective disorders with significant hostility or aggressive behavior	Slower titration to a lower maintenance dose may improve tolerability, , Metabolized via CYP3A4	Serious psychiatric and behavior reactions, falls	Dizziness, ataxia, sedation, irritability, and weight gain.
Phenobarbital (III) Tablet, Elixir*; injectable solution*	1-4 mg/kg	60-200 mg	QD, BID		Use with etoh and benzos increases risk of overdose/death	Strong CYP3A4 inducer (may reduce warfarin efficacy); very slow taper recommended after prolonged use	Rash (SJS/TEN), liver dysfunction, teratogen	Behavioral changes, tolerance, dependence, altered sleep cycles, sedation, confusion
Phenytoin Extended release capsule; Liquid suspension, Injectable, Chewable tablet	Oral load 15-20 mg/kg in divided doses Q6 hours	300-600 mg	QD, TID		Diabetes, can increase blood sugar levels, absence seizures	Use fosphenytoin for IV infusion. Initial inhibition of CYP2C9 can increase S-warfarin, followed by induction of CYP2C9 and 2C19, which can lower S & R warfarin, monitor free phenytoin in pregnancy, elderly, or low albumin, divide doses of greater than 400 mg	Gingival hypertrophy, rash (SJS/TEN), liver dysfunction, purple glove and cardiovascular effects with IV infusion, teratogen, lupus like reactions, aplastic anemia	Confusion, slurred speech, diplopia, ataxia, sedation. Long term use may be associated with cerebellar atrophy or peripheral neuropathy
Pregabalin (V) Capsule*	100-150 mg	150-600 mg	BID, TID	Neuropathy, chronic pain	Pre-existing cognition issues	Renal excretion, Metabolized via CYP3A4	Possible teratogen. Potential for abuse when taken with opiates.	Somnolence, dizziness, ataxia, leg edema, weight gain
Primidone Tablet	100-125 mg	750-2000mg	TID, QID	Essential tremor		P450 inducer (warfarin interaction)	Megaloblastic anemia, rash, liver dysfxn, teratogen	Sedation, slurred speech, diplopia, ataxia, impotence
Rufinamide Tablet*	400-800 mg	3200 mg	BID		Familial short QT syndrome	Adjunctive therapy, do not use in severe liver impairment, modestly induces CYP 3A4	Nausea, vomiting, status epilepticus	Sedation, dizziness, headache, ataxia
Topiramate Sprinkle capsule*; Tablet; XR tablet*	25 mg/ increase by 25-50 mg every 2 weeks	100-400 mg	BID	Migraine, chronic pain, obese	Pre-existing cognitive issues, metabolic acidosis with concomittant metformin use	Moderate p450 inducer; slow titration to avoid cognitive SE, dose adjust in CrCl < 70 ml/min	Weight loss, renal stones, acute closure in narrow angle glaucoma, hyperthermia and oligohidrosis, metabolic acidosis, teratogen	Fatigue, nervousness, difficulty concentrating, confusion, language problems, anxiety, tremor, paresthesias
Valproate Delayed release sprinkle capsule*, Delayed release tablet; SA 24 hr tablet, Immediate release capsule; injectable solution	500-1000 mg	1000-3500 mg, max 60 mg/kg/day ER tabs have reduced bioavail—not equivalent dosing	BID (ER), TID DR), Q6h (caps)	Bipolar, Migraine	Women of childbearing potential, mitochondrial POLG mutations, urea cycle disorders	XR tabs should be dosed BID in epilepsy, CYP2C19 inhibitor (warfarin interaction), care when concurrent use of lamotrigine due to UGT inhibition	Thrombocytopenia, weight gain, liver dysfunction (esp. in mitochonfrial Disease), teratogen, SIADH, hyperammonemia, pancreatitis, DRESS	Tremor, dizziness, hair loss, sedation
Vigabatrin Tablet*; Powder packet*	1000mg increase by 500mg/week	2000-3000 mg	BID			Requires eye exams q3months, SABRIL REMS program registration	Progressive and permanent bilateral peripheral visual constriction	Sedation, fatigue, weight gain, blurred vision
Zonisamide Capsule	100 mg	100-600 mg	QD	Tremor	Sulfa allergy, pre-existing cognitive issues	Dose efficacy may plateau at 400 mg	Weight loss, renal stones, Rash, metabolic acidosis, DRESS	Sedation, ataxia, confusion, depression, difficulty concentrating, language difficulties
Rescue medications--consultation with neurology and/or epilepsy specialist is recommended for prescribing rescue medications								
Diazepam (Schedule IV) Rectal gel**	0.2 mg/kg	A second dose can be given 4-12 hrs after the first dose if needed				It is recommended that diazepam rectal gel be used to treat no more than 5 episodes per month and no more than 1 episode every 5 days. See Note**		
Lorazepam (Schedule IV) Tablet	2mg	Do not exceed 4mg				Oral tablet can be used sublingual or buccal		
**Strongly recommend patient education by prescribing provider and/or pharmacist prior to dispensing new Rx by mail or window								