Drug Class Review
Newer Anticonvulsant Agents

28:12:92 Anticonvulsants, Other

Brivaracetam (Briviact®)

Clobazam (Onfi®)

Eslicarbazepine (Aptiom®)

Ezogabine (Potiga®)

Felbamate (Felbatol®, others)

Gabapentin (Neurontin®)

Lacosamide (Vimpat®, others)

Lamotrigine (Lamictal®, others)

Levetiracetam (Keppra®, others)

Oxcarbazepine (Trileptal®, Oxtellar XR®, others)

Perampanel (Fycompa®)

Pregabalin (Lyrica ®)

Rufinamide (Banzel®)

Tiagabine (Gabitril®)

Topiramate (Topamax ®, Trokendi XR, Qudenxi XR, others)

Vigabatrin (Sabril®)

Zonisamide (Zonergan ®, others)

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Introduction

The history of seizures dates back to the Babylonians. Ancient peoples have considered seizures indicative of demonic possession; hence, the word "seizure" comes from the Latin, sacire "to take possession of". Greeks believed it to be a curse of the gods and referred to it as the Sacred Disease.[1,2] The first medications used for seizures included bromide in the 19th century and phenobarbital as the first synthetic organic compound in the early 20th century.[3] The medications found useful to control seizures are diverse in mechanism of action and pharmacologic class, including hydantoins (phenytoin, fosphenytoin, ethotoin), anti-seizure barbiturates (phenobarbital, pentobarbital), iminostilbenes (carbamazepine), succinimides (ethosuximide), valproic acid and derivatives, benzodiazepines (clonazepam, clorazepate, midazolam, diazepam, lorazepam, clobazam) and others (acetazolamide, brivaracetam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, magnesium sulfate, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin and zonisamide). Newer agents were developed in an attempt to minimize adverse effects, drug interactions, safety concerns and offer an improved risk:benefit ratio.[4] Some of these agents are new chemical entities and others are analogues of currently available medications. Eslicarbazepine and oxcarbazepine are carbamazepine derivatives, pregabalin is a gabapentin derivative and brivaracetam is a levetiracetam derivative.[5]

This report will focus on the comparative clinical efficacy and safety evidence of the following "newer" agents, brivaracetam, clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin and zonisamide for use in seizure disorders and epilepsies. One combination agent (topiramate/phentermine, Qsymia®) used exclusively for weight loss is not included in this review.

All 17 agents are available in oral tablet or capsule formulations.[6-8] Ten of the seventeen agents are available for administration as oral liquid formulations: clobazam, felbamate, gabapentin, oxcarbazepine (suspension), brivaracetam, clobazam, gabapentin lacosamide, levetiracetam, pregabalin, rufinamide (solution) and vigabatrin (powder for solution). Topiramate is available as both immediate- and extended-release oral sprinkle formulations. Three agents are available for injection: brivaracetam, lacosamide and levetiracetam (also available premixed in sodium chloride). Lamotrigine is available in chewable/dispersible tablets, orally disintegrating tablets and titration kits. Lamotrigine and gabapentin are available as starter packs. Five extended-release oral dosage form products are available: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. These medications are each FDA approved for use in at least one seizure disorder, including infantile spasms, Lennox-Gastaut syndrome, myoclonic seizures, partial-onset seizures (mono/adjunct therapy), partial-onset seizures with complex symptomatology, refractory complex partial seizures and tonic-clonic seizures (mono/adjunct therapy). Some of the agents have additional, non-seizure disorder indications including bipolar disorder (lamotrigine), fibromyalgia (pregabalin), migraine prophylaxis (topiramate), neuropathic pain (pregabalin) and postherpetic neuralgia (gabapentin and pregabalin). Three of the agents are DEA Schedule V medications (lacosamide, ezogabine, pregabalin). A comparison of the newer antiepileptic agents is found in Table 1 and 2.

Table 1. Comparison of Newer Anticonvulsant Agents[7,8 3,6,8-30]

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
Brivaracetam **(Briviact®)**	Oral Tablets: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg Solution; oral: 10 mg/mL Injection, solution: 10 mg/mL	Partial-onset seizures: Adjunctive therapy in the treatment of partial-onset seizures in adults and adolescents 16 years and older with epilepsy	Partial-onset Seizures: 50-200 mg daily, divided twice a day	16 years and older: • 50-200 mg daily, divided twice a day	No
Clobazam **(Onfi®)**	Oral Suspension: 2.5 mg/mL Oral Tablet: 10 mg, 20 mg	Lennox-Gastaut syndrome: Adjunctive treatment in patients ≥2 years	>30 kg: • Initial dosage: 5 mg twice daily for 7 days then increase to 10 mg twice daily and after 14 days to 20 mg twice daily. ≤ 30 kg: • Initial dosage: 2.5 mg twice daily for 7 days then increase to 5 mg twice daily and after 14 days to 10 mg twice daily.	≤30 kg: • Initial dosage: 5 mg once daily, increase after ≥ 1 week to 5 mg twice daily and then to 10 mg twice daily. >30 kg: • Initial dosage: 5 mg twice daily for ≥1 week, then increase to 10 mg twice daily and 20 mg twice daily at intervals of at least 1 week.	No
Eslicarbazepine Acetate **(Aptiom®)**	Oral Tablet: 200 mg, 400 mg, 600 mg, 800 mg	Partial-onset seizures: Monotherapy or adjunctive therapy in the treatment of partial-onset seizures	Partial-onset seizures: Monotherapy 800-1600 mg once daily • Adjunctive therapy 800-1600 mg once daily not recommended with oxcarbazine • Higher doses may be required with enzyme inducing antiepileptic drugs (phenobarbital, phenytoin, primidone) • Dose adjustment of either carbamazepine or eslicarbazepine may be required when used together	Not established	No

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
Ezogabine (Potiga®) **Schedule V**	Oral Tablet: 50 mg, 200 mg, 300 mg, 400 mg	Partial-onset seizures: As adjunctive treatment for partial-onset seizures in patients 18 years and older who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity	Partial-onset seizures: 200-400 mg three times daily; Maximum 1200 mg/day	Not established	No
Felbamate (Felbatol®)	Oral Suspension:600 mg/5 ML Oral Tablet: 400 mg, 600 mg Felbatol Oral Suspension: 600 mg/5 ML Felbatol Oral Tablet: 400 mg, 600 mg	Not indicated as a first-line antiepileptic treatment; for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use. If these criteria are met and the patient has been fully advised of the risk and has provided written, informed consent, felbamate can be considered for monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.	Partial seizure, With and without generalization Monotherapy: Not systematically studied • Initial dosage: 1,200 mg/day in divided doses 3 or 4 times daily. Conversion to Monotherapy: • Initial dosage of 1200 mg daily in 3 to 4 divided doses with a reduction of concomitant anticonvulsant dosage by one-third at the initiation of therapy. At week 2, increase felbamate to 2400 mg/day and reduce the other anticonvulsant by an additional one-third. At week 3 felbamate may be increased to 3600 mg/day. Continue to reduce the dosage of the other-anticonvulsant as clinically indicated Adjunctive Therapy • Initiate therapy with 1200 mg/day orally in 3 to 4 divided doses.	Partial seizure, With and without generalization The majority of patients 14 years and older received 3,600 mg/day in clinical trials evaluating its use as both monotherapy and adjunctive therapy. Lennox-Gastaut syndrome in children 2–14 years of age: • 15 mg/kg daily administered in 3 or 4 divided doses. Dosage may be increased by 15 mg/kg daily at weekly intervals to a maximum dosage of 45 mg/kg daily administered in 3 or 4 divided doses. With the addition of felbamate to an anticonvulsant regimen the dosage of other anticonvulsants must be decreased by at least 20T	Yes

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
			Decrease the dose of concomitant anticonvulsants by 20% with further dosage reductions as needed to minimize side effects due to drug interactions. Then weekly felbamate dosage increases of 1200 mg/day up to 3600 mg/day	and then as necessary with further felbamate dosage increases.	
Gabapentin **(Fanatrex FusePaq®, Gralise®, Horizant®, Neurontin®, others)**	Oral Tablet: 600 mg, 800 mg Oral Capsule: 100 mg, 300 mg, 400 mg Oral Solution: 250 mg/5mL Fanatrex FusePaq: Oral Suspension: 25 mg/mL Gralise: Oral Tablet: 300 mg, 600 mg Gralise Starter Pack: containing 78 tablets: 9 x 300 mg tablets and 69 x 600 mg tablets Horizant: Oral Tablet, Extended-Release: 300 mg, 600 mg Neurontin: Oral Capsule: 100 mg, 300 mg 400 mg Neurontin: Oral Tablet: 600 mg, 800 mg Neurontin: Oral Solution: 250 mg/5mL	Postherpetic neuralgia: Management of postherpetic neuralgia (PHN) in adults. Seizures, partial onset (excluding Gralise): As adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and pediatric patients 3 years and older with epilepsy Off-label uses: Cough, chronic (refractory); diabetic neuropathy, episodic migraine prevention (adults); fibromyalgia; hiccups, hot flashes, prevention of spinal opioid-related pruritus; pruritus (brachioradial); pruritus (uremic); restless legs syndrome	Postherpetic neuralgia (except Gralise): • 1800-3600 mg/day in divided doses. • Gralise: Titrated to 1800 mg once daily with evening meal Seizures, partial onset (excluding Gralise): • Usual dosage: 900 to 1,800 mg/day in divided doses (3 times a day). Doses of up to 2,400 mg/day have been tolerated in long-term clinical studies; up to 3,600 mg/day has been tolerated in short-term studies.	Seizures, partial onset: Age > 12 years: • 900-1800 mg in 3 divided doses. Doses of up to 2,400 mg/day have been tolerated in long-term clinical studies; up to 3,600 mg/day has been tolerated in short-term studies. Ages 5-11 years: • 25-35 mg/kg/day in 3 divided doses (up to 50 mg/kg/day). Ages: 3-4 years: • 40 mg/kg/day in 3 divided doses (up to 50 mg/kg/day) Age < 2 years: Not established	Yes Except Fanatrex FusePaq

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
Lacosamide (Vimpat®) **Schedule V**	Oral Tablets: 50 mg, 100 mg, 150 mg, 200 mg Oral Solution: 10 mg/mL Intravenous Solution: 200 mg/20mL	Partial-onset seizures: As monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients 17 years and older with epilepsy	Partial-onset seizures, monotherapy: • 150-200 mg twice a day. • Partial-onset seizures, adjunctive therapy: • 200 mg twice a day	Not established	No

Lamotrigine (Lamictal®, Lamictal ODT®, Lamictal Starter Kit®, Lamictal XR®, Lamictal XR Patient Titration Kit® others)	Oral Tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg Oral Tablets, extended-release: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg Oral Tablets, chewable, dispersible: 2 mg, 5 mg, 25 mg Oral Tablets, orally disintegrating: 25 mg, 50 mg, 100 mg, 200 mg Lamictal 2 mg, 5 mg, and 25 mg chewable/dispersible tablets may contain saccharin. Lamictal ODT (GlaxoSmithKline) 25 mg, 50 mg, 100 mg, and 200 mg ** Lamictal Orally Disintegrating Tablets (ODT) and Lamictal ODT Patient Titration Kits may contain mannitol and sucralose. **See table footnotes for Lamictal Starter and Titration Kit(s) information	Bipolar I disorder (maintenance): Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. **Immediate release products only Epilepsy: Adjunctive therapy (immediate release, IR): Adjunctive therapy for partial-onset seizures, generalized seizures of Lennox-Gastaut syndrome (LGS), and primary generalized tonic-clonic seizures in adults and children 2 years and older. Adjunctive therapy (extended-release, ER): Primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization in patients 13 years and older. Monotherapy: IR: Conversion to monotherapy in adults (16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED). ER: Conversion to monotherapy in patients 13 years and older with partial-onset seizures who	Dosing is highly dependent upon concomitant medications, indication and patient age. **Dosage adjustment mandatory with hepatic enzyme inducers (e.g. carbamazepine, phenytoin, phenobarbital, primodone) or inhibitors of glucuronidation (e.g. valproic acid) Bipolar Disorder (maintenance) Target Dose: 200 mg/day No interacting drugs: 25 mg immediate-release (IR) product daily x 2 weeks > 50 mg daily x 2 weeks, then double weekly to maintenance dose of 200 mg/day Receiving carbamazepine or other hepatic enzyme inducer: 50 mg IR daily x 2 weeks > 100 mg in 2 divided doses x 2 weeks, then double weekly to maintenance dose of 400 mg/day in divided doses. Receiving valproic acid or divalproex sodium: 25 mg every other day x 2 weeks > 25 mg daily x 2 weeks, then double weekly to maintenance dose of 100 mg/day Lennox-Gastaut syndrome (LGS), partial and partial-generalized tonic-clonic seizures: Based on concurrent medications.	Bipolar disorder (maintenance): Target Dose: 200 mg/day Adjunct therapy in LGS, partial and partial-generalized tonic-clonic seizures: Age ≥ 2 to 12 years (13 years for extended release product): dosage based on concurrent medications **Maximum concomitant immediate-release dose: • Taking valproate: 200 mg/day • Taking carbamazepine, phenobarbital, phenytoin, or primidone (not valproate): 400 mg/day • Not taking carbamazepine, phenobarbital, phenytoin, primidone, or valproate: 300 mg/day	Yes

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
		are receiving treatment with a single AED. Off-label uses: Bipolar depression, depression, obesity, rectal administration, pediatric absence seizures, juvenile myoclonic epilepsy, temporal lobe seizures. Unsupported Uses: Episodic migraine prevention, restless legs syndrome.	**Adding additional medication therapy to stable lamotrigine regimen: Reduce lamotrigine dose 50% when valproic acid is added. Double lamotrigine dose over 3 weeks when carbamazepine or other hepatic enzyme inducer is added.		

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
Levetiracetam **(Keppra®, Keppra XR®, Spritam®, others)**	Oral Tablets, Extended Release 24 hour: 500 mg, 750 mg Oral Tablets: 250 mg, 500 mg, 750 mg, 1000 mg Oral Solution: 100 mg/mL, 500 mg/mL Intravenous Solution: 500 mg/5mL Levetiracetam in NaCl: 500 mg/100 mL, 1000 mg/100 mL, 1500 mg/100 mL	Myoclonic seizures: Immediate release: Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years and older with juvenile myoclonic epilepsy. Partial-onset seizures: Immediate release: Adjunctive therapy in the treatment of partial-onset seizures in adults and children 1 month and older (Keppra) or 4 years and older and more than 20 kg (Spritam) with epilepsy. Extended release: Adjunctive therapy in the treatment of partial-onset seizures in adults and adolescents 12 years and older with epilepsy. Primary generalized tonic-clonic seizures: Immediate release: Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years and older with idiopathic generalized epilepsy.	Myoclonic seizure; Adjunct: 500 mg twice a day (IV or oral), increase by 1000 mg/day every 2 weeks to target 3000 mg/day Partial seizure, Monotherapy in newly diagnosed or untreated epilepsy: 500 mg daily x 2 weeks, increase to 500 mg twice daily and over 2 weeks, up to 3000 mg/day in 2 divided doses <u>Partial seizure; Adjunct:</u> Immediate release products; 500 mg twice a day (IV or oral), increase by 1000 mg every 2 weeks (max 3000 mg/day) Extended-release tablets: 1000 mg once daily, increase by 1000 mg/day every 2 weeks to max 3000 mg/day Tonic-clonic seizure, Primary generalized; Adjunct: 500 mg (IV or oral) twice daily, increase by 1000 mg/day every 2 weeks to max 3000 mg/day		Yes Except Premix IV
Oxcarbazepine **(Trileptal®, Oxtellar XR®, others)**	Oral Suspension: 300 mg/5 ML Oral Tablet: 150 mg, 300 mg, 600 mg	Partial Seizures: Monotherapy and Adjunct Therapy Immediate release: Monotherapy or adjunctive therapy in adults; monotherapy in children 4 years and older;	Partial Seizures, Monotherapy: 300 mg twice daily, increasing by 300 mg every 3 days to target 1200-2400 mg. Conversion to Monotherapy:	Partial seizure, Monotherapy: 4 to 16 years: • 8-10 mg/kg/day in 2 divided doses, increase by 5mg/kg/day every 3 days, to target.	No

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
	Oxtellar XR, Oral Tablet, Extended Release: 150 mg, 300 mg, 600 mg Trileptal Oral Suspension: 300 mg/5 ML Trileptal Oral Tablet: 150 mg, 300 mg, 600 mg	adjunctive therapy in children ≥ 2 years. Extended release: Adjunctive therapy in adults and children ≥ 6 years. Off-label uses: Idiopathic muscle cramps, neuropathic pain, Unsupported uses: Migraine prophylaxis, bipolar disorder	300 mg twice daily, increasing by 600mg/day weekly to target dose over 2-4 weeks of 2400 mg/day, while tapering concomitant medication(s) Partial seizure; Adjunct: Immediate-release tablets or suspension: 300 mg twice daily, increase by 600 mg/day weekly to target 1200 mg/day. Extended-release tablets: 600 mg daily for 1 week, increase by 600 mg/day weekly to target 1200-2400 mg/day. Avoid use with HLA B*1502 gene	Conversion to Monotherapy 4 to 16 years: • 8-10 mg/kg/day in 2 divided doses, increase by up to 10 mg/kg/day weekly while tapering concomitant medication(s). Usual Partial seizure; Adjunct: Extended-release Tablet: 6 to 17 years old: • 8 to 10 mg/kg/day (max. 600 mg), increase by 8-10 mg/kg/day to target Immediate-release tab/susp 4 to 16 years old: • 8 to 10 mg/kg/day in 2 divided doses (max 600 mg/day), increase over 2 weeks to target. 2 to < 4 years old: • 8-10 mg/kg/day in 2 divided dose (max 600 mg/day) to target dose over 2 to 4 weeks (max 60 mg/kg/day) **Maintenance Doses based upon body weight **Extended-release tablets are not approved at age < 6 years.	

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
Perampanel (Fycompa®)	Oral Tablet 2 mg, 4 mg, 6 mg 8 mg, 12 mg	Partial-onset seizures: Adjunctive therapy for partial-onset seizures +/- generalization in adults and children ≥ 12 years of age Primary generalized tonic-clonic seizures: Adjunctive therapy for primary generalized tonic-clonic seizures in adults and children ≥12 years of age	Partial seizure, Adjunct: Not receiving concomitant enzyme-inducing antiepileptic drugs Initial: 2 mg daily at bedtime. Dosage increases of 2mg/day at > 7 day intervals as tolerated. Maintenance dose: 8 to 12 mg daily at bedtime (range 4-12 mg with more adverse events at 12mg dose) Receiving concomitant enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, oxcarbazepine) Initial: 4 mg daily at bedtime. Dose increases of 2mg/day at > 7 day intervals as tolerated. Maintenance dose not established (clinical trials used up to 12 mg daily) Primary generalized tonic-clonic seizures, Adjunct: Not receiving concomitant enzyme-inducing antiepileptic drugs Initial: 2 mg once daily at bedtime; may increase dose by 2 mg/day at > 7 day intervals as tolerated. Maintenance dose: 8 mg daily at bedtime. Max: 12mg/daily Receiving concomitant enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, oxcarbazepine)	Partial seizure, Adjunct: Refer to Adult Dosing Primary generalized tonic-clonic seizures, adjunct: Refer to adult dosing	No

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
			Initial: 4 mg daily at bedtime; may increase dose by 2 mg/ at ≥ 7 day intervals as tolerated. Maintenance dose not been established (clinical trials used up to 12 mg daily).		
Pregabalin (Lyrica®) **Schedule V**	Oral Capsule: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg Oral Solution: 20 mg/mL	Fibromyalgia: Neuropathic pain associated with diabetic peripheral neuropathy Neuropathic pain associated with spinal cord injury Partial-onset seizures, adjunctive therapy (adults) Postherpetic neuralgia Off-label uses: Episodic migraine prophylaxis;, hot flashes	Fibromyalgia: Initial dose 75 mg twice daily; maintenance: 300-450 mg/day Neuropathic pain associated with diabetic peripheral neuropathy: Initial dose: 50 mg three times daily; maintenance dose: 300 mg/day Neuropathic pain associated with spinal cord injury: Initial dose: 75 mg twice daily maintenance dose: 600 mg/day Partial-onset seizure, Adjunct: Initial dose: 150 mg daily in divided doses; maintenance dose: 150-600 mg/day in divided doses Postherpetic neuralgia: Initial dose: 150 mg daily in divided doses; maintenance: 150- 300 mg/day in divided doses; max dose 600 mg/day	Not established	No

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
Rufinamide (Banzel®)	Oral Tablets: 200 mg, 400 mg Oral Solution: 40 mg/mL	Lennox-Gastaut syndrome: Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in adults and pediatric patients 1 year and older.	Lennox-Gastaut syndrome, Adjunct: 400 to 800 mg/day in 2 divided doses; increase 400 to 800 mg/day every other day (max 3200 mg/day) **Administer with food	Lennon-Gastaut syndrome, Adjunct: Age 1 to 16 years: • 10 mg/kg/day in 2 divided doses, increase by 10 mg/kg every other day; target 45 mg/kg/day (max 3200 mg/day) Age ≥ 17 years: • 400 to 800 mg/day in 2 divided doses, increase by 400 to 800 mg/day (max 3200 mg/day) **Administer with food	No
Tiagabine (Gabitril®)	Oral Tablets: 2 mg, 4 mg, 12 mg 16 mg	Partial seizures: Adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures.	Adults take enzyme-inducing antiepileptic's: Initial: 4 mg orally once daily (no loading dose); Maintenance: 32 to 56 mg/day in 2 to 4 divided doses; max dose 56 mg/day **When used concomitantly with non-enzyme-inducing antiepileptic's use lower doses and slower titration	Children age 12-18 years taking concomitant enzyme-inducing antiepileptic's: • Initial: 4 mg orally once daily (no loading dose); Maintenance: Titrated to response; Maximum dose: 32 mg/day Children age 12-18 years NOT taking concomitant enzyme-inducing antiepileptic agents: Initial: • Begin with lower doses and titrate more slowly	Yes some strengths
Topiramate	Oral Tablet: 25 mg, 50 mg, 100 mg, 200 mg	Epilepsy:	Migraine (prophylaxis) Topamax:	Migraine (prophylaxis); > 12 years: Refer to adult dosing	Yes

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
(Qudexy XR®, Topamax®, Topamax Sprinkle®, Topiragen®, Trokendi XR®, others)	Oral Tablets, Extended Release: 100 mg, 200 mg, 300 mg Oral Capsule, Extended-Release 24 hours: 25 mg, 50 mg, 100 mg, 200 mg Oral Capsule, Sprinkle: 15 mg, 25 mg Oral Capsule, Extended Release, Sprinkle: 25 mg, 50 mg, 100 mg 150 mg, 200 mg Topamax Oral Tablet: 25 mg, 50 mg, 100 mg, 200 mg Topamax Sprinkle: 15 mg, 25 mg Trokendi XR Capsule ER, 24 hours: 25 mg, 50 mg, 100 mg, 200 mg Qudexy XR Capsule ER 24 Hour Sprinkle: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg	Monotherapy: As initial monotherapy in patients 2 years and older (immediate release and Qudexy XR) or 10 years and older (Trokendi XR) with partial-onset or primary generalized tonic-clonic seizures Adjunctive therapy: As adjunctive therapy in patients 2 years and older (immediate release and Qudexy XR only) or 6 years and older (Trokendi XR only) with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome Migraine (immediate release only): Prophylaxis of migraine headache in adults and adolescents 12 years and older.	Initial dose 25 mg in the evening. Maintenance dose of 50 mg twice daily Lennox-Gastaut syndrome (adjunct) Topamax: Initial dose 25-50 mg/day. Maintenance dose is 200-400 mg/day in 2 divided doses. Qudexy XR and Trokendi XR: Initial dose is 25-50 mg daily. Maintenance dose is 200-400 mg/day Partial seizure (monotherapy) Topamax: Initial dose 25 mg twice daily. Maintenance dose of 200 mg twice daily (max dose) Qudexy XR and Trokendi XR: Initial dose is 50 mg daily. Maintenance dose is 400 mg once daily Partial seizure, Adjunct Topamax: Initial 25-50 mg daily. Maintenance dose 200-400 mg/day in 2 divided doses. Qudexy XR and Trokendi XR: Initial dose is 25-50 mg daily. Maintenance dose is 200-400 mg/day Tonic-clonic seizure, primary generalized (adjunct) Topamax:	Partial-onset and generalized tonic-clonic seizure (monotherapy) age 2 to <10 IR formulations: • 25mg bedtime, increase after one week to twice daily dosing and then to target weight based dose twice daily ER (Qudexy XR): • 25 mg bedtime for one week and increase to 50 mg at bedtime and then to target weight-based dosing once daily. Age ≥ 10 years use adult dosing Lennox-Gastaut syndrome, partial-onset and generalized tonic-clonic seizures (adjunct): Topamax, other IR formulation Age 2-16 years: • Initial dose 1-3 mg/kg/day. Maintenance dose is 5-9 mg/kg/day in 2 divided doses. Qudexy XR Age 2 to < 6 years: • Initial dose 1-3 mg/kg/day in the evening. Maintenance dose is 5-9 mg/kg/day once daily.	Not Trokendi XR

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
			Initial dose is 25-50 mg daily. Maintenance dose is 400 mg/day in 2 divided doses Qudexy XR and Trokendi XR: Initial dose is 25-50 mg daily. Maintenance dose is 400 mg/day in 2 divided doses. Tonic-clonic seizure, primary generalized (monotherapy) Topamax: Initial dose is 25 mg twice daily. Maintenance dose is 200 mg twice daily. Qudexy XR and Trokendi XR: Initial dose is 50 mg daily. Maintenance dose is 400 mg daily.	Qudexy XR and Trokendi XR Age > 6 to 16 years: • Initial dose 1-3 mg/kg/day in the evening. Maintenance dose is 5-9 mg/kg/day once daily Age >16 years: Use adult dosing **Trokendi XR and Qudexy XR are not bioequivalent or interchangeable with each other or other topiramate products	
Vigabatrin (Sabril®)	Oral Tablet: 500 mg Oral Packet: 500 mg	Infantile spasms: As monotherapy for pediatric patients 1 month to 2 years of age with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss. Refractory complex partial seizures: As adjunctive therapy for adults and pediatric patients 10 years and older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the	Refractory Complex Partial Seizures: 1000 mg/day in 2 divided doses, increasing by 500 mg weekly to usual effective dose of 3000 mg/day	Infantile Spasms, age 1 month to 2 years: • 50 mg/kg/day in 2 divided doses, increasing by 25-50 mg/kg/day every 3 days; Maximum dose 150 mg/kg/day	No

	Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic Available
		potential benefits outweigh the risk of vision loss.			
Zonisamide **(Zonegran®, others)**	Oral Capsule: 25 mg, 50 mg, 100 mg	Partial seizures: Adjunct treatment of partial seizures in adolescents older than 16 years and adults with epilepsy.	Partial Seizures (adjunct): 100 mg daily x 2 weeks, then increase dose every 2 weeks to usual effective dose of 100 to 400 mg/day in 1 or 2 divided doses (doses up to 600 mg/day have been used) **Encourage drinking 6-8 glasses of water daily	> 16 years see Adult Dosing	Yes

KEY: IM=intramuscular, IV=intravenous, hr=hour; LGS= Lennox-Gastaut syndrome; ER = Extended-release; IR=Immediate-release; ODT=orally dissolving tablet; Lamictal® (lamotrigine) Starter and Titration Kit Information: ǂ**Lamictal "Blue" Starter Kit** is for patients already taking valproate and contains 35 of the 25 mg tablets. **Lamictal "Green" Starter Kit** is for patients taking carbamazepine, phenytoin, phenobarbital, or primidone, and not taking valproate, and contains 84 of the 25 mg tablets and 14 of the 100 mg tablets. **Lamictal "Orange" Starter Kit** is for patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, and contains 42 of the 25 mg tablets and 7 of the 100 mg tablets. **Lamictal "Blue ODT" Titration Kit** is for patients already taking valproate and contains 21 of the 25 mg ODT tablets and 7 of the 50 mg ODT tablets. **Lamictal "Green ODT" Titration Kit** is for patients already taking carbamazepine, phenytoin, phenobarbital, or primidone, and not taking valproate, and contains 42 of the 50 mg ODT tablets and 14 of the 100 mg ODT tablets. **Lamictal "Orange ODT" Titration Kit** is for patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, and contains 14 of the 25 mg ODT tablets, 14 of the 50 mg ODT tablets, and 7 of the 100 mg ODT tablets. **Lamictal "Blue XR" Titration Kit** is for patients already taking valproate and contains 21 of the 25 mg extended-release (ER) tablets and 7 of the 50 mg ER tablets. **Lamictal "Orange XR" Titration Kit** is for patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, and contains 14 of the 25 mg ER tablets, 14 of the 50 mg ER tablets, and 7 of the 100 mg ER tablets. **Lamictal "Green XR" Titration Kit** is for patients already taking carbamazepine, phenytoin, phenobarbital, or primidone, and not taking valproate, and contains 14 of the 50 mg ER tablets, 14 of the 100 mg ER tablets, and 7 of the 200 mg ER tablets.[6]

Table 2: FDA-Approved Indications for Newer Anticonvulsant Agents[7,8 3,6,8-30]

	Bipolar Disorder (maintenance)	Fibromyalgia	Infantile Spasms	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Myoclonic Seizures	Neuropathic Pain	Partial-onset Seizures (adjunct therapy)	Partial-onset Seizures (monotherapy)	Partial-onset seizures with complex symptomology	Postherpetic Neuralgia	Refractory Complex Partial Seizures	Tonic-clonic Seizures (Adjunct therapy)	Tonic-Clonic Seizures (monotherapy)
Brivaracetam								X						
Clobazam				X										
Eslicarbazepine								X	X					
Ezogabine								X						
Felbamate (not primary therapy)				X				X	X	X				
Gabapentin								X		X	X			
Lacosamide								X	X					
Lamotrigine	X			X				X	X	X adjunct			X	
Levetiracetam						X		X					X	
Oxcarbazepine								X	X					
Perampanel								X		X adjunct			X	
Pregabalin		X					X	X			X			
Rufinamide				X										
Tiagabine								X						
Topiramate				X	X			X	X				X	X
Vigabatrin			X									X		
Zonisamide								X						

Disease Overview

The International League Against Epilepsy (ILAE) defines an epileptic seizure as, "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[31]" Epilepsy is a common, chronic disease. It is the fourth most common neurologic disease in the US following migraine, stroke and Alzheimer's disease. The average incidence of epilepsy in the US is 150,000 cases per year with 1 in 26 persons developing epilepsy sometime during their life.[32] It is estimated that 5.1 million US persons are affected by epilepsy; 4.3 million adults and 750,000 children.[33] Epilepsy displays a bimodal age distribution. The incidence of epilepsy is highest in children less than 5 years of age with another peak in the elderly.[34] The annual incidence of epilepsy in people between the ages of 65-69 is 85.9 per 100,000 people. At ages greater than 80 the incidence increases to 135 per 100,000 people.[35] Compared with the general population, active epilepsy is associated with more physician visits (86.4% vs 66.1%). Older patients with epilepsy visit a physician more often than younger adults with epilepsy (93.1% vs 65.7%).{, #2287} Symptomatic epilepsy is associated with life expectancy reductions of as much as 10 years.[36] The standardized mortality rate (SMR) for epilepsy is 1.6-9.3 times higher than in the general population.[37] Mortality is 2-3 times higher in elderly patients with epilepsy than those without. Seizures in the elderly often present as status epilepticus, associated with a 40% mortality rate and a strong predictor for stroke. Conversely, stroke (cerebrovascular disease) acts as a risk factor for epilepsy, increasing the risk by 20%. The strong interplay between epilepsy and stroke risk defines one basis for the higher incidence of epilepsy observed in the elderly. Reports of anticonvulsant use in the elderly find 10% of patients in nursing homes and 20% in a Veterans administration setting receive more than one anticonvulsant medication with 42-79% (respectively) receiving the medication for a non-epilepsy diagnosis.[35,38-41] Older veterans with an epilepsy diagnosis had lower physical and mental health status scores than those without ($p<0.01$), whether newly or previously diagnosed with epilepsy ($p\leq0.01$).[35,38-40]

Although 80% of patients with epilepsy are successfully treated with antiepileptic drugs, another 20-30% suffer with intractable, uncontrolled seizures, significant adverse events and higher morbidity and mortality.[42,43] Particular to epilepsy is the occurrence of sudden unexpected death in epilepsy (SUDEP) which may be responsible for up to 17% of deaths.[44] Epilepsy's greatest impact on quality of life relates to the effects of antiepileptic drug therapy on cognitive function and coordination.[45] The financial burden from informal care and medical expenditures associated with the treatment of epilepsy is $15.5 billion annually in the US. The average lost lifetime wages associated with uncontrolled epilepsy is estimated at $317,000 for men and $140,000 for women.[46]

A seizure is a paroxysmal event resulting from abnormal neuronal activity in the cerebral cortex resulting in excessive excitation or loss of inhibition. Simply stated, a seizure is the result of a malfunction in ion channels affecting neurotransmission through the synapse[2,47]. Seizures are single specific events which may recur as a result of reversible or correctable causes. Seizures may result from hypoxia, ischemia, prenatal injury, developmental disorders (e.g. autism), head trauma, tumor, structural changes, stroke, Alzheimer's disease, infections, hypoglycemia, electrolyte abnormalities, medications or genetic influences. Seizures occur from unidentifiable causes in up to two-thirds of people.[48]Differences in seizure presentation reflect the site of abnormal stimulation within the brain. The affected neocortex produces impulses which stimulate corresponding muscle fascicles producing seizure-like activity. A seizure may manifest with a loss of consciousness,

increase or decrease muscle tone, paresthesia, Deja-vu or hallucinations. Treatment of a seizure is directed toward reversing the etiology, when known. Epilepsy on the other hand, is a clinical disease process constituting a number of seizure types and etiologies which often requires chronic antiepileptic therapy.[2]

A standard definition of epilepsy was adopted by the International League Against Epilepsy (ILAE) in 2014.[49] It updated and expanded the prior definition of 2 or more unprovoked seizures occurring at least 24 hours apart to include; two or more unprovoked/reflex seizures occurring > 24 hours apart, or a single unprovoked/reflex seizure with and recurrence risk probability of at least 60% over the next 10 years following two unprovoked seizures or the diagnosis of an epilepsy syndrome.[49] ILAE defines epilepsy resolution as being past the age of an age-dependent epilepsy syndrome or off medications for 5 years with 10 seizure-free years. Using these definitions, ILAE defines the incidence of epilepsy between 0.3-0.5% and prevalence at 5 to 30 per 1000 patients.[2,49] Epilepsy is refractory or uncontrolled when even a single seizure occurs on therapy. Managing refractory epilepsy is important. Seizures may cause falls, broken bones, or sudden unexplained death in epilepsy patients (SUDEP). Although two-thirds of patients will respond to medications the remaining 1/3 of patients do not respond, continue to have seizures and are at higher morbidity and mortality risk.[43] Epilepsy is not a single disease entity. It represents a range of underlying neurological disorders. Within the broad classification of epilepsy, an epilepsy syndrome involves a cluster of symptoms which may be specified by seizure type, age of onset, precipitating factor, specific part of the brain involved, EEG pattern, genetic predisposition, etc.[49,50]

Continuing advances in epidemiology, electrophysiology, neuroimaging, genomics and molecular biology have expanded our understanding of seizures and epilepsy. This led to the ILAE updating the classification system for seizures and epilepsy in 2010.[31] See Table 3 for the current ILAE classification system. New classifications combine clinical characteristic with specific electrophysiological findings.[51] Seizures are described by, 1) mode of onset as generalized (affecting both brain hemispheres), focal (originating and remaining limited to one brain hemisphere) and unknown (it remains unclear if these seizures are focalized, generalized or both; e.g. epileptic spasms). Epilepsy has a focal origin in approximately 2/3 of patients and generalized origin in 1/3 of patients; 2) etiology, now defined as genetic (e.g. Dravet syndrome), structural (e.g. congenital-tuberous sclerosis or acquired-trauma), metabolic (e.g. mitochondrial disorders) or unknown (normal imaging and no other etiology identified); 3) diagnostic specificity, determined with electro-clinical information (e.g. West syndrome); 4) distinctive constellations reflecting underlying pathology, some of which are known to respond to surgical intervention (e.g. Rasmussen encephalitis); 5) structural or metabolic epilepsies now described by the underlying cause. Finally, 30% of epilepsies fall into a heterogeneous group of epilepsies of unknown cause.[31,52]

Table 3: Classification of Seizures[31]

1. Generalized Seizures
    a. Tonic-clonic
    b. Absence
        i. Typical
        ii. Atypical
        iii. Absence with Special Features
            1. Myoclonic Absence
            2. Eyelid Myoclonia
    c. Myoclonic
        i. Myoclonic
        ii. Myoclonic Absence
        iii. Myoclonic Tone
    d. Clonic
    e. Tonic
    f. Atonic
2. Focal Seizures
3. Unknown
    a. Epileptic Spasm

Patients having a single seizure may not require pharmacologic treatment. Avoiding the likely precipitant(s) is often sufficient. When more than one seizure occurs or there is risk of recurrence (e.g. abnormal MRI, EEG or partial-onset seizure) pharmacotherapy is recommended. In this case, anticonvulsant medications are chosen on the basis of the diagnosis of epilepsy or an epileptic syndrome.[2,50,51]

Generalized tonic-clonic seizures produce a loss of consciousness with tonic muscle spasms followed by repetitive clonic movements. Vocalizations from air passing over the larynx, tongue biting, cyanosis, and loss of sphincter tone are common. Upon completion of the seizure, consciousness is regained often accompanied by post-ictal lethargy and confusion. Seizures can begin in both hemispheres of the brain (primary) or in one hemisphere that spreads to the other hemisphere (secondary). Aura's reflect a partial-onset seizure having hemispheric spread. Tonic and clonic seizures do not always occur together.[2,3,32,51,53]

Absence seizures occur most commonly in children. The may cease in adolescence although development of a second type of seizure is not uncommon. Seizures begin abruptly, are associated with a short loss of consciousness lasting a few seconds to a half minute and are not associated with a post-ictal state. Manifestations may include a blank stare and upward eye rotation. Atypical absence seizures have a milder onset and offset. They are often associated with a loss of muscle tone leading to a gradual slump or myoclonic jerks. EEG testing is often required to differentiate this seizure type and allow for selection of the appropriate therapy.[2,3,32,51,53]

Focal seizures may present with motor or sensory symptoms. If the seizure remains within one hemisphere symptoms are asymmetric. Focal seizures may progress to a larger area within the same hemisphere or progress to include both hemispheres (secondary generalization). Consciousness is maintained and additional symptoms reflect the area of the brain that is affected. Symptoms may reflect motor (e.g. twitch), sensory (e.g. altered taste, smell, visual or auditory hallucinations) or psychic experiences (e.g. déjà vu). If focal impulses spread, the patient may lose consciousness, experience automatisms (e.g. lip smacking, wandering, picking at clothes) and exhibit a brief postictal period.[53].[2,3,51,53]

Myoclonic seizures result in a brief contraction of a muscle or muscle group followed by relaxation. These often present as very brief bilateral, symmetrical muscle jerking or twitching lasting only a few seconds. Juvenile myoclonic epilepsy has on onset around puberty, affects the upper body, is most commonly experienced upon awakening and persists throughout life. [32,53]

Atonic seizures result in a loss of muscle tone. Manifestations may include eyelid drooping, head nodding, dropping of a limb or slumping to the ground. [32,53]

Epilepsy may present with a particular seizure type or in combination with other findings, including specific precipitating factors, EEG patterns, severity, chronicity, age of onset, family history and prognosis. Some constellations of signs may constitute an epilepsy syndrome. West Syndrome (Infantile Spasms) is a rare age-specific epileptic disorder of infancy and early childhood (incidence of 0.015–0.02% in children $\leq$ 10 years of age) of which 90% of cases are diagnosed in the infant's first year. [54-56 54-56 54-56 54-56 32-3454,57] It has three main characteristics: infantile spasms, mental retardation, and hypsarrhythmia. Other common characteristics include psychomotor retardation and impaired mental development. Although 90% of children become seizure free by age 5, up to 50% will develop another seizure disorder. [54,5854,5854,5854,5832,36] Lennox-Gastaut syndrome (LGS) is an age-specific epilepsy syndrome accounting for 1-10% of childhood epilepsies. One-fifth of cases are preceded by West's syndrome. It most commonly affects males between 3-5 years of age although it has been diagnosed in children up to 8 years. LGS is characterized by a triad of signs including multiple types of epileptic seizures, abnormal slow spike waves on the wakening EEG and severe intellectual impairment. Behavioral and psychiatric comorbidities are common (i.e. Attention-deficit hyperactivity disorder, anxiety, aggressive behavior, psychosis and depression).[59,60] Juvenile myoclonic epilepsy (JME) is another epilepsy syndrome affecting children and adolescents age 6-22 years with 50% of cases found in 13-16 year olds. JME is characterized as a generalized epilepsy with myoclonic jerks upon awakening and specific EEG findings. Treatment of JME is challenging. Life-long pharmacotherapy is required and often associated with significant adverse events. Problematically, up to 20% of patient do not respond to therapy.[61,62]

The diagnosis of epilepsy or an epilepsy syndrome is crucial in determining treatment options. Clinicians may not witness the seizure. Astute observation and detailed reporting are important in diagnosing epilepsy. Factors that assist in making a diagnosis include what the person was doing prior to the seizure, the manifestation of symptoms including changes which may reflect generalization, time of day, duration or seizure, loss of consciousness, other movements, vocalizations, the patient's status following the seizure and the length of time before returning to baseline. Assessment continues with a medical history, neurologic examination and diagnostic testing (e.g. EEG, CT scan or MRI).

Treatment of epilepsy depends on the type of epilepsy or epilepsy syndrome identified. Pharmacotherapy may reduce the likelihood of recurrence, reduce associated morbidity and mortality, increase quality of life and lessen the risk for SUDEP.[2] Achieving early control of seizures enhances the likelihood that long-term therapy may result in successful discontinuation of antiepileptic drug therapy in the future.[53] Non-pharmacologic treatments may include surgery, dietary modifications (ketogenic diet), vagus nerve stimulation and avoidance of any suspected precipitogen (e.g. alcohol, lack of sleep, caffeine, flashing/flickering lights). The goal of pharmacotherapy in epilepsy is to reduce, control, or eliminate seizures without causing unacceptable adverse side effects.[63]

A number of antiepileptic medications have been associated with the exacerbation or precipitation of seizures in treated patients. This may occur when the original diagnosis of the seizure type or syndrome was in error, when a seizure-specific-contraindicated-agent was administration and in the presence of high doses or polypharmacy. Further research is needed to elucidate the epileptogenic mechanisms.[64] A list of the antiepileptic drugs associated with worsening seizures is found in Table 4.

Table 4: Newer Antiepileptic Drugs Which May Exacerbate Seizures

Seizure Type/Syndrome of Misuse	Drugs	Exacerbated Seizure Type
Lennox-Gastaut syndrome	**Clobazam**	Tonic seizures
Myoclonus	**Gabapentin**	Myoclonus
Absence Epilepsy	**Gabapentin** **Vigabatrin**	Absence seizure
Juvenile Myoclonic Epilepsy Severe Myoclonic Epilepsy	**Lamotrigine**	Myoclonic seizures
Rolandic Epilepsy	**Oxcarbazepine**	Atypical absences
Symptomatic Generalized Epilepsy	Oxcarbazepine	Myoclonic seizures
Idiopathic Generalized Epilepsy	**Oxcarbazepine** **Tiagabine**	Absence, myoclonic seizures
Focal Cortical Dysplasia	**Vigabatrin**	Myoclonic seizures
Epilepsies with myoclonus	Vigabatrin	Myoclonus

Decision making concerning antiepileptic therapy should involve the patient, parent and carers; give consideration to race, culture and specific needs; involve the development of a comprehensive care plan involving primary and secondary practitioners; and individualize treatment considering seizure type, syndrome, patient age, concomitant medications, comorbidity, patient lifestyle and preferences.65,66 Important safety issues, include adverse events, bone health, psychological issues, pregnancy and sudden unexpected death in epilepsy patients. Recommendations address HIV-patients in which non-enzyme inducing medications are preferred as well as specific safety issues with felbamate and valproate. Practice Guidelines are found in Table 5 Briefly, the most commonly recommended antiepileptic drugs for the various epilepsies/syndromes, include:

Lennox Gastaut syndrome: Valproate
Infantile Spasms: Vigabatrin
Partial-Onset, Monotherapy: Lamotrigine, carbamazepine, levetiracetam, valproate
Partial-Onset, Adjunctive: Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate, clobazam
Generalized-Onset, Monotherapy: Valproate, lamotrigine > topiramate, carbamazepine, oxcarbazepine (for children, phenobarbital, carbamazepine, valproate, topiramate)
Generalized-Onset, Adjunctive: Valproate, lamotrigine, levetiracetam, topiramate > clobazam
Partial-Onset, Refractory, Monotherapy: Lamotrigine, topiramate, oxcarbazepine
Partial-Onset, Refractory, Adjunctive: Gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, zonisamide
Generalized, Refractory, Monotherapy: Topiramate
Myoclonic: Valproate, levetiracetam, lamotrigine, topiramate

Table 5: Clinical Practice Guideline Recommendations for Epilepsy

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics (2015) [67]	Infants with tuberous sclerosis complex • Vigabatrin (level C) o Non-response ACTH/oral steroids fants without tuberous sclerosis complex • ACTH for short-term control of spasms (level B) • Alternative options: oral steroids, vigabatrin, valproate (level C) o ACTH/oral steroids may → better long-term neurodevelopmental outcome in children with epileptic spasms due to unknown etiologies than vigabatrin (level C evidence) • Continuing hypsarrythmia +/- spasms • Vigabatrin, valproate, benzodiazepines, topiramate, levetiracetam, surgery, ketogenic diet

Evidence-based guideline update: medical treatment of infantile spasms: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, (2012)[68]	Evidence Supports • Vigabatrin for short-term treatment of infantile spasms (excluding tuberous sclerosis complex) (Grade C) • ACTH remains preferred with Grade B evidence supporting both treatment response and improved neurodevelopmental outcomes. sufficient Evidence • Evidence is insufficient to support treatment with valproic acid, levetiracetam, zonisamide or topiramate.
Treatment of Lennox-Gastaut Syndrome (2013)[60]	ennox-Gastaut Syndrome • First-line therapy is valproate • Second-line therapy is one or two of the following, lamotrigine, levetiracetam, rufinamide, topiramate, zonisamide • Third-line therapy following non-pharmacologic interventions (ketogenic diet, vagus nerve stimulation) and alternative second-line agents, consider acetazolamide, bromides, carbamazepine, ethosuximide, felbamate, phenobarbital, phenytoin, vigabatrin
Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology (2009)[59]	ochrane Review • Useful add-on therapies: lamotrigine, topiramate and felbamate • Drop attacks were reduced by lamotrigine and topiramate o Atonic seizures were reduced by felbamate • Tonic-clonic seizures were reduced by felbamate and lamotrigine (unreported for topiramate)
Evidence-based guideline: management of an unprovoked first seizure in adults (2015)[69]	A first, unprovoked seizure has a recurrence rate of 21-45% over 2 years. • Recurrence rate increases with stroke, trauma, abnormal EEG, imaging abnormality or nocturnal seizures • Recurrence rate may be reduced by 35% over 2 years with use of antiepileptic drugs Antiepileptic drugs do not increase quality of life over 3-year period At 3 years, post-seizure, use of antiepileptic therapy affords no benefit in seizure remission or prognosis A second seizure increases the risk of additional seizures by 57% at 1 year, 73% at 4 years • Antiepileptic therapy is recommended after a second seizure
Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy (2004)[70]	Agents evaluated, included gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide Monotherapy in Newly Diagnosed Partial/Mixed Seizure disorder (adult and adolescent) • Recommend: Gabapentin, lamotrigine, topiramate and oxcarbazepine (level A)

	• Base selection on specific individual characteristics (level A) • Absence Seizures in Children • Recommend: Lamotrigine (level B)
ILAE Treatment Guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, 2006 [71]	Partial-Onset Seizures in Adults Newly Diagnosed or Untreated (Noted a paucity of Class I and Class II RCTs) • First-line mono-therapy may include phenytoin and carbamazepine (Grade A) or valproic acid with a rating of probably efficacious/effective (Grade B) • Evidence supports a rating of possibly efficacious/effective for gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin (Grade C) • Evidence supports a rating of potentially efficacious/effective for clonazepam and primodone (Grade D) Partial-Onset Seizures in Children Newly Diagnosed or Untreated (Noted a paucity of Class I and Class II RCTs) • First-line mono-therapy recommendation is oxcarbazine (Grade A) • Rated as possibly efficacious/effective are carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid (Grade C) • Rated as potentially efficacious/effective are lamotrigine and vigabatrin (Grade D) Partial-Onset Seizures in Elderly Adults (Noted a paucity of Class I and Class II RCTs) • First-line monotherapy may include lamotrigine or gabapentin (Grade A) • Rated as possibly efficacious/effective for initial monotherapy is carbamazepine (Grade C) • Rated as potentially efficacious/effective for initial monotherapy are topiramate and valproic acid (Grade D) Generalized-Onset Seizures in Adults (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly effective/efficacious with carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin topiramate and valproic acid (Grade C) • Drugs which should be used with caution because they may aggravate or precipitate generalized tonic-clonic or other generalized seizures include oxcarbazepine and phenytoin (Grade D) • Rated as potentially efficacious/effective as initial monotherapy are gabapentin and vigabatrin (Grade D) Generalized-Onset Seizures in Children (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly efficacious/effective with carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid (Grade C) • Rated as potentially efficacious/effective as initial monotherapy is oxcarbazepine.

	• Drugs which should be used with caution because they may aggravate or precipitate generalized tonic-clonic or other generalized seizures include carbamazepine, oxcarbazepine and phenytoin (Grade D) Absence Seizures in Children (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly efficacious/effective with ethosuximide, lamotrigine or valproic acid (Grade C) • Rated as inefficacious/ineffective is gabapentin (Grade F) • The following AEDs may precipitate absence seizures, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin (Grade D) Children with benign epilepsy with centrotemporal spites (BECTS) (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A or B) • First-line monotherapy may be possibly efficacious/effective with carbamazepine and valproic acid (Grade C) • Rated as potentially efficacious/effective are gabapentin and sulthiame (Grade D) • Some data supports anticonvulsive therapy may not be necessary (Grade D) Juvenile Myoclonic Epilepsy (Evidence was deficient in power and seizure-specific studies. No evidence was Grade A, B or C) • First-line monotherapy recommendations which may have some efficacy, include carbamazepine, lamotrigine, levetiracetam, topiramate, valproic acid or zonisamide (Grade D) • The following AEDs may precipitate or aggravate absence and myoclonic seizures, carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and valproic acid
Diagnosis and management of epilepsy in adults. A national clinical guideline (2015)[72]	Focal Onset Seizures Monotherapy • Lamotrigine is the drug of choice o Carbamazepine and levetiracetam are options when lamotrigine is not tolerated (Grade A) Focal Onset Epilepsy Adjunct Therapy • Carbamazepine, gabapentin, Lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproate and zonisamide (Grade A) Generalize Epilepsy Adjunct Therapy • Lamotrigine, levetiracetam ethosuximide, valproate and topiramate (Grade A) • Match drug choice to the type of seizure and limit to 2-3 antiepileptic medications (Grade B) Genetic Generalized Epilepsy or Unclassified Epilepsy • Valproate is the drug of choice. o Lamotrigine and topiramate are options when valproate is not tolerated and in women of childbearing age (Grade A)

	o Recommend against switching between manufacturers Management of Older Adults with Epilepsy • Focal-onset seizures: Consider lamotrigine or levetiracetam first-line (Grade B) • Gabapentin is an alternate for monotherapy or adjunct therapy Drug-resistant Epilepsy • Failure to respond may reflect an incorrect diagnosis or adherence issues • Use combination therapy after treatment with two first-line agents have failed or only a reduction of seizures during phased substitution Provoked Seizures • Long-term prophylaxis is not indicated, treatment for provoked seizures should be discontinued and drug therapy is not indicated for concussive convulsions Adverse Drug Effects • Patients should be educated about common adverse effects, instructed to seek medical care urgently if rash, bruising, somnolence or vomiting occur particularly during the first week(s) of treatment. • Routinely monitor liver function and complete blood count Bone Health • To reduce the risk of osteoporosis, patients should receive dietary and lifestyle advice Psychiatric/Behavioral Adverse Effects • The choice of antiepileptic agent should include consideration of these negative psychotropic effects (Grade B) Pregnancy • Discuss contraception, pre-pregnancy counseling (Grade B) • Discuss fetal, neonatal/childhood outcomes, breastfeeding
Diagnosis and management of the epilepsies in adults children: summary of updated NICE guidance (2012)[65]	Focal Onset Seizures Newly Diagnosed • First-line: Carbamazepine or lamotrigine o Alternatives include levetiracetam, oxcarbazepine and valproate. o If one of the 5 medications fails, try another of this group o If a second well-tolerated AED is ineffective consider adjunctive therapy Focal Onset Seizures Refractory Adjunct • Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate • If adjunctive therapy fails include a tertiary epilepsy specialist. Treatment may include eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin (caution permanent visual effects) or zonisamide Generalized, Tonic-Clonic Seizure (GTC), newly diagnosed • First Line: Valproate (discuss risks with females of child-bearing potential) o Alternatives: Lamotrigine followed by carbamazepine and oxcarbazepine

	▪ Caution: may exacerbate myoclonic seizures Generalized, Tonic-Clonic Seizure (GTC) Adjunct • Consider: Clobazam, lamotrigine, levetiracetam, valproate or topiramate o If myoclonic seizures/epilepsy is suspected/present do not use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin Absence seizures • First-line: Ethosuximide or valproate (valproate is preferred with risk of GTC seizures, caution for teratogenicity) o Alternative is lamotrigine Infantile Spasms (care should include tertiary pediatric epilepsy specialist) • First-line: Steroid (prednisolone or tetracosatide) or vigabatrin (non-tuberous sclerosis) • First-line: vigabatrin for tuberous sclerosis associated seizures • Prolonged or Repeated Seizures, Convulsive Status Epilepticus • For use in the community, first-line therapy is buccal midazolam. Rectal diazepam may be used if preferred or buccal midazolam unavailable. Continuation of Epilepsy Drug Therapy • Remain vigilant for the emergence of adverse events (e.g. reductions in bone density) and neuropsychiatric problems (e.g. suicidality) which may occur with all AEDs and as early as 1 week into therapy Discuss with females of childbearing potential and younger girls likely to require treatment as they become of child-bearing potential and their caregivers and parents • Risk of AED-caused malformations, possible neurodevelopmental impairments with different agents, especially valproate with increased risk at doses > 800 mg/day and poly-therapy. • Estrogen-based contraceptive use may reduce lamotrigine serum levels and loss of seizure control Monitoring AED levels routinely is not required; it may be helpful in pregnancy or when a loss of seizure control occurs, especially with phenytoin or lamotrigine
Epilepsies: Diagnosis and Management, (NICE CG137)[73]	General Considerations • Recommendations included for children (28 days to 11 years), adolescents/young people (12-17 years), adults (> 18 years) and older people (> 65 years) • Antiepileptic drug treatment (AED) should be individualized with consideration for type of seizure, epilepsy syndrome, co-medication and co-morbidity, patient's lifestyle and preferences of patient, family and/or caregivers. Sudden unexpected death in epilepsy (SUDEP)

	o Discuss the importance of optimizing seizure control and the consequences of nocturnal seizures • Diagnosis: Every attempt should be made to determine the diagnosis/etiology • Monotherapy is preferred when possible. At least two monotherapy trials of alternative agents should be attempted • Add new agent to old, titrate to 'therapeutic' dose and taper off first drug • Women & Girls o Discuss therapy with females of childbearing potential and younger girls likely to require treatment as they become of child-bearing potential and their caregivers and parents o Counsel regarding contraception, conception, pregnancy, caring for children, breast-feeding and menopause o Risk of AED-caused malformations, possible neurodevelopmental impairments with different agents, especially valproate with increased risk at doses > 800 mg/day and polytherapy. o Progesterogen: Progesterogen-only pills and implants are not recommended o Use of enzyme-inducing antiepileptic drugs and oral contraception or depot progesterogen should consider additional barrier method contraception. o Estrogen-based contraceptive use may reduce lamotrigine serum levels and loss of seizure control o Offer folic acid 5 mg/day for women/girls on antiepileptic drugs before they become pregnant • Monitoring AED levels routinely is not required; it may be helpful in pregnancy or when a loss of seizure control occurs, especially with phenytoin or lamotrigine • Older People: Careful consideration for pharmacokinetic/ pharmacodynamics issues, polypharmacy and comorbidities Focal Seizures (children, young people, adults) • First-line (newly diagnosed): Lamotrigine or carbamazepine • If above are unsuitable/not tolerated/ineffective: levetiracetam, oxcarbazepine, valproate. Refractory Focal Seizures Adjunctive Treatment (children, young people, adults) • Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate • Tertiary care providers may consider eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide. • Risk: benefit vigabatrin due to potentially irreversible effects on visual field. Generalized Tonic-Clonic Seizures (GTC) (children, young people, adults) • First Line (newly diagnosed): valproate • If valproate is unsuitable consider lamotrigine

	• Lamotrigine may exacerbate myoclonic seizures or juvenile myoclonic epilepsy • Consider: carbamazepine and oxcarbazepine • Caution: may exacerbate myoclonic and absence seizures Generalized Tonic-Clonic Seizures, Adjunctive Treatment (children, young people, adults) • First Line: Clobazam, lamotrigine, levetiracetam, valproate or topiramate • Myoclonic/absence seizure risk, avoid carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin Absence Seizures (children, young people, adults) • First Line: Ethosuximide, valproate (valproate preferred with a history of GTC seizures) • Alternative: Lamotrigine Absence Seizures, Adjunctive Treatment (children young people, adults) • If two first-line agents fail, consider combination with two of ethosuximide, lamotrigine, valproate • If adjunctive therapy fails involve a tertiary epilepsy specialist who may consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide. DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Myoclonic Seizures (children, young people, adults) • First Line: Valproate • If valproate is unsuitable/not tolerated: Levetiracetam or topiramate Myoclonic Seizures Adjunctive Treatment (children, young people, adults) • Levetiracetam, valproate, topiramate • If adjunctive therapy fails involve a tertiary epilepsy specialist who may consider clobazam, clonazepam, piracetam or zonisamide. DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Tonic or Atonic Seizures (children, young people, adults) • First-Line: Valproate Tonic or Atonic Seizures (children, young people, adults) • First-Line: Valproate Tonic or Atonic Seizures Adjunctive Treatment (children, young people, adults) • Lamotrigine • If adjunctive therapy fails involve a tertiary epilepsy specialist who may consider rufinamide or topiramate. DO NOT use carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. Infantile Spasms • Involve a tertiary epilepsy specialist • First Line (non-tuberous sclerosis): Prednisolone or tetracosatide or vigabatrin • First Line (tuberous sclerosis): Vigabatrin

	o If vigabatrin fails, use prednisolone or tetracosatide Dravet Syndrome (children) • Involve a tertiary epilepsy specialist: • Consider valproate, topiramate Dravet Syndrome (children, young people, adults) • Involve a tertiary epilepsy specialist: Clobazam or stiripentol • DO NOT use carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Lennox-Gastaut Syndrome (child) • Involve a tertiary epilepsy specialist • First Line: Valproate Lennox-Gastaut Syndrome Adjunctive Treatment (children, young people, adults) • Lamotrigine • DO NOT use carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin • Tertiary epilepsy specialist may consider rufinamide and topiramate o Felbamate is an option ONLY with epilepsy specialist care and all other treatments have proven ineffective or not tolerated. Benign Epilepsy with Centrotemporal Spikes (BECTS), Panayiotopoulos syndrome or Late-Onset Childhood Occipital Epilepsy (Gastaut type) (children, young people) • Determine with family, patient, caregivers if treatment is indicated • First-Line: Carbamazepine or Lamotrigine o If above are unsuitable/not tolerated/ineffective: levetiracetam, oxcarbazepine, valproate. Benign Epilepsy with Centrotemporal Spikes (BECTS), Panayiotopoulos syndrome or Late-Onset Childhood Occipital Epilepsy (Gastaut type) Adjunctive Treatment (children, young people) • Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate o If above are ineffective or not-tolerated, involve a tertiary epilepsy specialist who may consider: eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. o Risk: benefit vigabatrin due to potentially irreversible effects on visual field. Idiopathic Generalized Epilepsy (IGE) (children, young people, adults) • First-Line: Valproate o If above ineffective, unsuitable, not tolerated consider lamotrigine or topiramate o Lamotrigine may exacerbate myoclonic seizures Idiopathic Generalized Epilepsy (IGE) Adjunctive Treatment (children, young people, adults) • Consider lamotrigine, levetiracetam, valproate or topiramate

	o If above are ineffective or not tolerated, involve a tertiary epilepsy specialist who may consider: clobazam, clonazepam or zonisamide • DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin Juvenile Myoclonic Epilepsy (children, young people, adults) • First-Line: Valproate o If above is unsuitable or not tolerated consider: lamotrigine, levetiracetam or topiramate o Lamotrigine may exacerbate myoclonic seizures Juvenile Myoclonic Epilepsy Adjunct Treatment (children, young people, adults) • Consider: lamotrigine, levetiracetam, valproate or topiramate o If above are ineffective or not tolerated involve a tertiary epilepsy specialist who may consider: clobazam, clonazepam or zonisamide • DO NOT offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin Generalized Tonic-Clonic Seizures (children, young people, adults) • First-Line: Lamotrigine, valproate (valproate is preferred with myoclonic seizures of juvenile myoclonic epilepsy) • Alternative first-line, may consider: carbamazepine, oxcarbazepine • Caution: May exacerbate myoclonic or absence seizures Generalized Tonic-Clonic Seizures Adjunctive Treatment (children, young people, adults) • First-Line: Clobazam, lamotrigine, levetiracetam, valproate, topiramate Childhood Absence Epilepsy, Juvenile Absence Epilepsy or other Absence Epilepsy Syndromes (children, young people, adults) • Ethosuximide, valproate (preferred with risk of generalized tonic-clonic seizures) o If above are ineffective, unsuitable or not tolerated consider: lamotrigine Childhood Absence Epilepsy, Juvenile Absence Epilepsy or other Absence Epilepsy Syndromes Adjunctive Treatment (children, young people, adults) • If two of the above agents are ineffective, consider a combination of two agents (lamotrigine, valproate, ethosuximide) o If above are ineffective or not-tolerated, involve a tertiary epilepsy specialist who may consider: clobazam, clonazepam, levetiracetam, topiramate or zonisamide • DO NOT use carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin Prolonged/Repeated Seizures and Convulsive Status Epilepticus (children, young people, adults) Community Setting: • First-line: Buccal midazolam • Rectal diazepam may be used if preferred or buccal midazolam unavailable • If intravenous is/becomes available, lorazepam (IV) may be used

	Hospital Setting: • IV lorazepam (diazepam if lorazepam is unavailable or buccal midazolam if IV access is unavailable • Continued seizures: phenobarbital, phenytoin • Refractory Status Epilepticus (see published protocols) Other Syndromes, epilepsies, EEG abnormalities: Refer to tertiary epilepsy specialist Other Considerations: • Vigilance for treatment-emergent adverse effects • Assess and optimize adherence • Monitoring antiepileptic drug levels • Adherence issues • Suspected toxicity • Phenytoin dose adjustment • Management of pharmacokinetic interactions • Clinical conditions (e.g. pregnancy, organ failure, status epilepticus) • Treatment Discontinuation: When seizure free for at least 2 years, consider tapering-off one drug at a time over 2-3 months. Monitor for withdrawal symptoms and seizure recurrence. • Other Treatment Options o Psychological interventions (relaxation, cognitive behavioral therapy, biofeedback) o ketogenic diet o vagus nerve stimulation
Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy (2004) [42]	Agents evaluated, included gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide as well as older established antiepileptic drugs Monotherapy in refractory partial epilepsy • Oxcarbazepine and topiramate (level A evidence) • Lamotrigine (level B evidence) • Insufficient evidence for gabapentin, levetiracetam, tiagabine or zonisamide Partial Epilepsy Add-on therapy in refractory partial therapy • Appropriate agents: gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam and zonisamide o Efficacy and side effects increase with increasing doses. Slow titration recommended o Oxcarbazepine had the highest drop-out rate at the highest dose (67%) Refractory Generalized Epilepsy • Topiramate is effective in adults and children • Insufficient evidence for other agents Children: Refractory Partial Epilepsy Adjunctive Therapy

	• Evidence supports gabapentin, lamotrigine, oxcarbazepine and topiramate • Safety concerns o rash with lamotrigine o hypohidrosis with zonisamide and topiramate Lennox-Gastaut Syndrome • Evidence supports lamotrigine and valproic acid • Appropriate agents for drop attacks: topiramate and lamotrigine o Caution for worsening myoclonic seizures: lamotrigine and gabapentin
Antiepileptic drug selection for people with HIV/AIDS (2012)[74]	Statistics • Seizures will develop in 2.6-6.1% of HIV patients • 55% of people taking antiretroviral medications may require an antiepileptic medication (AED) Pharmacotherapy • Phenytoin → increase dosage of lopinavir/ritonavir 50% • Valproic Acid → zidovudine dosage reduction may be required • Dosage adjustments are not required with combinations of valproic acid/efavirenz, lamotrigine/raltegravir/atazanavir • Lamotrigine → increase dosage increases of ritonavir/atazanavir 50% The use of enzyme inducing AEDs should be avoided when HIV/AIDS regimens include protease inhibitors or nonnucleoside reverse transcriptase inhibitors. If required, pharmacokinetic assessments are recommended to prevent antiviral treatment failure or the development of viral resistance.
Medicines and Healthcare Products Regulatory Agency (MHRA) :Pharmacovigilance and risk assessment committee (PRAC) (2014)[75]	Statement Concerning Use of Valproate Restrictions to valproate use due to • Birth defects when used in pregnant women, 11% ↑ • Developmental problems found in 30-40% of exposed children • Autism spectrum disorder 3x ↑ in exposed children Recommend provision of additional education and materials Restrict routine valproate prescribing • Not used routinely for epilepsy or bipolar disorder in girls/women who are/might become pregnant. • Use only after other treatments fail or produce serious adverse effects. Valproate-treated women should use effective women
Practice advisory: The use of felbamate in the treatment of patients with intractable epilepsy (1999)[76]	Class I evidence supports felbamate • Adjunct and monotherapy of partial seizures in adults age 18 to 65 • Adjunct therapy in Lennox–Gastaut syndrome Class III evidence supports felbamate • Primary generalized tonic-clonic convulsions • Absence seizures

	Class III evidence for felbamate therapy benefits • less sedation and weight loss Class I evidence side effect risks • gastrointestinal disturbance, headache, anorexia, insomnia, dizziness, diplopia, ataxia, and rash Class III strong evidence for serious risks • aplastic anemia, hepatic failure, serious rash (including Stevens–Johnson and toxic epidermal necrolysis) Felbamate is indicated in patients for whom risk/benefit ratio supports use • Lennox–Gastaut patients over age 4 unresponsive to primary AEDs • Intractable partial seizures in patients over 18 years of age who have failed standard AEDs at therapeutic levels (monotherapy: data indicate a better risk/benefit ratio for felbamate used as monotherapy) • Patients on felbamate more than 18 months • Felbamate risk/benefit assessment does not support the use of felbamate for • New onset epilepsy in adults or children • Patients who have experienced significant prior hematologic adverse events • Patients in whom follow-up and compliance will not allow careful monitoring • Patients unable to discuss risks/benefits (i.e., with mental retardation, developmental disability) and for whom no parent or legal guardian is available to provide consent Patients in whom risk/benefit ratio is unclear and based on case reports and expert opinion (Class III) only, but under certain circumstances depending on the nature and severity of the patient's seizure disorder, felbamate use may be appropriate: • Children with intractable partial epilepsy • Other generalized epilepsies unresponsive to primary agents • Patients who experience unacceptable sedative or cognitive side effects with traditional AEDs Lennox–Gastaut syndrome under age 4 unresponsive to other AEDs

Abbreviations: EKG – electrocardiogram; AED-antiepileptic drug

Pharmacology

Seizures are understood to result from abnormal, excessive, synchronous neuronal depolarizations.[2,3] Anticonvulsant medications exert their effects by blocking the initiation or spread of impulses via interacting with a number of possible sites and processes associated with the development of a seizure, including neurons, ion channels, receptors, glia, excitatory and inhibitory synapses. The goal of pharmacotherapy is to achieve a balance in postsynaptic potential between excitatory and inhibitory influences. Many medications act at multiple sites and others have unknown mechanism(s) of action.

The most common mechanisms involved in anticonvulsant activity, involve:[2,3,45,77,78]

1) interaction to block impulses at Na+ (sodium) ion channels. Active Na+ channels allow sodium to be transported into the cell and produce an action potential allowing the axon to fire. This is followed by the refractory period where the ion channel is inactive and during which the action potential cannot be propagated. Medications active at this site, stabilize the Na+ channel in an inactive state, preventing the development of an action potential and axonal firing. The medications active at the Na+ channel, include clobazam, eslicarbazepine, felbamate, lacosamide, lamotrigine, oxcarbazepine, rufinamide, topiramate and zonisamide.

2) interaction at the GABA (γ-aminobutyric acid) receptor to enhance GABA activity. Gabaminergic activity is mediated at both GABA-A and GABA-B receptors. The GABA-B receptor is an active part of the potassium channel while GABA-A receptor stimulation facilitates the intracellular transport of chloride. Due to the negative charge of the chloride ion, the resting membrane potential is lowered making it more difficult for the cell to achieve an action potential. Medications active at GABA sites, include direct binding to GABA-A receptors (clobazam, topiramate), blocking presynaptic GABA reuptake (tiagabine), inhibiting GABA transaminase mediated GABA metabolism (vigabatrin) or increasing GABA synthesis (gabapentin).

3) interaction at the voltage-gated Ca++ channel to inhibit impulse propagation. Three forms of calcium channels are known to exist (L, N and T). Activation of these channels allows calcium influx resulting in a partial depolarization of the cell membrane. Inhibition of these channels diminishes the development of an action potential. Medications that inhibit T-calcium channels in the thalamus can stop absence seizures (felbamate, gabapentin, lamotrigine, oxcarbazepine, pregabalin, zonisamide).

4) interaction with glutamate receptors to reduce cell excitation. Activation of the glutamate receptor results in the influx of sodium and calcium, and efflux of potassium ions which favors the development of an action potential. The glutamate receptor has 5-binding sites. Two of these sites are targeted by antiepileptic agents. Perampanel and topiramate act at the AMPA/kainite [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] site and felbamate, lamotrigine, levetiracetam, topiramate and zonisamide act at the NMDA (N-methyl-D-aspartate) site.

5) interaction at the SV2A (synaptic vesicle glycoprotein 2A) protein ligand appears to stabilize the vesicle, reduce release of contents and decrease action potential-dependent neurotransmission (brivaracetam, levetiracetam).

6) interaction at potassium ion channels activates potassium currents which hyperpolarize the cells and stabilize the membrane (clobazam, ezogabine, levetiracetam).

7) interaction to inhibit carbonic anhydrase activity resulting in an increased intracellular concentration of hydrogen ions, reduction in pH and extracellular shift of potassium ions for acid-base balance. This results in cellular hyperpolarization and an increased seizure threshold (topiramate, zonisamide).

8) interaction to inhibit HCN (hyperpolarization-activated cyclic nucleotide-gated) channels, controlling Na+ and K+ current, resting membrane potential, rhythmic activity of the brain and synaptic transmission (lamotrigine, gabapentin).

Pharmacokinetics

Pharmacokinetic considerations are important in using antiepileptic medications. [11,79]The newer anticonvulsants are associated with superior safety profiles, linear pharmacokinetics, consistent absorption, low plasma protein binding, few active metabolites and reduced potential for drug interactions. Dosing and monitoring these newer agents is simpler which may improve efficacy, safety and tolerability. Pharmacokinetic and regression analysis of seizure frequency and plasma concentrations of newer anticonvulsant medications were unable to adequately establish a pharmacodynamic relationship between plasma concentration and seizure frequency.[80] Antiepileptic drug monitoring is not generally recommended.[65,81] Monitoring may be useful in the presence of physiologic change (e.g. pregnancy), in cases of toxicity or in assessing adherence issues.

Most patients respond well to recommended regimens however interpatient variability, comorbid conditions and concurrent medications mandate a familiarity with the pharmacokinetics of the agents. The newer antiepileptic drugs may be stratified by inter-individual pharmacokinetic variability; potentially significant for clobazam, felbamate, gabapentin, lamotrigine, tiagabine, topiramate and zonisamide; moderate with eslicarbazepine, oxcarbazepine and low with lacosamide, levetiracetam, pregabalin and vigabatrin.[82]

Gabapentin is associated with non-linear, saturable, dose-dependent absorption. The balance between increasing bioavailability with more frequent administration of smaller doses must be weighed against patient inconvenience.[83] Active metabolites are found with clobazam, eslicarbazepine, ezogabine and oxcarbazepine. Knowledge of the factors affecting drug absorption, distribution, metabolism and excretion when combined with drug-disease state and drug-drug interactions will allow a prescriber the best opportunity to offer a patient optimal care with minimal risk of harm.

Generic substitution may affect intrapatient variability. Yamada et al[84], performed a systematic review of 20 studies assessing generic substitution of antiepileptic drugs in patients with epilepsy (prospective, n=6; retrospective n=7) and in normal volunteers (n=7). The medications included lamotrigine, topiramate, carbamazepine, phenytoin and multiple undefined agents in 4 studies. Retrospective studies of lower quality (Class III) suggest use of generic products increases utilization of medical resources and switchback rates. Prospective studies of lesser quality (Class II) in healthy adults found significant differences in carbamazepine pharmacokinetics. Small, good quality (Class I) prospective studies did not find a difference in pharmacokinetics or bioequivalence between generic and brand drugs in patients with epilepsy. The data suggests switching among multiple generics may be associated with greater pharmacokinetic variability and poorer clinical outcomes. They suggest consistency in the product selected, regardless of whether it is generic or brand and minimizing product substitution.

Drug Interactions

A meta-analysis was performed comparing the efficacy of enzyme-inducing antiepileptic drugs with non-enzyme inducing antiepileptic drugs. Included were 37 studies involving 9,860 patients with refractory epilepsy. Meta-regression analysis for 50% reduction in seizure frequency found no difference in relative risk of 1.1 (95% CI 0.77-1.34, p=0.92) for enzyme-inducing vs non-

enzyme inducing antiepileptic drugs. A similar non-significant relative risk was found for the proportion of patients remaining seizure-free (RR 1.38; 95% CI 0.60-3.16, p=0.43).[85] The choice of non-enzyme inducing antiepileptic drug therapy may be preferred to prevent negative consequences associated with drug interactions but does not increase efficacy.

The pharmacokinetics of the newer antiepileptic drugs is found in Table 5; information concerning hepatic metabolism and effects on hepatic enzymes is found in Table 6; the interaction between antiepileptic drugs is presented in Table 7; and the interaction between the newer anticonvulsant medications and others drugs is presented in Table 8.

Table 6: Pharmacokinetics of the Newer Antiepileptic Drugs[7,8 3,6,8-30]

Agents	Absorption	Distribution	Active Metabolite	Excretion	Elimination Half-life
Brivaracetam (Briviact®)	BA: ~100% Tmax: 1 hour	Vd: 0.5 L/kg PB: <20%	No	Renal > 95%	9 hours
Clobazam	BA: 87% Tmax: 0.5-4 hours	Vd: 100 L PB: 80-90%	N-desmethyl-clobazam	Fecal 11% Renal 82%	Parent: 36-42 hours Metabolite: 71-82 hours
Eslicarbazepine Acetate (Aptiom®)	BA: > 90% Tmax: 1-4 hour	Vd: 0.87 L/kg PB: <40%	(S)-licarbazepine Minor oxcarbazepine (R)-licarbazepine	Renal 90%	13 – 20 hours
Ezogabine (Potiga®) Schedule V	BA: 60% Tmax 0.5-6 hour	Vd: 2-3 L/kg PB: 80%	NAMR (N-acetyl metabolite)	Fecal 14% Renal 85%	7-11 hours (parent and NAMR)
Felbamate (Felbatol®)	BA, Tmax: Not determined	Vd: 0.7-1.0 L/kg PB: 22-25%	No	Renal: 90%	20-23 hours
Gabapentin (Fanatrex FusePaq®, Gralise®, Horizant®, Neurontin®, others) Gabapentin (Fanatrex FusePaq®, Gralise®, Horizant®, Neurontin®, others)	BA: 27% to 60% (inversely proportional to dose) Tmax: ER 8 hour IR 2 hour Food: ↑ rate and extent of absorption vs fasting	Vd: 58 L PB <3%	No	Fecal 10% to 23% Renal 76% to 81%	Adults: 5 to 7 hours Pediatrics: 4.4 hours
Lacosamide (Vimpat®)	BA: 100% Tmax: 1-4 hour	Vd 0.6 L/kg PB <15%	No	Fecal: < 0.5% Renal excretion: 95%	13 hours

Agents	Absorption	Distribution	Active Metabolite	Excretion	Elimination Half-life
Lamotrigine (Lamictal®, Lamictal ODT®, Lamictal Starter Kit®, Lamictal XR®, Lamictal XR Patient Titration Kit®‡, others)	BA: 98% Tmax: Adult: 1.4 to 4.8 hours Pediatric: 1.6 to 5.2 hr Extended Release: 4 to 11 hr (varies with concomitant drugs)	Vd 1.1 L/kg PB 55%	No	Fecal: 2% Renal: 94%,	Adults (epilepsy): 12.6 to 58.8 hr; (shorter with concomitant enzyme-inducer(s) and longer with concomitant valproic acid only)
Levetiracetam (Keppra®, Keppra XR®, Spritam®, others)	BA ~100% Tmax: IR: 1 hour ER: 4 hours	Vd 0.5-0.7 L/kg PB: <10%	No	Enzymatic hydrolysis: 24% Renal: 66%	6 to 8 hours
Oxcarbazepine (Trileptal®, Oxtellar XR®, others)	BA: ~100% Tmax: IR: 4.5 hours Oral Suspension: 6 hours ER: 7 hours	Vd: 49 L PB: 67%	10–monohydroxy-carbazepine	Fecal 4%: Renal 95%	IR: 2 hours ER: 7 to 11 hours Active Metabolite: 9 to 11 hours
Perampanel (Fycompa®)	BA: 100% Tmax: 0.5 to 2.5 hours Food: ↓ Cmax 28% to 40%; ↑Tmax 2 to 3 hour	PB: 95%	No	Fecal: 48% Renal: 22%	105 hours
Pregabalin (Lyrica®)	BA: 90% Tmax: 1.5 hours	Vd: 0.5 L/kg PB: none	No	Fecal < 0.1% Renal: 90%	6.3 hours

Agents	Absorption	Distribution	Active Metabolite	Excretion	Elimination Half-life
Rufinamide (Banzel®)	BA: 85% Tmax: 4 to 6 hours Food: ↑ 34%	Vd: 50 L PB: 21%	No	Renal: 85%	6 to 10 hours
Tiagabine (Gabitril®)	BA: 90% Tmax: 45 minutes	Vd: Not determined PB: 96%	No	Fecal: 63%* Renal: 25%* *as metabolites	7 to 9 hours
Topiramate (Qudexy XR®, Topamax®, Topamax Sprinkle®, Topiragen®, Trokendi XR®, others)	BA: 80% Tmax: - IR: 1.5 to 4 hours - ER Single dose: 20 to 24 hours -ER: Multiple dose: 6 hours Food: -Qudexy XR: Tmax ↑ 4 hours -Trokendi XR: Cmax ↑ 37% Tmax ↓8 hours	Vd: 0.6-0.8 L/kg PB: 15-41%	No	Renal 70%	IR: 21 hours ER: 31 hours Trokendi XR: 31 hours Qudexy XR: 56 hours
Vigabatrin (Sabril®)	BA: 50% Tmax: Tab: 1 hour Solution: 1.0-2.5 hour	Vd: 1.1 L/kg PB: Not determined	No	Renal: 95%	Adults: 10.5 hours Children (10 to 16 years): 9.5 hours Infants(5 to 24 months): 5.7 hours
Zonisamide (Zonegran®, others)	BA: 100% Tmax: 2 to 6 hours Food: ↑Tmax 4 to 6 hours	Vd 0.8-1.6 L/kg PB 40-60%	No	Fecal 3% Renal 62% (35% unchanged)	Adults 63 hours

Table 7: Newer Antiepileptic Drug Metabolic Pathways and in-vitro Hepatic Enzyme Effects [3,6,8,9,11-30]

Drug	Major Hepatic Enzymes Substrate	Induced	Inhibited
Brivaracetam	2C19	None	None
Clobazam	CYP2B; CYP2C19; CYP3A4	CYP3A4	CYP2D6
Eslicarbazepine	UGT2B4	CYP3A4	CYP2C19
Ezogabine	None	None	None
Felbamate	None	2C19	None
Gabapentin	Not metabolized		
Lacosamide	2C19; CYP3A4, CYP2C9	None	None
Lamotrigine	Gluconyl transferase Caution: Auto induction Possible		None
Levetiracetam	Non-hepatic hydrolysis	None	None
Oxcarbazepine	None	CYP2C19	CYP3A4/5
Perampanel	CYP3A4/5, CYP1A2, CYP2B6	CYP 2B6; CYP3A4/5	CYP2C8; CYP3A4
Pregabalin	Not metabolized		
Rufinamide	None	CYP2E1	CYP3A4
Tiagabine	CYP3A4	None	None
Topiramate	CYP2C19	CYP2C19; CYP3A at doses > 200 mg/day	CYP2C19
Vigabatrin	None	CYP2C9	None
Zonisamide	CYP3A4	None	None

Table 8: Drug Interactions Between Newer Antiepileptic Agents [3,6,8,9,11-30]

Drug	Concomitant Medication	Resultant Effects
Brivaracetam	Carbamazepine Levetiracetam Phenytoin	↓ Brivaracetam concentration

Drug	Concomitant Medication	Resultant Effects
Clobazam	Eslicarbazepine Felbamate Perampanel Rufinamide	↑ Clobazam concentration
Eslicarbazepine	Carbamazepine Phenobarbital Phenytoin Primidone	↓ Eslicarbazepine concentration
Ezogabine	Carbamazepine Phenytoin	↓ Ezogabine concentration
Felbamate	Carbamazepine Phenytoin	↓ Felbamate concentration
	Valproic Acid	↑ Felbamate concentration
Gabapentin	None known	
Lacosamide	Carbamazepine Phenobarbital Phenytoin	↓ Lacosamide concentration
Lamotrigine	Carbamazepine Perampanel Phenobarbital Phenytoin	↓ Lamotrigine concentration
	Primidone	↑ Lamotrigine concentration
	Valproic Acid	
Levetiracetam	None known	
Oxcarbazepine	Carbamazepine Phenobarbital Phenytoin	↓ active metabolite concentration
	Perampanel	↑ active metabolite concentration
Perampanel	Carbamazepine Oxcarbazepine Phenytoin Topiramate	↓ Perampanel concentration
Pregabalin	None known	
Rufinamide	Carbamazepine	

Drug	Concomitant Medication	Resultant Effects
	Phenobarbital Phenytoin Primodone	↓ Rufinamide concentration
	Valproate	↑ Rufinamide concentration
Tiagabine	Carbamazepine Phenytoin	↓ Tiagabine concentration
Topiramate	Carbamazepine Phenytoin Valproic Acid	↓ Topiramate concentration
Vigabatrin	None known	
Zonisamide	Carbamazepine Phenobarbital Phenytoin	↓ Zonisamide concentration

Table 9: Interactions Between Newer Anticonvulsant Medications and Other Drugs[3,6,8,9,11-30]

Drug	Concomitant Medication	Resultant Effects
Brivaracetam	Rifampin	↓ brivaracetam concentrations
Clobazam	Hormonal contraceptives Ketoconazole	↓ contraception effectiveness ↑ clobazam concentration
Eslicarbazepine	Omeprazole Simvastatin, Rosuvastatin Warfarin	↑ omeprazole concentration ↓ simvastatin, rosuvastatin concentration ↓ warfarin concentration
Ezogabine	Digoxin	↑ Digoxin concentration
Felbamate	None	
Gabapentin	Antacids	↓ gabapentin absorption
Lacosamide	Strong inhibitors of CYP3A4 and CP2C9 (e.g. azoles, protease inhibitors, macrolides)	↑ lacosamide concentration
Lamotrigine	Hormonal contraceptives	↓ contraception effectiveness
Levetiracetam	None	

Drug	Concomitant Medication	Resultant Effects
Oxcarbazepine	Hormonal Contraceptives Cyclosporine	↓ contraception effectiveness ↓ cyclosporine concentration
Perampanel	Rifampin, St. John's wort Hormonal contraceptives	↓ perampanel concentration ↓ contraception effectiveness
Pregabalin	None	
Rufinamide	Hormonal contraceptives Triazolam	↓ contraception effectiveness ↓ triazolam AUC and peak concentration
Tiagabine	None	
Topiramate	Hormonal contraceptives	↓ contraception effectiveness
Vigabatrin	None	
Zonisamide	None	

Special Populations[9,12-30]

Recommendations for use in special populations are presented in Table 9.

Pregnancy/Lactation

Topiramate is FDA category D while other agents are classified as category C. Many of the medications are excreted in breast milk and cautious use should follow a risk/benefit assessment. Issues relating to teratogenicity are discussed below under Safety. The FDA does not consider post-marketing information and update the categorization of pregnancy risk. The initial determination of pregnancy category by the FDA is often based only on in-vitro or animal data and may not correlate with real-world use of the medications.[86]

Children

The definition of child varies among agents used for epilepsy; from under 12 years for gabapentin and perampanel to 16 years with eslicarbazepine, lacosamide and levetiracetam, to 18 years with pregabalin and ezogabine. The dose (mg/kg) of antiepileptic medications in children may be 30% higher than adults due to more rapid renal and hepatic clearances. Efficacy of these medications does not differ significantly between children or adults. Children, however, are more prone to idiosyncratic reactions (see Safety).[87]

Renal

The agents most likely to require dosing adjustments due to renal dysfunction are those agents eliminated unchanged by the kidney or undergoing minimal metabolism, including; gabapentin, pregabalin, vigabatrin and topiramate. Some modification and caution in use may be required for those eliminated by a combination or renal elimination and hepatic metabolism, including eslicarbazepine, ezogabine, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, zonisamide. Hemodialysis removes ethosuximide, gabapentin, lacosamide, levetiracetam, pregabalin and topiramate.[88]

Hepatic

The agents most likely to require dosing adjustments due to hepatic dysfunction are those eliminated via biotransformation, including, brivaracetam, clobazam, ezogabine, felbamate, lacosamide, lamotrigine, perampanel, rufinamide, tiagabine and zonisamide.[88]

Geriatric

The use of antiepileptic medications in the elderly involves a number of considerations. The clearance of renally and hepatically eliminated unbound drugs is reduced 20-40%.[40]. Metabolic oxidative and hydroxylation reactions (phase I) are diminished while glucuronidation, acetylation and sulfonation reactions (phase II) are less affected.[38]The healthy elderly typically have low-normal albumin levels. Those with concomitant rheumatoid disease, malnutrition and renal insufficiency often have lower albumin levels resulting in increased unbound drug concentrations.[35,38,39] Pharmacodynamic interactions are common in the elderly receiving antiepileptic agents. [35,38,39] An interaction between oxcarbazepine and thiazide diuretics may produce significant hyponatremia. The sedative effects of antiepileptic drugs are augmented when added to other centrally acting depressants and a reduction in the body's homeostatic, counter-regulatory mechanisms makes the elderly more sensitive to adverse effects. Cognitive impairment appears to increase when elderly patients with epilepsy are placed on antiepileptic drugs when compared to normal elderly.

Drug interactions are common in the elderly who take on average 7 medications, with 25% receiving 15 or more medications.[35] Enzyme inducing antiepileptic drugs interact with many medications taken chronically (e.g. warfarin, statins, corticosteroids). Enzyme induction results in reduced vitamin D levels which may predispose to osteoporosis and increased fracture risk. Enzyme induction also reduces sex hormone levels and may result in sexual dysfunction. Additionally, multiple prescribers or a lack of regular review of the patient medication regimen places the elderly at increased risk of adverse events.[4,38,39,82]

The appropriate selection of an antiepileptic medication in the elderly considers pharmacokinetic and pharmacodynamic issues, drug-drug and drug-disease state interactions as well as safety and efficacy information. For instance, in the presence of conduction abnormalities or ventricular arrhythmias oxcarbazepine and lamotrigine may be preferred. When concern for hepatic enzyme interactions or plasma protein binding is present gabapentin, lamotrigine, levetiracetam, tiagabine and vigabatrin may be preferred.[40,89 89]

Table 10: Special Populations[15,40,90]

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (excreted in breast milk)	Pediatric	Geriatric
Brivaracetam (Briviact®)	No Adjustment (ESRD with hemodialysis: Not recommended)	Hepatic impairment (all stages) start with 25 mg twice daily Maximum dosage is 75 mg twice daily.	C	Unknown Consider the risk/benefit of therapy		Data unavailable (use caution)
Clobazam (Onfi®)	Mild to moderate insufficiency: No change Severe: Unknown	Child-Pugh score 5-9: Adjust dose (no recommendation given) Severe Impairment: No information _____ Poor CYP2C19 metabolizers (will have increased active metabolite levels): Initiate therapy based on weight and titrate slowly ≤ 30 kg: • 5 mg daily; after 7 days 10 mg daily; after 14 days 20 mg daily > 30 kg: • 10 mg daily; after 7 days 20 mg daily; after 14 days 40 mg daily **Divided Doses for doses > 5 mg	C	Yes Consider the risk/benefit of therapy	Age < 2 years: Not established	Studies are lacking Start with 5 mg/day, titrate to 10-20 mg/day (Ma: 40 mg/day max)
Eslicarbazepine (Aptiom®)	CrCl < 50 mL/min: Reduce initial, titration and maintenance doses by 50% (titrate to response) End-stage renal disuse with hemodialysis: Use with caution	Mild to moderate impairment: No adjustment Severe impairment: Use not recommended	C	Yes Consider the risk/benefit of therapy	Age < 18 years: Not established	Use with caution
Ezogabine (Potiga®)	CrCl < 50 mL/min or ESRD on hemodialysis: 600 mg/day	Child-Pugh score 7-9: 750 mg/day Child-Pugh score >9: 600 mg/day	C	Unknown Consider the risk/benefit of therapy	No Information	Reduce dose to 750mg/day

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (excreted in breast milk)	Pediatric	Geriatric
Felbamate (Felbatol®)	Reduce starting and maintenance doses by one-half Further reductions in daily doses should be considered in patients with renal dysfunction receiving adjunctive therapy with drugs affecting felbamate plasma concentrations	Contraindicated in patients with a history of hepatic impairment	C	Yes Consider the risk/benefit of therapy	Established only in the setting of Lennox-Gastaut	Initiate therapy at lower end of the dosage range • ↓ dose by 10-20%
Gabapentin (Neurontin®)	CrCl ≥ 60 mL/min • 900-3600 mg/day CrCl 30-59 mL/min: • 400-1400 mg/day • CrCl 15-29 mL/min: 200-700 mg/day CrCl <15 mL/min: Non-hemodialysis: Administer daily dose as a proportion of CrCl Hemodialysis: Administer maintenance dose based on CrCl above and give post 4-hr dialysis supplemental dose	No adjustment	C	Yes Exposure of 1 mg/kg/day Consider the risk/benefit of therapy	Age < 3 years: Adjunctive therapy of partial seizures, not established	Start with lower dosages due to age anticipated reductions in hepatic, renal, cardiac function comorbidities and concomitant medications • ↓dose by 30-50%
Lacosamide (Vimpat®)	CrCl ≤ 30 mL/min and ESRD: 300 mg daily (Consider supplemental dosage of up to 50% after hemodialysis)	Mild to moderate impairment: • 300 mg daily Severe impairment: Not recommended	C	Unknown Consider the risk/benefit of therapy	Age < 17 years: Not established	Titrate cautiously
Lamotrigine (Lamictal®)	Reduce initial, escalation and maintenance doses	Consider reduced maintenance doses	C	Yes Use with caution Exposure up to 50% of maternal serum levels Risk if pre-pregnancy dose is not reduced Effects: apnea, drowsiness, poor sucking	Age < 2 years: Not established Age 1-24 months: Increased incidence of infectious and respiratory adverse events	Start with lower dosages due to age anticipated reductions in hepatic, renal, cardiac function comorbidities and concomitant medications • ↓ dose by 35%

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (excreted in breast milk)	Pediatric	Geriatric
Levetiracetam (Keppra®)	CrCl > 80 mL/min • 500-1500 mg every 12 hours CrCl 50-80 • 500-1000 mg every 12 hours • CrCl 30-50 • 250-750 mg every 12 hours • < 30 mL/min • 250-500 mg every 12 hours ESRD with dialysis • 500-1000 mg every 24 hours (with 250-500 mg supplemental dose post dialysis)	No Adjustment	C	Yes Consider the risk/benefit of therapy	< 12 years: Not established	No differences noted between young and old, however, age-related reductions in renal function should be considered • ↓ by 20-40%
Oxcarbazepine (Trileptal®)	Mild to Moderate: No adjustment CrCl <30 mL/minute: • Initiate therapy at ½ the usual starting dose (300 mg) and slowly titrate by 300-450 mg at weekly intervals ESRD (on dialysis): • Do not use extended-release formulations	Mild to Moderate: No adjustment Severe: No information	C	Yes Consider the risk/benefit of therapy	Age < 2 years: Not established	Geriatric AUC values were 30-60% higher than younger patients, primarily due to differences in renal function caused by age • ↓ by 25-35%
Perampanel (Fycompa®)	CrCl > 50 mL/min: No adjustment CrCl 30-49 mL/min: Monitor closely Severe or undergoing dialysis: Not recommended	Mild to Moderate: Initial dose is 2 mg daily. Doses are increased by 2 mg no more often than every 2 weeks. Mild: Max dose 6 mg Moderate: Max dose 4 mg Severe: Not recommended	C	Unknown Consider the risk/benefit ratio In rats the concentration in breast milk is higher than corresponding maternal serum concentrations	Age < 12 years: Not established	Due to increased likelihood of adverse events, titrate slowly
Pregabalin	CrCl 30 to 60 mL/min • 75 to 300 mg/day in 2 to 3 divided doses	None	C	Unknown	Not established	Dose reduction required with renal insufficiency

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (excreted in breast milk)	Pediatric	Geriatric
(Lyrica®)	CrCl 15 to 30 mL/min • 25 to 150 mg/day given once daily or in 2 divided doses CrCl < 15 mL/min • 25 to 75 mg once daily Hemodialysis: Give supplemental dose immediately after 4-hour dialysis session <table><tr><th>Dose</th><th>Supp. Dose</th></tr><tr><td>25 mg daily</td><td>25-50 mg</td></tr><tr><td>250-50 mg daily</td><td>50-75 mg</td></tr><tr><td>50-75 mg daily</td><td>75-100 mg</td></tr><tr><td>75 mg daily</td><td>100-150 mg</td></tr></table>			Consider the risk/benefit of therapy		
Rufinamide (Banzel®)	CrCl < 30 mL/min No adjustment needed Hemodialysis: Reduces exposure by 30% dose adjustments should be considered	Child-Pugh score 5-9 Use with caution Child-Pugh score 10-15 Use not recommended	C	Unknown Consider the risk/benefit of therapy	Age < 4 years: Not established	Dose reduction required based upon renal insufficiency
Tiagabine (Gabitril ®)	No adjustment necessary	Child-Pugh Class B Reduce initial and maintenance doses and consider longer dosage intervals	C	Unknown Consider the risk/benefit of therapy	Age <12 years: Not established	No recommendation • ↓ by 30%

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (excreted in breast milk)	Pediatric	Geriatric
Topiramate (Topamax®, Qudexy XR®, Trokendi XR®)	CrCl < 70 mL/min: • Use 50% the usual dose Hemodialysis: May require supplemental dose. Consider dose reduction or discontinuation with chronic dialysis.	No recommendation	D	Unknown Consider the risk/benefit of therapy	Age < 2 years: Not established	Dose reduction required based upon renal insufficiency • ↓ by 20%
Vigabatrin (Sabril®)	CrCl > 50 to 80 mL/min: • Decrease dose by 25% CrCl > 30 to 50 mL/min: • Decrease dose by 50% CrCl > 10 to 30 mL/min: • Decrease dose by 75% Hemodialysis ↓ plasma concentrations 40-60%	No recommendation	C	Unknown Consider the risk/benefit of therapy	Clearance differs by age: Infants (5 months – 2 years) • 2.4 L/hr Children (10-16 years) • 5.8 L/hr Adults • 7 L/hr	No recommendation • ↓ by 50-85%
Zonisamide (Zonegran®)	Titrate more slowly and increase monitoring frequency	Titrate more slowly and increase monitoring frequency	C	Unknown Consider the risk/benefit of therapy	Age < 16 years: Not established	No recommendation

Abbreviations: Pregnancy category C – Animal studies demonstrate fetal risk but there are no adequate or well-controlled studies in humans. Potential benefit should be weighed against potential risks in pregnant women; Pregnancy category D - There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

Methods

A literature search was conducted to identify articles evaluating the safety and efficacy of newer antiepileptic agents by searching the MEDLINE database (1950 – 2016), EMBASE database (1966-2016), the Cochrane Library and reference lists of review articles. Only trials published in English were included. Non-comparative and placebo-controlled trials were excluded.

Clinical Efficacy

French et al, points out that most trials performed according to FDA requirements use seizure reduction as a surrogate marker for disease improvement as the primary outcome measure. Studies do not capture quality of life concerns, seizure severity or patterns. FDA requirements for studies of new antiepileptic drugs as monotherapy in refractory partial epilepsy are not true efficacy studies but rather compare deterioration with the comparison group. [42] The Clinical Efficacy is presented in Appendix I.

Juvenile Monoclonic Epilepsy

Liu et al, published a Cochrane review of 3 randomized, controlled trials found topiramate better tolerated and as effective as valproate in producing a 50% reduction in monoclonic and primary generalized tonic clonic seizures with no difference in achieving seizure free status.[91]

Benign Epilepsy of Childhood with Centrotemporal Spikes

Coppola et al, 2007 evaluated levetiracetam and oxcarbazepine in 39 children with benign epilepsy of childhood with centrotemporal spikes (BECTS). At 18 months, there was no statistical difference between levetiracetam and oxcarbazepine in the proportion of patients that were seizure free (90.5% vs 72.2%, p=0.410). Adverse events were generally mild (i.e. transient appetite decrease, cephalalgia, headache and sedation). Two levetiracetam patients were switched to alternative therapy due to adverse effects and one patient required a dosage increase. Five oxcarbazepine patients received alternative therapy due to a lack of seizure control. Larger studies are required to clearly demonstrate equivalence between the agents, however, oxcarbazepine and levetiracetam appear equally safe and effective in the treatment of BECTS.

Lennox-Gastaut Syndrome

No comparative trials were identified.

Generalized, Unclassified, Mixed Epilepsy

Kowalick et al, 2008 report on an open-label, non-interventional trial in epilepsy patients at least 12 years old experiencing either a treatment failure or tolerance issue with oxcarbazepine or carbamazepine (n=140). Topiramate therapy was added to the current regimen and the physician evaluated whether the baseline medication was able to be discontinued after dose-titration was completed. Monotherapy was achieved in 73% of 140 topiramate-treated patients when dosed at 150 mg/day vs 100 mg/day ($p<0.05$). A reduction in seizures of at least 50% was achieved in 91% of patients with 43% remaining seizure free. Quality of life improvements were significantly improved by both patient and physician assessment ($p<0.001$). Adverse events were reported in 34%

of patients and matched the general adverse event profile of topiramate. A statistically significant reduction in body weight of approximately 1.9 kg was observed. The most common serious adverse event was convulsions noted eight-times in 6 patients. Treatment with topiramate resulted in improved seizure control and quality of life determinations.

Bootsma et al performed an electronic extraction of information and chart review of 1,066 patients at a tertiary care epilepsy center treated with either lamotrigine, levetiracetam or topiramate to compare retention rates. Data was extracted over more than decade. Epilepsy types included partial, generalized, unclassified and undetermined. The primary outcome measured was retention rate. Statistical analysis found lamotrigine superiority in retention at both 1- and 2-years. Outcome measures found the ability to achieve a 6-month seizure free response best with levetiracetam and lowest with lamotrigine although the difference was not significant. Discontinuation rates due to adverse events were most common with topiramate then levetiracetam followed by lamotrigine. The differences between each of the agents was statistically significant. Retention rates reflected tolerability to a greater extent than efficacy. It is possible that the results reflect a bias in topiramate data reflected the period 1993-2002, lamotrigine 1996-1997 and levetiracetam 2001-2003. More recently treated patients may reflect a subset that was inadequately controlled by medications released a decade earlier and may reflect a more refractory population.[92]

Anand et al, published a Cochrane review of treatment of new-onset partial or generalized seizures in children and adults (2 studies, n=163) with clobazam, alternative antiepileptic drug or placebo. One trial found clobazam and carbamazepine treatment yielded similar results for 12-month retention rates. At 6-months, clobazam had higher retention rates than carbamazepine but statistical significance was not achieved. A second trial found clobazam with better retention rates compared with phenytoin.[93]

Rosenow et al, compared levetiracetam with lamotrigine in 409 patients at least 12 years of age with new-onset, focal or generalized seizures. No difference between levetiracetam (2000 mg/day) and lamotrigine (200 mg/day) was found for the rate of seizure-free patients at 6-weeks (67.5% vs 64.0%) or 26-weeks (45.2% vs 47.8%). Adverse events occurred in a similar proportion of patients although discontinuation due to an adverse event occurred significantly more often with levetiracetam (p=0.07). The authors concluded there were no significant differences with regard to safety or tolerability between levetiracetam and lamotrigine.

Marson et al, reported on the findings of the Standard and New Antiepileptic Drug (SANAD) study, arm B. A total of 716 patients for whom therapy with valproate was considered first-line were randomized in an unblinded manner to monotherapy with either valproate, lamotrigine or topiramate. Hazard ratios found valproate superior to topiramate in the time to treatment failure (1.57, 95% CI 1.19-2.08) and equivalent in time to 12-month remission overall. Similar findings were observed in the subset of patients with idiopathic generalized epilepsy. Lamotrigine was not different than valproate in time to treatment failure but statistically inferior with respect to time to 12-month remission (0.76, 95% CI 0.62-0.94). In the subset analysis of patients with idiopathic generalized epilepsy, valproate was superior to lamotrigine. Valproate was superior to topiramate and lamotrigine in time to first seizure. No differences in quality of life measures were noted between treatments although patients attaining seizure control reported more positive outcomes. The development of at least one adverse event was found for topiramate 45%, lamotrigine 37% and valproate 36%. The most common adverse events associated with valproate were weight gain 16%, tired/drowsy/fatigue/lethargy 12%. Weight gain was the most common adverse event reason for

valproate discontinuation (4%). Most commonly noted with topiramate were tired/drowsy/fatigue/lethargy 20%, behavior/personality change/aggression 18%, psychiatric symptoms 15%, weight loss 12% and memory problems in 10%. Discontinuation of therapy due to adverse effects was most commonly a result of psychiatric, cognitive, tiredness, and fatigue effects. The only adverse event noted at a rate greater than 10% for lamotrigine was allergic rash which was the most common adverse event resulting in treatment discontinuation. Overall, valproate was more efficacious than lamotrigine and better tolerated than topiramate.[94]

Arif et al, conducted a retrospective review of 417 outpatients ≥ 55 years of age, receiving antiepileptic medications (carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproic acid or zonisamide) to determine retention rates, efficacy and adverse events. Statistical analysis identified only the specific antiepileptic drug as a predictor of 12-month retention. Twelve-month retention rates were better with lamotrigine and levetiracetam. Lamotrigine performed statistically better than carbamazepine, gabapentin, oxcarbazepine, phenytoin, topiramate. Levetiracetam was statistically superior to carbamazepine and oxcarbazepine. Oxcarbazepine performed poorest of all agents. Twelve-month seizure free rates were highest with lamotrigine and levetiracetam. Overall, the most common adverse effects were imbalance, drowsiness and gastrointestinal symptoms. The most common adverse events by medications, were lamotrigine (imbalance >10%), levetiracetam (drowsiness >20%, psychiatric effects >10%), phenytoin (allergies 5-10%), topiramate (cognitive effects and drowsiness >20%), valproate (tremor >10%), zonisamide (cognitive and gastrointestinal effects >10%), carbamazepine (drowsiness > 10%), clobazam (drowsiness > 20%), gabapentin (drowsiness > 20%), oxcarbazepine (drowsiness and dizziness >10%). In older adults, lamotrigine and levetiracetam were the most effective agents while oxcarbazepine was the least effective.[34]

Secondary, Generalized Tonic-Clonic Seizures

Hemery conducted a meta-analysis evaluating antiepileptic therapy in secondary, generalized tonic-clonic seizures. A total of 24 randomized, controlled trials were found, assessing 7,823 patients. Responder rates were identified for lacosamide, perampanel, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide in 13 studies. Median reductions from baseline at 28-day analysis were identified for carisbamate, levetiracetam, oxcarbazepine, perampanel, pregabalin, rufinamide and topiramate in 14 studies. Only lacosamide, perampanel and topiramate demonstrated greater efficacy than placebo, however, relative risk confidence intervals overlapped for all antiepileptic drugs except pregabalin, which demonstrated significantly lower efficacy than lacosamide, perampanel and topiramate.[95]

Partial-Onset Epilepsy, Monotherapy

Zhou et al, performed a Cochrane Review comparing monotherapy with pregabalin to lamotrigine or gabapentin. In comparison to lamotrigine in newly diagnosed patients, pregabalin affords similar tolerability but inferior efficacy. Pregabalin produced more weight gain, somnolence and convulsion than lamotrigine. Pregabalin was further compared with gabapentin for treatment of refractory partial epilepsy in a hospital setting. A short follow-up period (8 days) prohibited any generalizations applicable to outpatient clinical practice.[96]

Kwan et al, performed a randomized, phase III, non-inferiority trial comparing monotherapy with pregabalin to lamotrigine in the treatment of 660 adult patients newly diagnosed with partial-

onset seizures. Fewer pregabalin treated patients achieved a 6-consecutive month seizure free status. The median time to a new seizure was 85 days for pregabalin and 211 days for lamotrigine. Pregabalin did not achieve the end-point of non-inferiority. Tolerability was similar between agents.[97]

Cumbo et al, assessed the effectiveness of levetiracetam, lamotrigine and phenobarbital on seizures and cognitive function in 95 antiepileptic-drug naïve adults with Alzheimer's disease and partial-onset epilepsy. The 12-month response rate (levetiracetam 71%, phenobarbital 64% and lamotrigine 59%, p=0.34 between groups) and seizure free rates (levetiracetam 29%, phenobarbital 29%, lamotrigine 24%) were not different demonstrating each medication was effective in reducing seizures. Cognitive effects were assessed by three tools. Results of Mini Mental State Examinations demonstrated levetiracetam superiority over all agents; phenobarbital superiority over lamotrigine; and all antiepileptic agent's superior over baseline. Results of the Alzheimer Disease Assessment Scale-Cognitive found levetiracetam superior to lamotrigine with each of the agents showing improvements over baseline. The Cornell Scale for Depression found levetiracetam superior to lamotrigine and phenobarbital; phenobarbital superior to lamotrigine; with only levetiracetam showing improvement from baseline. Adverse events reflected the known effects of the agents and were not significantly different, however withdrawal due to an adverse event occurred only in patients receiving phenobarbital (17%) primarily due to sedation. Overall, the agents are equally effective with levetiracetam showing better effects on cognition. [98]

Marson et al, reported on the findings of the Standard and New Antiepileptic Drug (SANAD) study, arm A. A total of 1,721 patients for whom therapy with carbamazepine was considered first-line were randomized in an unblinded manner to monotherapy with either carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate. Lamotrigine therapy was not different than oxcarbazepine and was superior (hazards ratio) in time to treatment failure versus carbamazepine (0.78, 95% CI 0.63-0.97), gabapentin (0.65, 95% CI 0.52-0.80) and topiramate (0.64, 95% CI 0.52-0.79). Carbamazepine was superior to gabapentin in the time to 12-month remission (0.75, 95% CI 0.63-090) while lamotrigine demonstrated non-inferiority. Treatment failure, defined as the likelihood of terminating treatment for any reason (including adverse events) was highest for lamotrigine > carbamazepine > oxcarbazepine > gabapentin > topiramate. Termination due specifically to adverse events was highest with carbamazepine and topiramate. Failure due to inadequate seizure control was most common with gabapentin and least common with carbamazepine. Treatment failure due to unacceptable adverse effects was highest with carbamazepine and topiramate and least likely with gabapentin and lamotrigine. Quality of life measures among agents did not differ significantly. Lamotrigine was found clinically-superior to carbamazepine. Lamotrigine also demonstrated superiority over carbamazepine in reduced cost per quality-adjusted life-year gained and cost-effectiveness (cost per seizure avoided).[99]

Partial-Onset Epilepsy, Adjunctive Therapy

Crawford et al, compared the efficacy and safety of gabapentin and lamotrigine in 83 learning disabled patients with partial-onset, refractory epilepsy. No differences were noted in responder rate or seizure-free rates. Gabapentin demonstrated superiority over lamotrigine in the behavioral outcomes of communication, cooperation and restlessness on the Cricton Royal Behaviour Rating Scale ($p<0.05$). Both agents demonstrated behavioral improvements over baseline and neither exacerbated the challenging baseline behaviors often seen in this population. Both agents were well tolerated. Gabapentin was associated with more ataxia and somnolence during the dose-titration

phase than lamotrigine, but during the evaluation phase no difference was noted. Gabapentin and lamotrigine appear to be effective and well tolerated in this population.[100]

Martyn-St James used conventional and network meta-analyses to assess the safety and efficacy of ezogabine with other antiepileptic drugs (eslicarbazepine, lacosamide, pregabalin, tiagabine, zonisamide) in the treatment of refractory partial epilepsy (20 studies; n=6,586 patients). No difference was noted between ezogabine and the other antiepileptic drugs with respect to responder rate or seizure free rates during either the double-blind or maintenance treatment period. There was no difference in the rate of withdrawals due to adverse events or the incidence of ataxia, dizziness, fatigue or nausea among agents. Ezogabine resulted in a lower response rate than pregabalin during the double-blind treatment period, a higher rate of withdrawal than eslicarbazepine and a higher incidence of somnolence than tiagabine. Overall the risks and benefits of ezogabine are similar to the other agents.[101]

Marson et al, 1996 performed one of the earliest meta-analysis of newer antiepileptic agents (gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin and zonisamide). The analysis compared the placebo-controlled trials of the agents to each other. Their review of 28 randomized controlled trials involving 3,883 patients found no difference in efficacy or tolerability among agents. The confidence intervals were wide and differences among agents could not be ruled out. [102]

Bhaumik et al, performed a retrospective case note study assessing vigabatrin, lamotrigine and gabapentin in adult outpatients with refractory epilepsy and learning disorders. Seventy-one treatment episodes in 51 patients were identified. No differences were found among agents for efficacy or safety measures. Of interest, vigabatrin produced more seizure-free periods than gabapentin, while lamotrigine produced none. Vigabatrin was associated more commonly with behavioral problems, gabapentin with drowsiness and unsteady gate. Lamotrigine was associated with increased seizures at higher doses (24%) and was the only agent to cause a rash.[103]

A retrospective, case review, identified 463 patients who received gabapentin, tiagabine, vigabatrin, lamotrigine or topiramate for treatment of refractory localization-related epilepsy who failed a prior, first–line drug. The response rate varied from 31% with gabapentin to 11% with tiagabine. No agents produced a seizure free rate of more than 10%. A 25% increase in seizures (loss of control) was noted in13% treated with tiagabine and less than 9% with other agents. Vigabatrin use resulted in the highest withdrawal rate due to a lack of efficacy (46%). The continuation rate was highest with lamotrigine (60%) and lowest with vigabatrin 38%. The rate of adverse effects was topiramate 42%, tiagabine 26%, vigabatrin 16%, gabapentin 16% and lamotrigine 15%. This study demonstrates the wide variability in efficacy and tolerability seen with use of these agents in clinical practice.[104]

Lindberger et al, evaluated the use of gabapentin or vigabatrin as the first add-on therapy in 102 patients who failed partial-onset seizure monotherapy. The study was stopped prematurely (not explained) and statistical power was limited. A 15% difference in efficacy between gabapentin and vigabatrin was not found. Overall, one-third of patients became seizure free with add-on therapy. Adverse event rate and type were similar between groups. Post-study perimetry identified 3 vigabatrin and no gabapentin patients with abnormal results.[105]

Zaccara et al, performed a non-inferiority trial in 509 patients with refractory partial seizures in which adjunctive therapy with levetiracetam was compared with pregabalin. Non-inferiority was

found between levetiracetam and pregabalin with respect to both the proportion of patients achieving a 50% reduction in seizure rate and actual percent change in seizure rate at 28 days. Additionally, a post-hoc analysis failed to demonstrate a difference between the agents for the proportion of patients who remained seizure free during the maintenance phase of the trail (levetiracetam > pregabalin; p=0.155) No differences in safety were noted. The incidence and type of adverse events was similar between agents.[106]

Gao et al, performed a meta- analysis of newer antiepileptic drugs, eslicarbazepine, ezogabine, carisbamate, lacosamide, brivaracetam and perampanel in the adjunctive treatment of adults with refractory partial-onset epilepsy whom had failed at least two kinds of antiepileptic drugs. Overall, the new agents performed better than placebo in responder and seizure free rates, but were associated with a higher withdrawal rate and more adverse events. Through indirect comparisons, brivaracetam and ezogabine appear to be more effective than the other antiepileptic agents while brivaracetam and perampanel are better tolerated.[107]

Costa et al, performed a meta-analysis of randomized controlled trials comparing new antiepileptic drugs (oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, zonisamide, eslicarbazepine and lacosamide) to each other or placebo, in refractory partial epilepsy. Sixty-two placebo-controlled (n=12,902) and 8 head to head (n=1,370) comparisons were analyzed. Antiepileptic drugs were associated with higher response rates and withdrawal rates compared with placebo. Indirect comparisons of response favored topiramate while gabapentin and lacosamide were found less efficacious. Analysis by number needed to treat favored topiramate and levetiracetam with gabapentin and tiagabine found less efficacious. Based on withdrawal rates, gabapentin and levetiracetam were better tolerated while oxcarbazepine and topiramate resulted in more drug withdrawals than other agents. The authors conclude that topiramate and levetiracetam may be more efficacious in reducing seizure frequency than gabapentin while gabapentin and levetiracetam may be better tolerated than oxcarbazepine and topiramate. Side effects were similar among all agents and all differences were of small magnitude suggesting that treatment decisions are appropriately made with consideration of other patient-related variables.[108]

Collins et al, performed a Kaplan-Meier survival analysis comparing lamotrigine, topiramate, gabapentin and vigabatrin in patients with complex, partial epilepsy patients (n=61, 126 cases). The time to 50% drop out rate was longest with lamotrigine (> 43 months) and shortest with topiramate (9.5 months). The drop-out rate due to a lack of efficacy was highest with gabapentin and vigabatrin (58.5 and 62%, respectively) and lowest with lamotrigine and topiramate (24% and 25%, respectively). Discontinuations due to side effects ranged from 12-25% for the agents. More patients continued on therapy with lamotrigine (60%) and topiramate (50%). Fewer patients remained on gabapentin and vigabatrin (20% and 30%, respectively). Overall, lamotrigine appeared to perform best.

Partial-Onset, with or without Generalization or Tonic-Clonic, Monotherapy

Brodie performed a double-blind, non-inferiority trial in the monotherapy treatment of partial-onset seizures with or without generalization or tonic-clonic seizures in patients over 16 years of age receiving either lamotrigine or gabapentin. Most patients were controlled with gabapentin 1800 mg/day or lamotrigine 150 mg/day. Kaplan-Meir assessments found no difference between the agents for the outcomes of combined safety/efficacy, time to first seizure, percent of patients completing the study, time to an exit event, withdrawal rates due to an adverse event, the percent

reporting at least 1 adverse event or the incidence of serious adverse events. Additionally, when stratified by seizure type, non-inferiority persisted. The most common adverse events in both groups were dizziness and asthenia.[109]

Faught et al, compared felbamate to valproic acid in 111 patients with uncontrolled partial-onset seizures with or without generalization. Felbamate and valproic acid were added to baseline antiepileptic drug therapy followed by a taper of baseline therapy in order to assess felbamate and valproic acid monotherapy. Patients were removed from the trial if they met 1 of 4 escape criteria, including a doubling of monthly seizure frequency; doubling of highest 2-day seizure frequency; development of generalized tonic-clonic seizure in patients having none at baseline; or significant prolongation of generalized tonic-clonic seizures. Felbamate therapy resulted in fewer escapes for each criteria and overall ($p<0.001$). Adverse events were mild and similar between groups. Those occurring at a rate > 10% for felbamate therapy were headache, nausea and somnolence and for valproic acid, nausea and headache. Four of 56 patients receiving felbamate had mild and transient SGOT/SGPT elevations. Of these four patients, one patient each was receiving lovastatin or phenytoin.

Non-comparative and placebo-controlled systematic reviews, meta-analysis and Cochrane Reviews

Lattanzi et al, performed a systematic review and meta-analysis of placebo-controlled, randomized controlled trials with add-on brivaracetam for refractory focal epilepsy. Six trials, including 2,399 patients were included in the analysis. Pooled analysis found brivaracetam treatment produced a relative risk (RR) for $\geq$ 50% reduction in seizure frequency 1.79 (95% CI, 1.51-2.12) and for seizure freedom 4.74 (95% CI, 2.00-11.25). Data did suggest a dose-dependent response, maximized at 50 mg/day. Patients previously treated with levetiracetam were less responsive to brivaracetam. The relative risk to develop at least one treatment emergent adverse effects was 1.08 (95% confidence interval 1.00-1.16). The most frequently noted adverse effects at 10% of more were somnolence 12.4% and headache 10.4%. No serious adverse effect or unexpected adverse events were noted.[110]

Xu, et al performed a metal-analysis of placebo-controlled trials evaluating rufinamide in refractory partial and tonic-atonic seizures. Five trials including 1,512 patients were included. rufinamide treatment resulted in both increased 50% and 75% relative risk responder rates (RR 1.852 and 8.547, $p<0.001$ for both). Relative risk for achieving a seizure free status did not achieve statistical significance compared with placebo. The 50% responder rate was higher with rufinamide doses of 1600 mg ($p<0.016$) and 3200 mg ($p<0.001$) compared with doses $\leq$ 800 mg/day. The incidence of at least one adverse events and withdrawal due to adverse events was higher with rufinamide treatment ($p<0.001$ for both). Adverse effects were consistent with the prescribing information. The incidence of serious adverse effects was not different than in the placebo arm.[111]

Marson et al, performed a systematic review and meta-analysis of 11 placebo-controlled trials including 2,871 patients who received levetiracetam, oxcarbazepine, remacemide or zonisamide as add-on therapy in the treatment of drug resistant, localization-related epilepsy. Overall, all agents demonstrated efficacy compared with placebo, with levetiracetam, oxcarbazepine and remacemide demonstrating a dose-response effect. Withdrawal rates for levetiracetam were not different than placebo. Although all analyses were placebo comparisons and not drug-drug specific, the authors define a “responder-withdrawal ratio” which favored levetiracetam > zonisamide > oxcarbazepine.[112]

Hsu et al, performed a systematic review and meta-analysis of 5 placebo-controlled trials including 1,678 patients who received perampanel in the treatment of partial-onset epilepsy. Response rates (50% reduction in seizure frequency) and rates of seizure freedom were statistically significantly higher with perampanel at 4, 8 and 12 mg/day versus placebo with no differences noted between the 8 and 12 mg doses. A 2 mg/day dosage did not demonstrate superiority over placebo in rates of response or seizure freedom. Adverse events demonstrated a dose-response relationship. At 8 mg an increase in dizziness and somnolence were noted, while the 12 mg dose was associated with dizziness. Withdrawal rates were higher in the 8 and 12 mg groups than the placebo groups. Perampanel was found effective in producing a response rate and well tolerated at 4 mg. [113]

Shi et al, performed a Cochrane Review of felbamate for add-on use in refractory epilepsy. Three studies including 153 patients were evaluated. Study methodology, choice of outcomes, inadequate reporting of data and risk of bias prohibited performing a meta-analysis. The available data suggests felbamate reduced the frequency of seizures, however convincing evidence is lacking. No serious adverse events (hepatic failure or aplastic anemia) were noted. The most common adverse events noted with felbamate therapy included headache, nausea and dizziness.[114].

Hancock performed a Cochrane Review of the treatment of Lennox-Gastaut syndrome. A total of total of nine studies evaluated treatment in 979 participants. The agents included in the study were cinromide, clobazam, felbamate, thyrotropin-releasing hormone (TRH), lamotrigine, rufinamide and topiramate. Different medications were used in 7 of the nine studies. Due to differences in methodology, entrance criteria, study populations and outcome measures significant heterogeneity was present and meta-analysis was not performed. It was noted that no study addressed the most important outcome measure for many families, behavior and cognitive functioning. No study identified any agent as superior in this setting.[115]

Hancock et al, performed a Cochrane Review of the treatment of Infantile Spasms. A total of 18 trials were identified with 2 of 18 trials having enrolled > 100 subjects. The literature represented treatment of 916 patients with 12 difference antiepileptic medications. Methodology was poor reflecting the ethical problems involved with placebo injection use in children. When placebo injections consistently performed more poorly than active treatment. Evidence is best to support the use or hormonal therapy with prednisolone or tetracosatide depot in time to resolution of spasms compared with vigabatrin. Evidence suggests long-term developmental outcomes may be improved with hormonal therapies while vigabatrin may be more effective in the setting of tuberous sclerosis. The authors conclude that current evidence does not clearly define optimal therapy for infantile spasms and further research is needed.[116]

Avanzini et al, enrolled 351 adults and children with refractory epilepsies into an open-label, compassionate-use trial of felbamate therapy. The response rate between adults and children was similar. Patients were grouped via epilepsy; localization-related +/- generalization, Lennox-Gastaut syndrome or other generalized/undetermined seizures. The responder rate was 52%, 60% and 60%, respectively. The percentage of patients achieving a seizure-free status was 10%, 6% and 12%, respectively. The most commonly reported adverse events were drowsiness, insomnia, loss of appetite, nausea and vomiting. An insignificant decline in WBC and platelets was found in one patient.[117]

Outcomes

One of the favored measures of long-term performance with AEDs in observational studies is retention rate. This measure reflects both drug efficacy and safety. It reflects the willingness of a patient to continue therapy, reflecting their estimation of drug efficacy (reduction in seizure frequency) as well as tolerability (adverse effects, toxicity).[92] Evidence suggests that retention rates are higher with clobazam, lamotrigine and pregabalin over lamotrigine and gabapentin.[118,119]

An evaluation of work absence in patients with partial-onset seizures receiving either gabapentin or pregabalin favored pregabalin. Higher acquisition costs for pregabalin were offset by statistically fewer days of sick leave and less short-term disability use. Pregabalin demonstrated statistically better adherence and longer persistence rates compared with gabapentin.[119]

One-year retention rates were determined for clobazam, topiramate and lamotrigine in 224 treatment episodes in 194 children with intractable seizures. All three drugs were well tolerated. One-year retention rates and seizure improvement were good with clobazam and lamotrigine with topiramate yielding smaller effects. Serious adverse events occurred once with clobazam (including seizures) and twice with lamotrigine (rashes).[118]

Safety

Black Box Warnings[6-8,16,19,29]

Felbamate may cause *aplastic anemia* occurring at a rate 100x the untreated population. Rates of death average 20-30% although rates as high as 70% have been reported. It is unknown if the reaction is correlated with dosage, cumulative dosage, duration of therapy or concomitant use of other antiepileptic drugs. Felbamate use is also associated with development of *liver failure*. It is believed the incidence is underreported at 6 cases per 75,000 patient-years of use. Earliest findings when present (anorexia, malaise, gastrointestinal symptoms) occurred after 3-weeks of therapy, led to jaundice and in 67% death or liver transplantation within 5 weeks of onset. It is unknown if the reaction is correlated with dosage, cumulative dosage, duration of therapy or use of other antiepileptic drugs.

Lamotrigine use is associated with the development of *severe rashes* including Stevens Johnson syndrome. Used for adjunctive therapy in epilepsy, the rate with immediate release lamotrigine in children is 0.8% and drops to 0.3% in adults. The rate in adults using lamotrigine monotherapy is 0.08% and for adjunctive therapy 0.13%. When used for the treatment of adult bipolar and mood disorders the rate is 0.08% with monotherapy and 0.13% for adjunctive therapy. The risk with use of the extended-release products is unknown but expected to mimic the immediate-release product. Rashes typically develop between 2-8 weeks of treatment but have occurred anytime during treatment. Benign rashes occur but it is impossible to predict the severity of the rash and the drug should be discontinued at the first sign of rash. Evidence is insufficient at present to determine if the risk is increased with concomitant valproate or lamotrigine therapy or the use of rapid titrations schedules or higher maintenance doses.

Vigabatrin may cause progressive and permanent concentric *visual field loss* of 30% or more in a high percentage of patients. Cases have been reported in infants, children and adults. Effects have been noted affecting visual acuity and retinal damage. Risk increases with total dose and duration but risk exists throughout therapy and perhaps afterwards. Treatment should be discontinued

as soon as visual changes are identified and as soon as it is determined that a treatment benefit is not achieved. Continuing therapy is not recommended, however, when visual field defects were found, discontinuing vigabatrin did not result in reversal of defects but continuation did not result in further progression. Vigabatrin is available only through a special restricted distribution program, Support, Help and Resources for Epilepsy (SHARE) requiring vision testing at baseline, every 3-6 months during therapy and 3-6 months following cessation of therapy.

Adverse Reactions

Newer antiepileptic agents afford enhanced safety and tolerability compared with older agents.[120,121]. Adverse effects occur more commonly at higher dosages.[45,122] A list of the adverse reactions associated with the newer antiepileptic medications occurring at a rate > 5% is presented in Table 11

Table 11: Adverse reactions associated with the newer antiepileptic agents occurring at >5% (BOLD = incidence > 10%)[7,8 3,6,8-30]

	Brivaracetam	Clobazam	Eslicarbazepine	Ezogabine	Felbamate	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Oxcarbazepine	Perampanel	Pregabalin	Rufinamide	Tiagabine	Topiramate	Vigabatrin	Zonisamide
Cardio-vascular						Peripheral edema			Increased blood pressure			Peripheral edema Edema	↓QT interval		Flushing		
Central Nervous System	Fatigue hypersomnia lethargy malaise drowsiness sedation dizziness equilibrium disturbance abnormal gait ataxia vertigo psychiatric disturbance (psychotic & nonpsychotic)	Drowsiness lethargy aggressive behavior irritability Ataxia Sedation insomnia	Dizziness Drowsiness fatigue hypersomnia, sedation lethargy malaise headache fatigue cognitive dysfunction aphasia lack of concentration psychomotor retardation speech disturbance ataxia vertigo	Dizziness Drowsiness Fatigue Confusion Vertigo coordination impairment lack of concentration memory impairment	Somnolence (children >adults) headache (children <adults) fever (children > adults) dizziness insomnia fatigue nervousness (children> adults) Abnormal thinking (children), ataxia emotional lability anxiety depression	IR: Dizziness drowsiness (IR), ataxia fatigue Children: hostility	Dizziness fatigue ataxia headache Drowsiness memory impairment equilibrium disturbance	Insomnia drowsiness fatigue dizziness	Behavioral: (aggression agitation anger anxiety apathy depersonalization emotional lability irritability) Neurosis (children > adults) headache drowsiness Psychotic symptoms (infants and children) irritability (infants-adolescents) fatigue aggressive behavior (children and adolescents)	Dizziness drowsiness headache ataxia abnormal gait fatigue vertigo	Dizziness Vertigo hostility aggressive behavior drowsiness abnormal gait fatigue headache irritability falling ataxia	Dizziness somnolence ataxia headache fatigue Neuropathy thinking abnormal confusion euphoria speech disorder attention disturbance amnesia incoordination	Headache (adults > children) drowsiness dizziness fatigue	Dizziness drowsiness nervousness lack of concentration Ataxia pain depression insomnia	Paresthesia (adolescents-adult > children drowsiness fatigue dizziness memory impairment mood disorder Lack of concentration depression insomnia	Somnolence (adults < infants) headache fever (adults < infants) fatigue dizziness irritability (adults < infants) sedation (infants) insomnia (infants) Memory impairment coordination impaired disturbance in attention depression lethargy seizure (infants)	Drowsiness Headache agitation irritability fatigue tiredness confusion depression insomnia lack of concentration memory impairment
Dermatologic					Purpura (children) Skin rash (children)			Skin rash						Bruise 6%		Rash (infants)	
Endocrine / Metabolic			Decreased sodium ↑ Cholesterol ↑ LDL cholesterol ↑ Triglycerides					Dysmenorrhea weight loss weight gain			Weight gain	Weight gain xerostomia			↓ **serum** bicarbonate weight loss	Dysmenorrhea	
Gastro-intestinal	Nausea Vomiting	Sialorrhea Constipation vomiting decreased appetite increased appetite dysphagia	Nausea vomiting	Nausea	Anorexia (children) vomiting (children) nausea dyspepsia constipation Hiccup (children) weight loss (children) taste change	Diarrhea (IR)	Nausea Vomiting Diarrhea	Nausea Vomiting dyspepsia abdominal pain xerostomia constipation anorexia peptic ulcer flatulence	Vomiting (young)) Upper abdominal pain (young) appetite ↓ (children and adolescents) diarrhea	Vomiting nausea abdominal pain Diarrhea dyspepsia constipation	Vomiting nausea	Constipation ↑ appetite	Vomiting (children) nausea	Nausea Diarrhea	Anorexia diarrhea	Vomiting (infants > adults) constipation diarrhea Nausea appetite ↓ weight gain viral gastroenteritis (infants)	Anorexia Nausea abdominal pain
Hematologic Oncologic					Leukopenia (children)				Eosinophilia (young)		Bruise						
Hepatic					Liver function tests increased												
Infection						Viral infection (children)			Infection			Infection		Infection	Viral infection Infection	Viral infection (infants) UTI	

	Brivaracetam	Clobazam	Eslicarbazepine	Ezogabine	Felbamate	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam	Oxcarbazepine	Perampanel	Pregabalin	Rufinamide	Tiagabine	Topiramate	Vigabatrin	Zonisamide
Neurological-Musculo-skeletal	Weakness			Tremor	Abnormal gait (children) pain (children) tremor	Weakness	Tremor	Back pain weakness arthralgia myalgia neck pain	Weakness			Tremor Balance disorder abnormal gait weakness arthralgia	Tremor	Weakness tremor		Tremor Arthralgia pain in extremity back pain	
Ophthalmic	Nystagmus		Diplopia blurred vision	Diplopia blurred vision	Miosis (children) diplopia	Nystagmus diplopia	Diplopia, blurred vision	Nystagmus visual disturbance		Diplopia Nystagmus visual disturbance		Blurred vision diplopia	Diplopia blurred vision nystagmus	Amblyopia		Visual field constriction nystagmus blurred vision Diplopia	Diplopia
Otic					Otitis media (children)											Otitis media	
Respiratory		Upper respiratory tract infection Cough pneumonia bronchitis			Upper respiratory infection (children) Pharyngitis (children) cough (children) rhinitis			Rhinitis cough pharyngitis bronchitis dyspnea epistaxis sinusitis	Nasopharyngitis Nasal congestion cough pharyngolaryngeal pain (young) pharyngitis	Rhinitis upper respiratory tract infection		Nasopharyngitis		Flu-like symptoms pharyngitis	Upper respiratory tract infection (young) Rhinitis	Upper respiratory tract infection (infants) bronchitis (infants) pharyngitis (infants) pneumonia (infants) nasal congestion (infants) Pharyngolaryngeal pain sinusitis (infants) cough sinus headache	
Misc.	Hypersensitivity reaction	Fever				Fever						Accidental injury		Accidental injury	Fever	Candidiasis (infants)	

IR=Immediate Release; young=children and adolescents

Comparative Evidence

Geriatric

A Veterans administration study of 593 elderly patients with newly diagnosed seizures found carbamazepine, gabapentin and lamotrigine equally efficacious as monotherapy. Lamotrigine and gabapentin were associated with significantly fewer early terminations of therapy than carbamazepine ($p<0.0001$ and $p=0.008$ versus carbamazepine, respectively). Termination due to adverse events was lowest with lamotrigine (lamotrigine vs carbamazepine $p<0.0001$, lamotrigine vs gabapentin $p=0.015$).[123]

Children

A random effects meta-analysis was performed to assess the effects of second-generation antiepileptic drugs (gabapentin, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) on ataxia and imbalance in children. Data was analyzed to determine if there was a dose-response effect and if these effects were consistent across this group of agents. The review included 16 studies of 4,279 antiepileptic-treated and 1,830 placebo-treated children. Overall, an increased relative risk of ataxia and imbalance was found with antiepileptic therapy at any dose (2.73; 95% CI 2.07-3.61) and at lowest dose (1.76; 95% CI 1.26-2.46). Individually, oxcarbazepine and topiramate increased risk at all doses while gabapentin and levetiracetam did not affect balance at any dose. Antiepileptic drugs effect on balance arises from a variety of reasons, drug toxicity, somatosensory dysfunction (neuropathy, folate deficiency), direct cerebellar effects, drug-drug interactions, effects on vestibular function, postural blood pressure or cognitive effects affecting gait stability. Levetiracetam and gabapentin did not increase imbalance risk in children.[124]

Special Issues

Contraception: Antiepileptic drugs may cause hormonal contraceptive failures. Induction of CYP450 enzymes and increased glucuronidation may lead to reduced serum concentrations of estrogen and/or progesterone by clobazam, eslicarbazepine, felbamate, lamotrigine, oxcarbazepine, perampanel, rufinamide, and at high doses, topiramate. The use of non-enzyme inducing antiepileptic drugs is preferred in women of child-bearing potential when possible.[72] For patients receiving an antiepileptic drug which induces CYP450 enzymes, alternative contraception methods may be required including depot-medroxyprogesterone acetate (administered more frequently), levonorgestrel, copper IUD, barrier methods or oral contraceptives containing > 50 mcg ethinyl estradiol. Due to the prolonged effect of the antiepileptic drugs on enzyme induction, enhanced contraception should continue for 4 weeks following discontinuation.[125,126]

Teratogenicity: Since the 1960's fetal effects associated with the use of antiepileptic drugs have been reported.[127]Maternal tonic-clonic seizures are associated with fetal lactic acidosis, hypoxia and often lead to poor cognitive performance in childhood. Status epilepticus is linked with fetal death. Antiepileptic drugs may be associated with higher spontaneous abortion rates for which folic acid appears to be protective.[87,128]

Most major congenital abnormalities occur during organogenesis (8-10 weeks post

conception) during which time the women may not know she is pregnant, and why contraceptive counseling is very important in women receiving antiepileptic therapy. The offspring of women receiving vs not receiving antiepileptic monotherapy have higher rates of congenital malformations (Odds Ratio 1.61; 95% CI, 1.18-2.19). Reported malformation rates are higher with valproate and phenobarbital than with carbamazepine and lamotrigine. The risk of malformation is highest with the use of valproate combination therapy, but is elevated with all polypharmacy antiepileptic drug regimens. Specific abnormalities are associated with each agent; valproate is associated with neural tube defects, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis. Of the drugs involved in this review, lamotrigine and topiramate are associated with cleft palate or cleft lip. Lamotrigine is associated with cognitive impairment in children exposed during pregnancy, but at a much lower rate than carbamazepine. Evidence suggests that risks of malformations, postnatal development and behavioral problems may occur more commonly with higher doses of lamotrigine (> 200 mg/day). Current evidence is insufficient to assess the risk with other, newer antiepileptic agents.[128,129]

Cardiac Effects: *Lacosamide* produced dose-dependent prolongation of the PR interval and AV block with cases of atrial fibrillation and flutter reported. The use of concomitant medications which may prolong the PR interval (e.g. beta-blockers, calcium channel blockers) should be avoided with lacosamide. Caution should be exercised when using lacosamide in patients with cardiac disease, myocardial infarction, heart failure or conduction disturbances.[18] *Rufinamide* shortens the QT interval placing patients at increased risk of ventricular arrhythmias and sudden death. Rufinamide should be avoided in patients with short QT syndrome.

Cutaneous Manifestations: *Lamotrigine* use is associated with the development of severe rashes including Stevens Johnson syndrome which require drug discontinuation and occasionally hospitalization. The incidence of Stevens Johnson syndrome is higher in children than adults (0.8% vs 0.3%) receiving lamotrigine adjunctive-therapy for epilepsy. Toxic epidermal necrolysis occurs rarely. Likely risk factors for skin reactions include the concomitant use of valproate, high initial lamotrigine doses or rapid titration. Rashes typically occur within 2-8 weeks of the initiation of therapy. Not all rashes are serious or will progress, however, lamotrigine should be discontinued at the first sign of a possibly drug-related rash.[19] *Oxcarbazepine* use has been associated with the development of Steven Johnson syndrome and toxic epidermal necrolysis at a median onset of 19 days.[21] *Rufinamide* is associated with a multi-organ hypersensitivity syndrome which often begins with a rash in children less than 12 years of age. Therapy should be discontinued in the presence of a rash with evidence of organ system involvement (fever, elevated liver function tests, etc.)[24]*Zonisamide* is a sulfonamide antiepileptic agent contraindicated in patients with sulfonamide hypersensitivity. Rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred.

Electrolyte Abnormalities: Hyponatremia: *Oxcarbazepine* is associated with the development of clinically significant hyponatremia, often within the first 3 months of therapy. The mechanism of hyponatremia is thought to involve either a direct effect on renal collecting tubules or an increase in their response to antidiuretic hormone. The use of concomitant diuretics appears to be a risk factor. Serum sodium levels should be monitored periodically as hyponatremia may occur anytime during therapy and patients should be monitored for lethargy, confusion or changes in seizure control.[21] Monitoring for hyponatremia is also recommended with use of *oxcarbazepine ER* (Oxtellar®) and may be indicated for patients receiving *eslicarbazepine* which was associated

with a 1% incidence of hyponatremia in initial clinical trials.[14,130] Most commonly, the electrolyte disturbance is without clinical significance but if overlooked or not treated appropriated can lead to serious complications.[131]

Metabolic Acidosis: *Topiramate* inhibits carbonic anhydrase resulting in renal bicarbonate loss which may progress to metabolic acidosis. Patients at risk of acidosis from diet, medications or disease should be closely monitored.[26]Metabolic acidosis has not been reported with use of topiramate ER formulations Qudexy® or Trokendi®.[27,28]

Psychiatric Issues: The selection of an antiepileptic drug should consider psychiatric and cognitive adverse effects. Patients should be screened for depression and suicidality.[72] *Levetiracetam* use has produced acute psychosis with visual/auditory hallucinations and delirium in adults and children within the first few weeks of therapy. The risk of psychotic symptoms is higher in patients with a history of mental illness.[132]

Suicide: Since 2009, the FDA has required manufacturers of antiepileptic drugs to provide information about the increased risk of suicidal thoughts and behavior associated with treatment. This resulted from an FDA review of 11 epilepsy mediations in 199 clinical trials which found antiepileptic medication usage associated with a two-fold increase in the risk of suicidal behavior or thoughts compared to patients receiving placebo. The finding was consistent among all 11 agents. Risk was noted within 1 week and extended throughout the entire 24 weeks of evaluated data. The risk of suicide was higher when these medications were prescribed for epilepsy compared to other uses. Although only 11 medications were included in the analysis it is believed the risk extends to any antiepileptic medication. Professionals involved in the care of patients should monitor patients for changes in behavior, depression or suicidal thoughts. If present, the contribution of the antiepileptic medication or underlying illness should be considered.[133,134]

Cognitive Issues: For antiepileptic drugs with comparative data (lacosamide, levetiracetam, pregabalin, tiagabine, topiramate), lacosamide and lamotrigine appear to produce the least effects on cognition while topiramate produces the most.[135-137]

Ciesielski et al, compared pregabalin to other antiepileptic drugs for cognitive changes in refractory partial epilepsy patients. Over the 8 weeks of the trial, levetiracetam use was associated with improvements in neuropsychological and psychiatric effects. Pregabalin was associated with significant impairments in episodic memory of both verbal and visual information as well as a trend toward higher anxiety and hostility scores. [135]

Blum et al, assessed the impact on cognition of adding adjunctive lamotrigine or topiramate to carbamazepine or phenytoin in the treatment of 193 adults with partial seizures. Lamotrigine demonstrated significantly less cognitive impact than topiramate ($p<0.001$, standardized cognitive tests multiple measures). Premature discontinuation due to cognitive decline were more common with topiramate ($p=0.013$).[136]

Helmstaedter et al, retrospectively compared cognitive function in patients with epilepsy receiving adjunctive lacosamide therapy to those receiving lamotrigine or topiramate (n=70). Verbal memory, self-perceived side effects and quality of life were also assessed. Seizure control at 32-week follow-up was best with lamotrigine 55% followed by lacosamide 16% and then

topiramate 13%. A significant deterioration in cognitive function was found with topiramate. Five of 9 patients treated with topiramate reported significant subjective cognitive complaints. No patient treated with lacosamide or lamotrigine experienced cognitive decline.[137]

Mills et al, assessed the effects of adjunctive lamotrigine and topiramate on cognitive function in 67 adults with partial seizures. Performance On-Line and neuropsychological tests revealed topiramate but not lamotrigine negatively impacted cognition at 8 and 16 weeks. The authors define the level of impairment with topiramate to mimic the effects of an alcohol breath level of 0.045% or alprazolam 0.5mg.[138]

Labiner et al, assessed the difference between adjunctive lamotrigine and levetiracetam on anger/hostility scores in patients treated for partial epilepsy. Scores on the Anger-Hostility subscale and Total Mood Disturbance questionnaires throughout 20 weeks of study demonstrated lamotrigine superiority at 8, 12 and 20 weeks compared with levetiracetam. Lamotrigine also demonstrated improvement in the Profile of Mood States subscales for Depression-Dejection, Vigor-Activity, Fatigue-Inertia and Confusion-Bewilderment.[139]

Huang et al, compared cognitive function at baseline and at 1-year in patients with intractable epilepsy treated with either topiramate or levetiracetam. At one year topiramate therapy was associated with a statistically significant reduction in orientation scores using the Cognitive Abilities Screening Instrument (CAS). The subset of patients taking topiramate with baseline cognitive deficits demonstrated improvements in memory. Levetiracetam was associated with a preservation of cognitive function.[140]

Fritz et al, compared the efficacy and cognitive side effects of topiramate and tiagabine as add-on therapy in refractory epilepsy and found comparable efficacy between the agents. Frontal-lobe associated cognitive functions were adversely affected by topiramate but not tiagabine. Topiramate therapy resulted in improvements in the initial poor health related quality of life (HRQOL) questionnaire over time.[141]

Sudden Unexpected Death in Epilepsy Patients (SUDEP): Sudden unexpected death in epilepsy appears to be seizure related. Additional risk factors include long-standing epilepsy and tonic-clonic seizures. Most commonly death is unwitnessed and occurs at night, when in the prone position. It is estimated to cause 7,000 deaths per year in Europe and the US and is second only to stroke in the number of deaths. The incidence is estimated at 1.16 deaths per 1000 epilepsy patients with young people up to 24 times more likely to die from sudden death than the general population. The risk of SUDEP is 7% in the general epilepsy population and 12% in patients who are untreated or uncontrolled (refractory, not in remission). No correlation between antiepileptic medication and SUDEP has been identified. Seizure reduction is the only strategy currently known to mitigate the risk as SUDEP is not well understood. [44,142,143]

Ryvlin et al, performed a meta-analysis to assess the risk of SUDEP in patients with refractory epilepsy. Patients receiving add-on antiepileptic medication were compared with those receiving add-on placebo therapy. They reviewed 112 trials and identified 18-probable and 2-possible SUDEP deaths. The rate of definite or probable SUDEP was significantly lower in patients receiving antiepileptic drug therapy than those epilepsy patients not receiving therapy. The rate of SUDEP per 1000 person-years in treated patients was 0·9 (95% CI 0·2-2·7) compared

with 6·9 (3·8-11·6) in those allocated to placebo.[144] The NIH (National Institutes of Health) has funded a new Center for SUDEP Research whose mission is to provide answers and strategies to manage this epilepsy-specific adverse outcome.[142,143]

Abuse Potential: Three antiepileptic drugs (pregabalin, lacosamide and ezogabine) were assigned DEA Schedule V status. An eight factor analysis was performed by the FDA to assess abuse potential.[145] These medications demonstrated a number of adverse effects which are considered markers for possible abuse potential. The presence of euphoria is linked with drug-liking and may produce psychic dependence. These antiepileptic drugs also exhibited other adverse events correlated with abuse, included somnolence, visual disturbances, paranoia, fear, confusion or hallucinations.

Fracture Risk: Studies have documented an increased risk of fractures in patients receiving antiepileptic therapy. This may reflect the effects of enzyme induction on vitamin D homeostasis. Enzyme-inducing antiepileptic drugs impair calcium absorption, increase vitamin D catabolism, interfere with vitamin K metabolism, increased parathyroid function increasing bone turnover and loss, the development of osteoporosis and ultimately development of fractures.[146] Patients may be at increased risk of a fall due to the central nervous system effects of the antiepileptic drugs. Cognition, somnolence, dizziness and drowsiness are common side effects. Patients with epilepsy often have underlying comorbid conditions (depression, bipolar illness) which produce symptoms predisposing to a fall. The risk of a fall increases 175% in elderly woman receiving antiepileptic drugs even when adjusting for other risk factors resulting in an adjusted odds ratio of 2.56.[147]Two large meta-analyses have evaluated this risk:

Shen et al, performed a meta-analysis of 22 studies evaluating fracture risk in patients receiving antiepileptic drug therapy.[148]The use of any antiepileptic drug was associated with an increase of fracture (Relative Risk 1.86; 95% CI, 1.62-2.12). The difference maintained significance for both enzyme-inducing and non-enzyme-inducing antiepileptic drugs. Enzyme-inducing antiepileptic drugs were associated with a greater risk than the non-inducing antiepileptic drugs (RR 1.18; 95% CI 1.11-1.25). Combination therapy was associated with a greater risk than monotherapy (RR = 1.61; 95% CI 1.40–1.87). Fracture risk increased significantly with phenobarbiturate 78% (RR 1.78, 95% CI 1.64-1.93), topiramate 39% (RR 1.39; 95% CI 1.02-1.90) and phenytoin 70% (RR 1.70; 95% CI 1.26-2.29).

Fraser et al, performed a meta-analysis evaluating enzyme-inducing antiepileptic drugs and fracture risk in people with epilepsy.[149] Thirteen studies (2 appearing in Shen et al) evaluated 68,973 adults. Studies results were divided with respect to the influence of enzyme-inducing antiepileptic drugs on either fracture risk and reduced bone mineral density. The largest study (N=63,239) was the most methodologically rigorous and demonstrated an increased hazard ratio (HR) for both any fracture (9-22%) or hip fracture (49-53%) with the use of an enzyme-inducing antiepileptic drug.

Ophthalmic Issues: *Topiramate* use is associated with a syndrome of acute myopia and secondary angle closure glaucoma. The syndrome typically occurs within one month of topiramate use in both adults and children. Initial signs include an acute onset of decreased visual acuity +/or ocular pain. Permanent vision loss is possible and topiramate therapy should be discontinued.[26] *Vigabatrin* can cause irreversible vision loss. The medication should only be continued beyond 2-

4 weeks of therapy if improvement in seizures is noted. Vision testing is recommended at baseline and every 3 months.[29]A study comparing retinal injury and electrophysiological changes compared vigabatrin to tiagabine. Vigabatrin patients were matched with a control group receiving other antiepileptic drugs (carbamazepine, phenytoin, gabapentin, lamotrigine, phenobarbital, primodone, topiramate, valproate and levetiracetam). Only vigabatrin was associated with retinal injury.[150] *Ezogabine* use has been associated with retinal pigment changes and blue/grey skin discoloration. The skin changes are considered cosmetic by the FDA but the retinal pigment changes may be associated with vision loss. Baseline and periodic (every 6 month) eye examinations while on therapy are recommended.[15]

Hypersensitivity Reactions: *Lamotrigine* is associated with the development of the anti-convulsant hypersensitivity syndrome. This is a hepatocellular toxicity which presents within 30-90 days of initiating lamotrigine therapy. The reaction presents with immune-allergic features (e.g. fever, rash, hepatitis and multi-organ abnormalities). It is potentially fatal**.** The reaction is more severe in sensitized individuals. Patients having had a reaction to carbamazepine, lamotrigine, phenytoin or phenobarbital should be placed on an alternative medication or retried on the same medication only with great caution. Fever and rash are common in 90% of cases. Hepatitis occurs in 50% of cases and is associated with a mortality rate between 18-40%. It is believed that the arene-oxide reactive metabolite is responsible for the liver damage. The ability to detoxify arene-oxides may be genetically determined accounting for familial clustering of cases.[151,152]

Children

Oligohidrosis: Oligohidrosis was first noted during phase III zonisamide trials in Japan. Following approval of zonisamide in the US, thirteen events of oligohidrosis or hyperthermia were reported in children (median age 6 years) in the first 3 years of use suggesting an incidence of 1 case per 4,590 patient-years.[30,153] Events are most common in children and during the summer. The reaction is reversible upon discontinuing zonisamide and can be minimized in hot weather by keeping the child cool and well hydrated.

Behavioral effects: Children with epilepsy have more behavioral problems than children without epilepsy. Antiepileptic drugs may exacerbate these problems. A systematic review (13 studies, 727 patients) of the behavioral side effects of levetiracetam therapy in children with epilepsy found treated patients with statistically significantly more hostility, nervousness and aggression. The relative risk was 2.18 for behavioral side effects.[154]

Cognitive impairment is common in children with epilepsy and may be potentiated by the use of antiepileptic drugs which affect ion channels, neurotransmitters and second messengers leading to reductions in memory, learning and emotional behavior. Effects are more common with some medications and may be dose-dependent. Further research is needed to define the risk associated with the various antiepileptic drugs. Some evidence suggests topiramate produces more impairment than levetiracetam or carbamazepine, while oxcarbazepine may not adversely affect cognitive impairment.

Idiosyncratic Reactions in Children: The incidence of adverse drug reactions, dose-related and idiosyncratic adverse drug effects are more common in children than adults. Predictors of idiosyncratic reactions, include a close relative having the reaction, concomitant

autoimmune disease, co-treatment with specific antiepileptic agent, history of a previous allergic drug reaction, initiation of therapy with higher than recommended doses or rapid, upward dose-titration.[132] Rapid initiation of high-dose antiepileptic drug therapy may preclude desensitization and explain the higher incidence of cutaneous reactions in children. Previous reactions are predictive of future reactions. A 50% rate of cross sensitivity exists for cutaneous reactions associated with the aromatic antiepileptic drugs. A history of a prior drug rash increases the likelihood of a rash with oxcarbazepine or lamotrigine.[132] Many of the idiosyncratic reactions can be explained by differences in drug metabolism between adults and children.[155]It is believed that faster CYP-mediated metabolism than glucuronidation may result in more reactive metabolites. Hepatotoxicity occurs as a result of high concentrations of reactive metabolites in the liver. This may also explain the increased incidence of idiosyncratic cutaneous reactions in children receiving lamotrigine, Stevens-Johnson syndrome occurs in 1:100 children but only 1:1,000 adults.[155]

Summary:

Up to one-third of epilepsy patients do not have adequate seizure control which affects their quality of life, morbidity and mortality. The medications found useful to control seizures are diverse in mechanism of action and pharmacologic class, including hydrations (phenytoin, fosphenytoin, ethotoin), anti-seizure barbiturates (phenobarbital, pentobarbital), iminostilbenes (carbamazepine), succinimides (ethosuximide), valproic acid and derivatives, benzodiazepines (clonazepam, clorazepate, midazolam, diazepam, lorazepam, clobazam) and others (acetazolamide, brivaracetam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, magnesium sulfate, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin and zonisamide. Newer agents continue to be developed in an attempt to control seizures, minimize adverse effects and drug interactions, minimize safety issues and offer an improved risk: benefit ratio to treatment. Each of the newer anticonvulsant agents (brivaracetam, clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin and zonisamide) is approved for the treatment of epilepsy or an epilepsy syndrome. Some of the agents have additional, non-seizure disorder indications including bipolar disorder (lamotrigine), fibromyalgia (pregabalin), migraine prophylaxis (topiramate), neuropathic pain (pregabalin) and postherpetic neuralgia (gabapentin and pregabalin). Three of the agents are DEA Schedule V (lacosamide, ezogabine, pregabalin). All are available as oral tablets or capsules. Many come in starter packs/kits to facilitate initiation of therapy. Many are available in oral disintegrating/dispersible/chewable tablets, oral sprinkles, oral solution, suspension, powder for solution and injectable formulations.

According to Clinical Practice Guidelines, decision making concerning antiepileptic therapy should involve the patient, parent and carers; give consideration to race, culture and specific needs; involve the development of a comprehensive care plan involving primary and secondary practitioners and individualize treatment considering seizure type, syndrome, patient age, concomitant medications, comorbidity, patient lifestyle and preferences. Important safety issues in patients with epilepsy, include adverse events, bone health, psychological issues, pregnancy and sudden unexpected death in epilepsy patients (SUDEP). Other issues covered include recommendations for HIV-infected individuals for which non-enzyme inducing medications are preferred as well as addressing specific safety issues with felbamate and valproate.

Practice Guidelines are found in Table 5 Briefly, the most commonly recommended antiepileptic drug for the various epilepsies/syndromes, include:

Lennox Gastaut syndrome: Valproate
Infantile Spasms: Vigabatrin
Partial-Onset, Monotherapy: Lamotrigine, carbamazepine, levetiracetam, valproate
Partial-Onset, Adjunctive: Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate, clobazam
Generalized-Onset, Monotherapy: Valproate, lamotrigine > topiramate, carbamazepine, oxcarbazepine (for children, phenobarbital, carbamazepine, valproate, topiramate)
Generalized-Onset, Adjunctive: Valproate, lamotrigine, levetiracetam, topiramate > clobazam
Partial-Onset, Refractory, Monotherapy: Lamotrigine, topiramate, oxcarbazepine
Partial-Onset, Refractory, Adjunctive: Gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, zonisamide
Generalized, Refractory, Monotherapy: Topiramate
Myoclonic: Valproate, levetiracetam, lamotrigine, topiramate

Clinical evidence supporting the efficacy of the newer antiepileptic agents may be stronger for lamotrigine and levetiracetam and poorer for oxcarbazepine, gabapentin and topiramate. Efficacy studies use seizure reduction as a surrogate marker for disease improvement and do not capture quality of life concerns, seizure severity or patterns. Attempts at pooling data to give more statistical power and robust estimate of the data are confounded by wide confidence intervals and large heterogeneity. Safety data suggests topiramate and lamotrigine are associated with more adverse events. Very few comparative clinical trials established safety endpoints as outcome measures. Comparative safety data is limited for the newest agents and the available data is inconsistent.

Significant differences are more easily defined with respect to the safety profile of the specific agents. Idiosyncratic reactions are common with this class of medications; hepatotoxicity is associated with use of felbamate, lamotrigine and oxcarbazepine; cutaneous reactions are possible with any antiepileptic drug however severe reactions are associated with use of lamotrigine, oxcarbazepine, zonisamide and rufinamide; ophthalmologic changes occur with vigabatrin, topiramate and ezogabine and hematologic reactions with felbamate. With respect to adverse effects, behavioral and psychiatric effects are common with levetiracetam. Zonisamide may cause oligohidrosis in children. Lacosamide and levetiracetam commonly cause adverse cognitive effects while two trials in cognitively-impaired patients found gabapentin demonstrated some benefit. Lacosamide, pregabalin and ezogabine are FDA Schedule V and have abuse potential. Cardiac conduction is affected by lacosamide and rufinamide. Teratogenicity issues must be considered when prescribing lamotrigine or topiramate. CYP450 enzyme effects occur with topiramate, oxcarbazepine and perhaps felbamate. Electrolyte changes are associated with oxcarbazepine, eslicarbazepine and metabolic acidosis with topiramate.

Overall, data is insufficient to determine if efficacy and safety differences between these agents exist. Individualization of therapy is recommended.

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Appendix 1: Clinical Trials Evaluating the Efficacy of Antiepileptic Agents for use in Seizure Disorders

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Liu et al, 2015[91] Cochrane Systematic Review of 3 RCTs	N=83	Juvenile monoclinic epilepsy	Monotherapy with • Topiramate • Valproic Acid • Placebo	Responder Rate (Proportion of Responders achieving 50% ↓ seizure frequency from baseline) Topiramate vs Valproic Acid • Myoclonic seizures o No significant difference (RR 0.88, 95% CI 0.67-1.15) 1 study • Primary generalized tonic-clonic seizure o No significant difference (RR 1.22 (0.68-2.21) 1 study • Achieved Seizure Free Status o No significant difference	Adverse Effects • Topiramate o moderate-to-severe • Valproate o 59% severe Systemic Toxicity Scores • Valproate > Topiramate
Coppola et al 2007[156] Open-Label, Parallel Group Trial	N=39	Newly diagnosed benign epilepsy of childhood with centrotemporal spikes (BECTS)	Levetiracetam Oxcarbazepine	Seizure-free at 18 months • Levetiracetam = Oxcarbazepine o 90.5% vs 72.2% (p=0.410)	Adverse Effects • Levetiracetam (3 patients) o Transient decreased appetited (3) o Cephalalgia (1) • Oxcarbazepine (2 patients) o Headache (1) o Sedation (1)
Kowalik et al, 2008[157] Open-label, Non-interventional Trial	N=140	Patients ≥ 12 years with any type of epilepsy or epilepsy syndrome failing oxcarbazepine or	Add-on with Topiramate After titration, clinician consideration for monotherapy	Final Treatment Regimen • Monotherapy 73% • Combination therapy 27% Topiramate Daily Dose (p<0.05) • Monotherapy 150 mg	Adverse Events 34% • ↓ Body weight 1.9 ± 3.7 kg, p<0.001 Serious Adverse Events (16 events in 9 patients) • Convulsions (8x in 6 patients) • Increased hepatic enzymes

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
		carbamazepine due to efficacy or tolerability issues		• Combination Therapy 100mg Reduction in Seizures by at least 50% • 91% (95% CI, 83.3-95.7%) Percent Achieving Seizure Free Status, 43% End of Study Evaluation (little-to-much better) • Patients 79.3% • Physician 80% Quality of Life in Epilepsy (QOLIE-10) • Change +17.7 ± 21.9, p<0.001	• Brain neoplasm • Staphylococcal infection • Acute renal failure • Hepatic encephalopathy • Asthenia • Psychomotor skill impairment • Personality disorder

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Bootsma et al, 2009[92] Medical Information System Automated Extraction and Patient Medical Record Review	N=106	Chronic, refractory epilepsy patients treated at a single tertiary epilepsy center	Add—on Therapy • Lamotrigine • Levetiracetam • Topiramate	Retention Rate at 1-year • Lamotrigine > Levetiracetam (p=0.008) • Lamotrigine > Topiramate (p<0.001) • Levetiracetam > Topiramate (p=0.002) Retention Rate at 2-years • Lamotrigine vs Levetiracetam (p<0.001) • Lamotrigine vs Topiramate (p<0.001) • Levetiracetam vs Topiramate (p=0.005) Seizure Free Rate at 6-month, 12-month and 18-months • Levetiracetam > Topiramate, Lamotrigine o Not statistically significant	Drug Discontinuation Due to an Adverse Event • Topiramate 35.9%, Levetiracetam 22.5%, Lamotrigine 15.5% o Topiramate > Levetiracetam (p<0.001) o Topiramate > Lamotrigine (p<0.001) o Levetiracetam > Lamotrigine (p-0.028) AEs → Treatment Discontinuation • Dizziness, tiredness, sleepiness (all 3 agents) • Mental slowing, dysphagia (Topiramate) • Rash (Lamotrigine, Topiramate) Overall Side Effect Profile • Mood, CNS Effects Levetiracetam • Neurocognitive Effects Topiramate • Positive Behavior Effect Lamotrigine
Anand et a, 2014 Cochrane Systematic Review of 2 RCT or quasi-RCTs	N=163	New onset partial or generalized seizures in adults and children > 6 months old	Monotherapy for at least 3 months with Clobazam vs • Other AED • Placebo	Retention at 12 months (tolerability and efficacy measure) • Clobazam = Carbamazepine Retention at 6 months • Clobazam > Phenytoin (not significant)	Discontinuation Rates • Phenytoin > Clobazam (not significant)
Rosenow et al, 2012[158]	N=409	Focalized and generalized seizures	Monotherapy for focalized and generalized seizures	Seizure free at 6 weeks and during 26-week treatment period • Levetiracetam = Lamotrigine	Adverse Events • Levetiracetam = Lamotrigine Discontinuation due to AE

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
		Age ≥ 12 years	• Lamotrigine • Levetiracetam		• Levetiracetam > Lamotrigine (p=0.07) Harms Ratio Levetiracetam vs Lamotrigine • 0.86 (CI, 0.61-1.22)
Marson et al, 2007[94] Unblinded, RCT Part B of the SANAD (Standard and New Antiepileptic Drug) study	N=716	Generalized and unclassified epilepsy where valproate was considered standard treatment	Monotherapy with • Valproate • Lamotrigine • Topiramate	Time to Treatment Failure (Hazards Ratio) • Valproate > Topiramate (1.57, 95% CI 1.19-2.08) • Valproate = Lamotrigine Time to Treatment Failure in Idiopathic Generalized Epilepsy • Valproate > Lamotrigine • Valproate > Topiramate Time to 12-month remission (Hazards Ratio) • Valproate > Lamotrigine (0.76, 95% CI 0.62-0.94) • Valproate = Topiramate Time to 12-month remission in idiopathic generalized epilepsy • Valproate > Lamotrigine (0.68, 95% CI 0.53-0.89) • Valproate = Topiramate Time to first seizure • Valproate > Topiramate > Lamotrigine Quality of Life • No difference among agents	Most common Adverse Events (>10%) Topiramate (45% pts ≥ 1 AE • Tired/drowsy/fatigue/lethargy 20% • Behavior/personality change/aggression 18% • Psychiatric symptoms 15% • Weight loss 12% • Memory problems 10% Lamotrigine (37% pts ≥ 1 AE) • Allergic rash 12% Valproate (36% pts ≥ 1 AE) • Weight gain 16% • Tired/drowsy/fatigue/lethargy 12% Treatment failure due to AE Topiramate • Psychiatric, cognitive, tiredness, fatigue Lamotrigine • Rash Valproate • Weight gain

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				• Positive response associated with remission of seizures	
Arif et al, 2010[34] Retrospective Review	N=417	Outpatients (≥ 55 years) Seen at a Tertiary Epilepsy Center	Analyzed for medications taken by ≥ 10 patients First-exposure to • Carbamazepine • Clobazam • Gabapentin • Lamotrigine • Levetiracetam • Oxcarbazepine • Phenytoin • Topiramate • Valproic Acid • Zonisamide	12-month Retention • No non-AED predictors of retention • Lamotrigine 79% > Carbamazepine 48%, Gabapentin 59%, Oxcarbazepine 24%, Phenytoin 59%, Topiramate 56%, (p at least <0.05) • Levetiracetam 73% > statistically better than Carbamazepine, Oxcarbazepine (p at least <0.05) • Oxcarbazepine < statistically lower than all other AEDs (p at least <0.001) Efficacy (12-month seizure-free rate) • Lamotrigine 54%, Levetiracetam 43% Retention and Efficacy data unchanged when stratified by non-refractory or refractory disease	Tolerability Most Common AEs • Imbalance (14.1%) o Lamotrigine 13.8% o >5% for Gabapentin, levetiracetam, Oxcarbazepine, Phenytoin, Valproate • Drowsiness (8.8%) o Levetiracetam (24.3%), Topiramate (20%), Carbamazepine, Clobazam, Gabapentin, Oxcarbazepine • Gastrointestinal symptoms (8.8%) o Zonisamide (13.6%) • Dizziness (6.8%) • Cognitive AEs (5.4%) o Topiramate (24%) o Zonisamide (13.6%) • Allergies (4.9%) o Phenytoin 9.1% • Psychiatric AEs (4.3%) o Levetiracetam (14.2%) • Tremor o Valproate (10.8%)

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Hemery et al, 2014[95] Meta-analysis of 24 RCTs	N=7823	Refractory Focal Epilepsy with generalized tonic-clonic seizures (secondary generalized tonic-clonic seizures)	Carisbamate (n=555) Eslicarbazepine (n=100) Lacosamide (n=204) Levetiracetam (n=204) Oxcarbazepine (n=169) Perampanel (n=442) Pregabalin (n=119) Rufinamide (n=332) Tiagabine (n=138) Topiramate (n=406) Vigabatrin (n=93) Zonisamide (n=73) Placebo (n=4988)	Responder Rate • Lacosamide, Perampanel, Topiramate > Placebo • Pregabalin < Lacosamide, Perampanel, Topiramate Median 28-day reduction from baseline SGTCS frequency • Perampanel 2 mg/day, 4 mg/day, pregabalin, rufinamide, topiramate 600 mg/day > Placebo • Each antiepileptic drug equivalent to others	Not Reported
Zhou et al, 2012[96] Cochrane Review of 2 RCTs	N=753	Newly diagnosed partial seizures (N=660) Hospitalized patients with refractory partial epilepsy (N=93)	Pregabalin Lamotrigine Pregabalin Gabapentin	Comparison 1: Time to 6-month Seizure-Free Period • Pregabalin HR 0.56 (95% CI 0.41-0.76) Seizure-Free Rate for ≥ 6 months • Pregabalin RR 0.76 (95% CI 0.67-0.87) Time to First Seizure • Pregabalin HR 1.74 (95% CI 1.26-2.39)	Comparison 1: Time to Withdrawal (Any Reason) • Pregabalin = Lamotrigine Time to Withdrawal (AEs) • No Difference Time to Withdrawal (Inadequate Seizure Control) Pregabalin HR 4.52 (95% CI 1.93-10.60) Experiencing ≥ 1 AE • Pregabalin=Lamotrigine Most Common AEs • Pregabalin > Lamotrigine for somnolence, weight gain, convulsion • Lamotrigine > Pregabalin for oropharyngeal pain

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
					Comparison 2: Time to Withdrawal (any Reason) • Pregabalin < Gabapentin HR 0.25 (95% CI 0.11-0.57) Time to Withdrawal (Inadequate Seizure Control) • Pregabalin < Gabapentin HR 0.41 (95% CI 0.18-0.92) Experience ≥ 1 AE – No difference Most Common AEs – No difference
Kwan et al, 2011[97] RCT, Phase III, Non-inferiority Trial	N=660	Adults with newly diagnosed partial seizures	Monotherapy with • Pregabalin • Lamotrigine	Seizure free for ≥ 6 consecutive months • Pregabalin < Lamotrigine (52% vs 68%; difference -0.16, 95% CI -0.24 to -0.09) Time to 6-month seizure freedom • Lamotrigine > Pregabalin (RR 0.74, p=0.0034) • Time to First Seizure • Pregabalin < Lamotrigine (85 vs 211 days; RR 1.47, p=0.0003)	Adverse Events • Similar and established
Combo et al, 2010[98] RCT, 3-arm parallel group, case-control study	N=95	Antiepileptic drug treatment naïve adults with Alzheimer's disease and partial epilepsy All patients receiving cholinesterase inhibitor therapy	Monotherapy with • Levetiracetam • Lamotrigine • Phenobarbital	Responder Rate at 12 months (p=0.34 between groups) • Levetiracetam 71% • Phenobarbital 64% • Lamotrigine 59% Seizure Free Rate at 12 months • Levetiracetam 29% • Phenobarbital 29% • Lamotrigine 24% Mini Mental State Examination	Adverse Events (p=0.09 between groups) • Levetiracetam 17.7%, somnolence, asthenia, headache, dizziness • Phenobarbital 43%, somnolence, asthenia • Lamotrigine 28% Withdrawal due to Adverse Event • Levetiracetam 0% • Phenobarbital 17% (1°sedation) • Lamotrigine 0%

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				• Levetiracetam > Lamotrigine • Levetiracetam > Phenobarbital • Levetiracetam > Controls • Phenobarbital > Lamotrigine • Phenobarbital > Control • Lamotrigine > Controls Alzheimer Disease Assessment Scale-Cognitive (lower score clinical improvement) • Levetiracetam < Lamotrigine • Levetiracetam < Controls • Phenobarbital < Controls • Lamotrigine < Controls Cornell scale for depression (lower score clinical improvement) • Levetiracetam = Controls Levetiracetam < Lamotrigine • Levetiracetam < Phenobarbital • Phenobarbital < Lamotrigine	
Marson et al, 2007[99] Unblinded, RCT Arm A of the SANAD (Standard and New Antiepileptic Drug) study	N=1721	Partial epilepsy where carbamazepine was considered standard treatment	Monotherapy with • Carbamazepine • Gabapentin • Lamotrigine • Oxcarbazepine • Topiramate	Time to Treatment Failure (Hazards Ratio) • Lamotrigine > Carbamazepine (0.78, 95% CI 0.63-0.97) • Lamotrigine > Gabapentin (0.65, 95% CI 0.52-0.80) • Lamotrigine > Topiramate (0.64, 95% CI 0.52-0.79) • Lamotrigine > Oxcarbazepine (non-significant)	Treatment Failure for Unacceptable Adverse Effects • Carbamazepine, Topiramate > others • Least common with Gabapentin and Lamotrigine

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				Time to 12-month remission (Hazards Ratio) • Carbamazepine > Gabapentin (0.75, 95% CI 0.63-0.90) • Lamotrigine non-inferior to Carbamazepine • Carbamazepine > lamotrigine, topiramate, oxcarbazepine (non-significant) Time to Treatment Failure for Any Reason Including Unacceptable Adverse Events • Lamotrigine > Carbamazepine, Oxcarbazepine > Gabapentin, Topiramate Treatment Failure due to Inadequate Seizure Control • Least likely Carbamazepine • Most likely Gabapentin of Life Measures • No difference among agents Cost per Seizure Avoided (cost-effectiveness) • Lamotrigine > Carbamazepine Cost per Quality-Adjusted Life-Year Gained • Lamotrigine > Carbamazepine	
Crawford et al, 2001[100]	N=83	Age ≥ 12 years	Add-on therapy • Gabapentin • Lamotrigine	Responder Rate • Gabapentin = Lamotrigine Seizure Free Rate	Adverse Events • Overall Incidence o No difference

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
RCT		Drug-resistant localization-related epilepsy Learning disability and DSM-IV criteria mental retardation		• Gabapentin 7.7% • Lamotrigine 11.4% Behavioral Scores • Benefit was seen vs baseline with both agents among various measures • Communication, Cooperation, Restlessness and Total Score o Gabapentin > Lamotrigine (p<0.05)	• Serious Adverse Events o No difference • Somnolence, Ataxia o Higher during gabapentin titration only • Withdrawal due to AE o No difference
Martyn-St James, 2012[101]			Eslicarbazepine Ezogabine Lacosamide Pregabalin Tiagabine Zonisamide	50% Responder Rate Fixed-Dose Maintenance Period Conventional meta-analysis • All AEDs except tiagabine > Placebo (p<0.001) • Placebo > Tiagabine (p=0.122) Network meta-analysis • All AEDs > Placebo Double-blind Period Conventional meta-analysis • All AEDs > Placebo (p< 0.0001) Network meta-analysis • Pregabalin > Ezogabine Seizure Free Rate Fixed-Dose Maintenance Period Conventional meta-analysis • Ezogabine > Placebo (p<0.026) Network meta-analysis • All AEDs > Placebo	Withdrawals due to AEs Conventional meta-analysis • All AEDs > Placebo (p<0.002) Withdrawal Due to Any Reason Conventional meta-analysis • All AEDs except eslicarbazepine > Placebo (p<0.0001) • Eslicarbazepine < Placebo (p=0.297), I^2=73% Network meta-analysis • Ezogabine > Eslicarbazepine • Ezogabine = Other AEDs Ataxia Conventional meta-analysis • Pregabalin, Ezogabine, Zonisamide > Placebo (p=0.047 to p<0.001) Network meta-analysis • Ezogabine = other AEDs Dizziness Conventional & Network analysis

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				Double-blind Period Conventional meta-analysis • All AEDs = Placebo • Networkmeta-analysis • Ezogabine > Placebo • Ezogabine = Other AEDs	• All AEDs > Placebo (p=0.03 to p<0.0001) Fatigue • Ezogabine > Placebo (p<0.001); this finding was not significant upon network meta-analysis Nausea • Eslicarbazepine > Placebo (p=0.004) • Lacosamide > Placebo (p=0.003) Somnolence • Pregabalin and ezogabine > Placebo (p<0.001) • Zonisamide > Placebo (P=0.003) • Network meta-analysis • Ezogabine > Tiagabine
Bhaumik et al, 1997[103] Retrospective Study	N=51	Adults with learning disabilities and refractory epilepsy 71 treatment episodes	Monotherapy or Add-on Therapy with • Vigabatrin • Lamotrigine • Gabapentin	Seizure Type • 73% Primary generalized Responder Rate • No differences among agents Seizure Free • Vigabatrin 26%, Gabapentin 4%, Lamotrigine 0% Efficacy • No difference among agents	Adverse Events • No difference among agents (p=0.58) Most Common AE by Agent • Vigabatrin - Behavior problems • Lamotrigine – Rash • Gabapentin – Drowsiness, unsteady gait Increase Seizures (no p value) • Lamotrigine 24%, Vigabatrin 8%, Gabapentin 9%
Datta et al, 2000[104] Retrospective case review	N=463	Refractory localization-related epilepsy Failed a first-line drug	Mono- or Add-on Therapy with • Gabapentin • Lamotrigine • Tiagabine • Topiramate	Responder Rate • Gabapentin 31%, Lamotrigine 25%, Topiramate 20%, Vigabatrin 19%, Tiagabine 11% Seizure Free Percentage	Withdrawal Due to Adverse Events • Topiramate 42% • Tiagabine 26%, • Vigabatrin 16% • Gabapentin 16% • Lamotrigine 15%

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
			• Vigabatrin	• Gabapentin 8%, Lamotrigine 6%, Vigabatrin 5%, Tiagabine 4%, Topiramate 1% Loss of Seizure Control (increase ≥ 25% in seizures) • Tiagabine 13%, Topiramate 9%, Gabapentin/Vigabatrin 6%, Lamotrigine 3% Withdrawal from Lack of Efficacy • Vigabatrin 46%, Topiramate/Tiagabine 30%, Gabapentin 25%, Lamotrigine 16% Percentage of Patients Continuing Therapy • Lamotrigine 60%, Gabapentin 51%, Topiramate 47%, Tiagabine 39%, Vigabatrin 38%	Most Common Drug-Specific AE (>10%) • Gabapentin – Drowsiness, • Lamotrigine – All < 10% • Vigabatrin – Psychiatric (depression), drowsiness • Topiramate – Psychiatric (depression, hallucinations, psychosis), cognitive effects, drowsiness, weight loss, headache • Tiagabine – Dizziness, drowsiness
Lindberger et al, 2000[105] RCT, multi-center, double-blind, dose-titration study	N=102	First add-on therapy for patients with partial seizures failing monotherapy N=79 per protocol N=102 intent to treat	Add-on with • Gabapentin • Vigabatrin	Improvement Rate* (≥ 50% seizure reduction without adverse events) • Gabapentin < Vigabatrin (48% vs 56%) Seizure Reduction Rate* (≥ 50% seizure reduction rate regardless of adverse events) • Gabapentin < Vigabatrin (54% vs 65%) Response Rate* (seizure-free patients without side effects) • Gabapentin < Vigabatrin (31% vs 39%)	Patients with ≥ 1 Adverse Events • Gabapentin < Vigabatrin (75% vs 86.5%) • Most common and similar between groups: tiredness, dizziness, respiratory infection, headache, diarrhea Discontinuations due to Adverse Events • Gabapentin – status epilepticus, psychiatric problem (family), epigastric pain, diplopia, vertigo and dizziness • Vigabatrin – depression, generalized seizure, rash, numbness and dizziness Perimetry results after study completion

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				*Due to wide confidence intervals equivalence was not found Quality of Life score • No difference	• Abnormal results 3 of 32 patients vigabatrin patients
Zaccara et al, 2014[106] RCT, non-inferiority	509	Adjunctive Therapy for Partial Seizures	Pregabalin Levetiracetam	Responder Rate • Pregabalin NOT inferior to Levetiracetam Percent change in 28-day seizure rate • Pregabalin = Levetiracetam Post-hoc analysis: Proportion of patient's seizure-free during maintenance phase • Levetiracetam > Pregabalin (p=0.0155)	Adverse events • No differences
Gao et al, 2012[107] Meta-analysis of 15 RCTs	N=5900	Adjunct therapy in adults with partial-onset seizures Failed prior AED therapy Treated a minimum of 4 weeks	Eslicarbazepine Ezogabine Carisbamate Lacosamide Brivaracetam Perampanel	Responder Rate • AEDs > Placebo [OR 2.16, 95% CI 1.82 to 2.57] • Carisbamate, Lacosamide, and Perampanel < Other AEDs • Brivaracetam, Ezogabine and Eslicarbazepine > Other AEDs • Seizure Free Rate • AEDs > Placebo • Lacosamide > Other AEDs Withdrawal Rate • AEDs > Placebo [OR 1.54, 95% CI 1.12 to 2.10]	Pooled Adverse Effects • AEDs > Placebo [OR 1.67, 95% CI 1.34 to 2.08] • Lacosamide and Ezogabine > Other AEDs Most Common: • Dizziness, headache, fatigue, somnolence, nausea, ataxia • Placebo < AEDs • All AEDs equivalent QT effects • Ezogabine= Placebo • Treatment Emergent AEs • Placebo < Pooled AEDs • Withdrawal Due to AEs • Placebo < Pooled AEDs

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				• Eslicarbazepine, Carisbamate, Brivaracetam and Perampanel < Other AEDs • Lacosamide and Ezogabine > Other AEDs Escalated Dose with Best 50% Seizure Free Rate • Eslicarbazepine 1200 mg • Ezogabine 1200 mg • Lacosamide 600 mg	
Costa et al, 2011[108] Meta-analysis of 70 RCTs 63 Placebo Trials 8 Head-to-head AEDs (1 Trial both)	N= 14,272	Refractory partial epilepsy Age >2 years	Adjunctive Therapy with: • Oxcarbazepine • Lamotrigine • Topiramate • Gabapentin • Pregabalin Levetiracetam • Tiagabine • Zonisamide • Eslicarbazepine • Lacosamide	Responder Rate • All AEDs > Placebo • NNT Range • Levetiracetam=8; Tiagabine=20 Dose-response relationship • Oxcarbazepine & Eslicarbazepine Seizure Free Rate (32 studies) • Topiramate, Levetiracetam, Eslicarbazepine > Placebo Indirect Adjusted Comparisons among AEDs Most Effective • Topiramate (OR 1.52, 95% CI 1.06-2.20) • Least Effective • Gabapentin (OR 0.67; 95% CI 0.46-0.97) • Lacosamide (OR 0.66, 95% CI 0.48-0.92)	Withdrawal Rate due to any Cause • Oxcarbazepine, Topiramate, Pregabalin, Zonisamide, Tiagabine, Lacosamide > Placebo • Lamotrigine, Gabapentin, Levetiracetam, Eslicarbazepine < Placebo • Dose-related with Oxcarbazepine, Gabapentin, Zonisamide Withdrawal Rate due to AEs • Tiagabine, Levetiracetam < Placebo Rate of AEs due to ataxia, dizziness, fatigue, headache, nausea and somnolence • All AEDs > Placebo Indirect Adjusted Comparisons Among AEDs Higher Withdrawal Rates • Oxcarbazepine OR 1.60 • Topiramate OR 1.68 Lower Withdrawal Rates • Gabapentin OR 0.65 • Levetiracetam OR 0.62

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				Responder Rate (NNT) Most Effective • Topiramate=0.83 • Levetiracetam=0.78 Least Effective • Gabapentin=1.90 • Tiagabine=1.00 Combined Direct and Indirect Evidence • Lamotrigine vs Gabapentin – No difference in Responder Rate, Withdrawal Rate or Seizure Free Rate ($p \geq 0.64$ all variables) • Lamotrigine vs Topiramate – Topiramate performed better at Responder Rate and Seizure Rate; Lamotrigine better for Withdrawal Rate ($p>0.51$ all variables) • Lamotrigine vs Pregabalin – Pregabalin was favored in Responder Rate with no differences in Seizure Free Rate or Withdrawal Rate ($p>0.41$ all variables) • Lamotrigine vs Levetiracetam – No difference in Responder Rate, Seizure Free Rate or Withdrawal Rate ($p \geq 0.21$ all variables)	Number Needed to Harm • Lamotrigine, Gabapentin, Levetiracetam, Eslicarbazepine = Placebo • Oxcarbazepine = 0.33 • Topiramate= 0.92 Rate of Specific AEs Ataxia – No differences Headache – Lacosamide > Others Dizziness – Pregabalin > Others Fatigue – Topiramate > Others; Lamotrigine < Others Nausea – Oxcarbazepine > Others; Gabapentin and Levetiracetam < Others Somnolence – Oxcarbazepine > Others; Tiagabine < Others

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Brodie et al, 2002[109] RCT, Double-blind, Non-inferiority Trial	N=309	Patients ≥ 16 years with newly diagnosed epilepsy Partial seizures +/- secondary generalization or Primary generalize tonic-clonic seizures	Monotherapy with • Gabapentin • Lamotrigine	Kaplan-Meier (safety/efficacy combined endpoint, all measures statistically equivalent) • Gabapentin = Lamotrigine • Stratified by seizure type • Completing Study, % Patients • Time to First Seizure Median Time to an Exit Event • Lamotrigine 48 days vs Gabapentin 69 days	Withdrawal Due to Adverse Event • Gabapentin 10.8% • Lamotrigine 15.2% statistically equivalent Percent Reporting ≥ 1 Adverse Event • Gabapentin 75.3% • Lamotrigine 75.5% Serious AE Related to Study Drug • Gabapentin (1) overdose • Lamotrigine (1) convulsion Most Common AEs (both groups) • Dizziness, Asthenia, Headache
Faugtht et al, 1993[159] RCT, double-blind, parallel group	N=111	Uncontrolled partial-onset seizures with or without generalized seizures in adolescents and adults	Monotherapy with • Felbamate (n=56) • Valproic acid (n=55)	Escape criteria met (2x ↑ monthly seizure frequency; 2x ↑ highest 2-day seizure frequency; generalized tonic-clonic seizure (none at baseline); or significant prolongation of generalized tonic-clonic seizures) • Felbamate < Valproic acid (p<0.001) for each criterion	Most Common Adverse Events (>10%) Felbamate • Headache, nausea, somnolence Valproic acid • Nausea, headache Hepatic Effects - Felbamate • 4/56 mild ↑SGPT/SGOT (concomitant lovastatin-1, phenytoin-1); reversible upon discontinuation
Marson et al, 2001[112] Systematic review and meta-analysis of 11 placebo-controlled, RCTs	N=2871	Drug resistant, localization-related epilepsy	Add-on with • Levetiracetam • Oxcarbazepine • Remacemide • Zonisamide	Responder Rate: Relative Risk (95% CI) • Levetiracetam 3.78 (2.62-5.44) • Oxcarbazepine 2.51 (1.88-3.33) • Remacemide 1.59 (0.91-2.97) • Zonisamide 2.46 (1.61-3.79) • Dose-Response Effect • Levetiracetam	Withdrawal Rate: Relative Risk (95% CI) • Levetiracetam 1.21 (0.88-1.66) • Oxcarbazepine 1.72 (1.35-2.18) • Remacemide 1.90 (1.00-3.60) • Zonisamide 1.64 (1.02-2.62) Withdrawal Rate: Risk Difference (RD) Not difference than placebo • Levetiracetam

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
				• Oxcarbazepine • Remacemide Responder-Withdrawal Ratio • Levetiracetam > Zonisamide > Oxcarbazepine	
Marson et al, 1996[102] Systematic review and meta-analysis of 28 placebo-controlled, RCTs	N=3883	Add-on Treatment in Partial Epilepsy	Add-on Therapy • Gabapentin • Lamotrigine • Tiagabine • Topiramate • Vigabatrin • Zonisamide	Responder Rate Individual Agent Vs Placebo Odds Ratio (95% Confidence Interval) • Gabapentin 2.29 (1.53-3.43) • Lamotrigine 2.32 (1.47-3.68) • Tiagabine 3.03 (2.01-4.58) • Topiramate 4.22 (2.80-6.35) • Vigabatrin 3.68 (2.45-5.51) • Zonisamide 2.47 (1.36-4.47) Comparison of each medication demonstration overlapping confidence intervals – No difference among agents	Withdrawal for Any Reason Odds Ratio (95% Confidence Interval) • Gabapentin 1.36 (0.75-2.49) • Lamotrigine 1.19 (0.79-1.79) • Tiagabine 1.81 (1.21-2.70) • Topiramate 2.42 (1.43-4.11) • Vigabatrin 2.58 (1.26-5.27) • Zonisamide 5.70 (1.76-18.49) Comparison of each medication demonstration overlapping confidence intervals – No difference among agents
Jacoby et al, 2015[160] Randomized, controlled, unblinded, multicenter, parallel-group United Kingdom	N=1575	New-onset epilepsy Baseline: N=1575 Questionnaire returned 3-month N=1,439 1 year N=1274 2 year N=1121 QOL assessment: age ≥ 5 years,	Focal-epilepsy group (Arm A) • Carbamazepine vs lamotrigine, gabapentin, oxcarbazepine, topiramate Generalize/unclassified epilepsy group (Arm B) • Valproate vs lamotrigine, topiramate	QOL Arm A: • Depression: Topiramate > oxcarbazepine [coefficient 1.27; 99% CI, 0.13-2.41] • Less worry about past seizures: Carbamazepine> lamotrigine [OR 0.35; 99% CI 0.13-0.94] • General health perception as fair/poor: gabapentin > oxcarbazepine [OR 3.44; 99% CI 1.17-0.09] QOL Arm B: No differences	• No differences between agents

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
		without learning disability	QOL Measures included • Newly Diagnosed Epilepsy QOL (NEWQOL) • Impact of Epilepsy Scale Global QOL	For all drugs: As the chance of 12-month remission increases, so do QOL measures.	

RCT – randomized-controlled trial, AED – antiepileptic drug, OL – open-label, PG – parallel group, MC – multicenter[15]