Table e-1. Summary of AEDs for treatment of new-onset epilepsy

AED	2004 Monotherapy focal/mixed (focal + IGE)	2004 Childhood absence epilepsy	2015 Monotherapy focal/mixed (focal + IGE)	2015 Childhood absence epilepsy
Clobazam	NA	NA	No (Level U)	No (Level U)
Eslicarbazepine	NA	NA	No (Level U)	No (Level U)
Ezogabine	NA	NA	No (Level U)	No (Level U)
Felbamate	NA	NA	No (Level U)	No (Level U)
Gabapentin	Yes (Level B, focal epilepsy only)	No (Level B)	Yes (Level B, focal >65 y)	No (Level U)
Lacosamide	NA	NA	No (Level U)	No (Level U)
Lamotrigine	Yes (Level A, mixed population)	Yes (Level C)	Yes (Level B, focal >65 y)	Not as effective as ETS or VPA (Level B)
Levetiracetam	No (Level U)	No (Level U)	Yes (Level C, focal)	No (Level U)
Oxcarbazepine	Yes (Level A, mixed population)	No (Level U)	No (Level U)	No (Level U)
Perampanel	NA	NA	No (Level U)	No (Level U)
Pregabalin	NA	NA	Should not consider (vs LTG)	No (Level U)
Rufinamide	NA	NA	No (Level U)	No (Level U)
Tiagabine	No (Level U)	No data	No (Level U)	No (Level U)
Topiramate	Yes (Level A, mixed population)	No data	No (Level U)	No (Level U)
Zonisamide	No (Level U)	No (Level U)	Yes (Level C, focal)	No (Level U)
Vigabatrin	NA	NA	Should not consider (vs CBZ)	No (Level U)

Abbreviations: AED = antiepileptic drug; CBZ = carbamazepine; ETS = ethosuximide; IGE = idiopathic generalized epilepsy; LTG = lamotrigine; NA: not available; VPA = valproic acid

Table e-2. Evidence table: Efficacy of GBP, LTG, OXC, PGB, TPM, and VGB in new-onset epilepsy

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
Patients with new onset focal epilepsy or unclassified GTC seizures									
Rowan, 2005[e16]	II (Downgraded because 25% of patients lost to follow-up)	Parallel-design double-blind RCT **GBP vs LTG vs CBZ-IR**	593	Data of 590 patients. Available for primary analysis.	**Treatment totals:** GBP: n = 194 LTG: n = 199 CBZ-IR: n = 197 **Mean daily dose:** GBP: 1424 mg ± 285 mg LTG: 131 mg ±34 mg CBZ-IR: 558 mg ± 1554 mg	12 months	276 (46.8%) patients completed the 12-month trial. CBZ-IR (64% [95% CI, 58%–71%]) had more terminations than GBP (51%, [95% CI, 44%–58%]) or LTG (44% [95% CI, 37–51%]). *p*=0.002, for comparison of three AEDs. Early termination was related to adverse events. Termination rates are listed as follows (*p*=0.001): LTG: 12.1% GBP: 21.6% CBZ-IR: 31%	See outcomes	The first year of the study (1998), patients aged 65 years and older were included; one year later, the age was reduced to 60 years and older to improve enrollment. The majority of patients had comorbid medical conditions, mainly vascular disease. A history of traumatic brain injury among patients was relatively high.
Saetre, 2007[e17]	I	Parallel-design double-blind RCT	184	99.5%	**Treatment totals:** LTG: n = 93 CBZ-CR: n = 91 **Mean daily dose:**	40 weeks (including a 4-week dose	There was no difference in the completion of the 40-week trial:	See outcomes	Study conducted in elderly patients aged

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
		LTG vs CBZ-CR			LTG: 91±28 mg CBZ-CR: 336±96 mg	escalation period)	LTG: n = 68 (73% [95% CI, 65%–83%]) CBZ-CR: n = 61 (67% [95% CI, 55%–74%])		65 years and older.
Brodie, 2007[e18]	II (downgraded because only 66.3% of patients completed the study)	Parallel-design double-blind RCT **LEV vs CBZ-CR**	579	66.3%	**Treatment totals:** LEV: n = 237 CBZ-CR: n = 235 **Target/daily dose (flexible dosing):** LEV: 1000 to 3000 mg CBZ-CR: 400 to 1200 mg	29 to 55 weeks	Seizure freedom for 26 weeks: No difference between patients randomized to LEV (79.4% [95% CI, 74%–84%]) and CBZ-CR (72.8% [95% CI, 67%–78%]) Seizure freedom for 52 weeks: No difference between patients randomized to LEV (56.6%) and CBZ-CR (58.5%)	Discontinuation related to AEs: LEV: 14.4% CBZ-CR: 19.2%	The majority of patients who achieved seizure-freedom for 6 and 12 months did so at the lowest doses of both LEV and CBZ-CR
Baulac, 2012[e19]	II (downgraded because only 60.5% of patients completed the study)	Parallel-design double-blind RCT **LTG vs CBZ-CR**	583	60.5%	**Treatment totals:** ZNS: n = 223 CBZ-CR: n = 233 **Target/daily dose (flexible dosing):** ZNS: 200 to 500 mg CBZ-CR: 400 to 1200 mg	32 to 84 weeks	Seizure freedom for 26 weeks: No difference between patients randomized to ZNS (79.4% [95% CI 74%–84%]) and CBZ-CR (83.7% [95% CI, 78%–88%]) Seizure freedom for 52 weeks: ZNS (67.6%) vs CBZ-CR (74.7%, p = ns).	Related to adverse events: ZNS: 11% CBZ-CR: 12%	No difference in treatment-emergent and related AEs SAEs between the two treatment arms.
Ramsay, 2010[e25]	II	Parallel-design double-	259	83.7%	**Treatment totals:** PHT: n = 128 TPM: n = 133	28 days	21.1% (95% CI, 15%–29%) of patients randomized to PHT and	Related to AEs: PHT: 12.5%	Noninferiority of TPM to

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
	(downgraded because of baseline differences in gender ratio, mean weight, and race)	blind RCT **TPM vs PHT**			**Dose:** PHT Dose: 1000 mg day 1, followed by 300 mg/day TPM: 100 mg/day		12.8% (95% CI, 8%–20%) randomized to TPM discontinued during the double-blind trial Discontinuation rate was related to AEs. There were no differences in time to first seizure. Mean AED blood levels: PHT: 8.5±7.1 mg/L TPM: 3.6±1.34 mg/L	TPM: 6%	PHT was not established.
Marson, 2007[e20]	III (open trial with unmatched unblended populations)	Parallel-design unblinded RCT **LTG vs GBP vs TPM vs OXC vs CBZ (CBZ-IR or CBZ-CR)** All were given at flexible doses.	1721		**Treatment totals:** GBP : n = 377 LTG : n = 378 OXC : n = 210 TPM: n = 378 CBZ (CBZ-IR or CBZ-CR): n = 378 **Mean (±SD) daily dose:** GBP: 2414±899 mg LTG 355±175 mg OXC: 1480±525 mg TPM 291±168 mg CBZ: 991±347 mg	24 months	**Time to treatment failure for any reason (all patients):** LTG better than CBZ: HR: 0.78 (95% CI, 0.63–0.97) LTG better than GBP: HR: 0.65 (95% CI, 0.52–0.8) LTG better than TPM: HR: 0.64 (95% CI, 0.52–0.79) LTG had no significant advantage over OXC HR: 1.15 (95% CI, 0.86–1.54).	See outcome	At least 1 adverse event: GBP: 47% LTG: 45% TPM: 53% OXC: 48% CBZ: 48%

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
							Time to 12-month remission: CBZ better than GBP: HR: 0.75 (95% CI, 0.63–0.90) CBZ had a no significant advantage over LTG (HR: 0.91 [95% CI, 0.77–1.09]), OXC (HR: 0.92 [95% CI, 0.73–1.18]) and TPM (HR: 0.86 [95% CI, 0.72–1.03]		
Kälviäinen, 1995[e22]	III (open trial not masked and more than 20% of patient dropped out [see Completion rate)	Parallel-design open-label RCT **VGB vs CBZ-IR**	100	72%	**Treatment totals:** CBZ-IR: n = 50 VGB: n = 50 **Mean (SD) daily dose:** VGB: CBZ-IR:	12 months	Seizure freedom at 12 months: VGB: 16/50 (32% [95% CI, 21%–46%) CBZ-IR: 26/50 (52% [95% CI, 39%–65%) Discontinuation because of adverse events: CBZ: 12/50 VGB: 0	28 (28%): 16 because of lack of efficacy and 12 because of AEs.	The follow-up period of the study was not long enough to assess visual disturbances.
Chadwick, 1999[e21]	I	Parallel-design double-blind RCT	459	See outcomes	**Treatment totals:** VGB: n + 229 CBZ-IR: n = 230 **Target daily dose:** VGB: 2 g		Time to first seizure was significantly longer on CBZ-IR (p=0.0001) Hazard ratio 1.57 (95% CI, 1.23-2.02) No differences between VGB and CBZ-IR on:	See outcome	Psychiatric symptoms: VGB: n = 58 (25%) CBZ-IR: n = 34 (15%)

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
		VGB vs CBZ-IR			CBZ-IR: 600 mg		Time to 6-month remission Time to withdrawal because of lack of efficacy		Weight gain: VGB: n = 11 (25%) CBZ-IR: n = 12 (5%) Rash: VGB: n = 7 (3%) CBZ-IR: n = 22 (10%)
Glauser, 2007[e26]	II (downgraded because seizure etiologies not described sufficiently)	Parallel-design double-blind RCT **TPM at 50 mg/d vs TPM at 400 mg/d**	151 Children and adolescents	88%	**Treatment totals and dose:** TPM 50 mg/d, n = 74 TPM, 400 mg/d, n = 77	6 months	Seizure freedom at 6 months and 12 months: TPM, 50 mg/d: 78% and 62% (95% CI, 52%–72%) TPM, 400 mg/d: 90% and 85% (95% CI, 75–91%) Adverse events: TPM, 50 mg/d: 4% TPM, 400 mg/d: 14%	Discontinuation because of AEs: n = 14 (9%)	More frequent cognitive adverse events among patients receiving 400 mg/d
PGB vs LTG Kwan, 2011[e24]	II (downgraded because only 73.6% of patients completed the study)	Parallel-design double-blind RCT **PGB vs LTG**	660 Patients aged 16 years and older	73.6%	**Treatment totals and dose:** PGB: 150 mg/d by 4 weeks and up to 600 mg /d by 24 weeks LTG: 100 mg/d by 4 weeks and 500 mg /d by 24 weeks	Titration: 4 weeks Efficacy double-blind period: 52 weeks	Seizure freedom for 6 months or longer: PGB: n = 162 (52%) LTG, n = 209 (68%) True difference in proportion: -0.16 (95% CI, -0.24 – -0.08). Time to withdrawal because of lack of efficacy: PGB, n = 19 (6%) LTG, n = 3 (1%)	PGB, n = 38 (12%), 25 (8%) were AED related LTG, n = 34 (10%), 24 (7%) were AED related	Of patients receiving LTG, 60% received 100 mg/d by week 24, and 55% received 150 mg/d by week 24

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
							RR 6.52 (95% CI, 1.93–22.04) Time to first seizure: RR: 1.47 (1.19–1.80) Time to 6 months of seizure freedom: RR: 0.74 (0.6–0.9)		
Adult and pediatric patients with GTC seizures secondary to GE or unclassified GTC seizures or secondary to focal epilepsy									
Marson, 2007[e27]	III (open trial with unmatched unblended populations)	Parallel-design open-label RCT **LTG vs TPM vs VPA** given at flexible doses	716	88%	**Treatment totals:** LTG: n = 239 TPM: n = 239 VPA: n = 238 **Mean (SD) daily dose at end of trial:** LTG: 341±169 mg TPM: 367±225 mg VPA: 1600±896 mg	24 months	Time to treatment failure for any reason (all patients): VPA better than TPM (HR 1.57 [95% CI, 1.19–2.08]) VPA and LTG did not differ (HR 1.25 [95% CI, 0.94–1.68]). Time to treatment failure for any reason (only patients with GE): VPA better than LTG (HR 1.55 [95% CI, 1.07–2.24] and TPM (HR 1.89 (95% CI, 1.32–2.70])	See outcomes	At least 1 adverse event: LTG: 37% TPM: 45% VPA: 86% 63% of patients had GE the frequency of AEs. 27% of patients had GTC seizures that could not be classified.

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
							Time to 1-year remission (entire group and IGE group): VPA was better than LTG (entire group: HR 0.76 [95% CI, 0.62–0.94]); (IGE group: HR 0.68 [95% CI, 0.53–0.89]) There were no differences between VPA and TPM for entire group.		The study included children, adolescents, and adults.
Monotherapy in adults and adolescents with new-onset focal, GE, or unclassified GTC seizures									
Trinka, 2013[e28]	III (open trial)	Parallel-design open-label RCT **LEV vs CBZ-CR or LEV vs VPA-XR**	1688	75%	**Treatment totals:** LEV vs VPA-XR: LEV: n = 349 VPA-XR: n = 347 LEV vs CBZ-CR: LEV: n = 492 CBZ-CR: n = 500 **Dose:** Given at flexible doses	12 months	Time to treatment failure for any reason (all patients): LEV was no different than VPA-XR or CBZ-CR.(HR 0.90 [95% CI, 0.74–1.08]) LEV vs VPA-XR: no differences (HR: 1.02 [95% CI, 0.74–1.41]) LEV vs CBZ-CR: no differences (HR: 0.84 [95% CI, 0.66–1.07]) Time to first seizure: Longer for VPA-XR or CBZ-CR than LEV (HR 1.20 [95% CI, 1.03–1.39]	LEV vs VPA-XR: LEV: 21.8% VPA-XR: 21.9% LEV vs CBZ-CR: LEV: 25.6% CBZ-CR: 28.8%	At least 1 AE: LEV: 70.3% VPA-XR: 62% CBZ-CR: 72.5% AEs led to drug discontinuation: LEV: 8.3% VPA-XR: 4.7% CBZ-CR: 18.8% Severe AEs LEV: 15.6%

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
							Estimated 12-month seizure-freedom rates from randomization: LEV vs VPA-XR LEV: 58.7%; VPA-XR: 64.5% LEV vs CBZ-CR LEV: 50.5%; CBZ-CR: 56.7% LEV not superior to VPA-XR or CBZ-CR.		VPA-XR: 13.3% CBZ-CR: 14% Serious AEs LEV: 12.7% VPA-XR: 5.8% CBZ-CR: 8.2%
Childhood absence epilepsy									
Glauser, 2010[e29]	I	Parallel-design double-blind RCT **LTG vs ETS vs VPA**	451	88.3%	**Treatment totals:** LTG: n = 146 ETS: n = 154 VPA: n = 146 **Highest daily dose of AEDs at week 16:** LTG: 12 mg/kg (or 600 mg) ETS: 60 mg/kg (or 2000 mg) VPA: 60 mg/kg (or 3000 mg)	20 weeks	Freedom from treatment failure: n = 206 (47%) Lack of seizure control: n = 109 (24%) Adverse events: n = 97 (27%) Seizure freedom: ETS: n = 81 (53%) VPA: n = 85 (58%) LTG: n = 43 (29%) AEs: ETS: n = 37 (24%) VAP: n = 35 (24%) LTG: n = 25 (17%)	See outcomes	See outcomes

Reference	Class	Design	Group Size	Completion rate	Treatment (total per treatment, dose)	Study duration	Outcomes	Dropouts	Comments
							Seizure reedom: ETS vs LTG: OR: 2.66 (1.65–4.28, *p*<0.001) VPA vs LTG: OR: 3.34 (2.06–5.42, p<0.001) Adverse events: *p*=0.2		

Abbreviations: AE = adverse event; AED = antiepileptic drug; CBZ = carbamazepine; CBZ-CR = controlled-release carbamazepine; CBZ-IR = immediate-release carbamazepine; CI = confidence interval; ETS = ethosuximide; GBP = gabapentin; GE = generalized epliepsy; GTC = generalized tonic–clonic; IGE = idiopathic generalized epilepsy; HR = hazard ratio; LEV = levetiracetam; LTG = lamotrigine; OR = odds ratio; OXC = oxcarbazepine; PGB = pregabalin; PHT = phenytoin; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SD = standard deviation; TPM = topiramate; VGB = vigabatrin; VPA = valproic acid; VPA-XR = extended-release valproic acid; ZNS = zonisamide.

Reference numbers of studies cited here taken from the complete guideline, published as a data supplement to the main article on Neurology.org.