Table e-1. Summary of first guidelines on the use of treatment-resistant epilepsy, based on level A and B recommendations[3]

AED	Adjunctive focal adult	Focal monotherapy	Generalized epilepsy	Lennox-Gastaut syndrome	Adjunnctive focal pediatric
Felbamate	Yes	No	No	Yes	No
Gabapentin	Yes	No	No	No	Yes
Lamotrigine	Yes	Yes	Yes (only in CAE)	Yes	Yes
Levetiracetam	Yes	No	No	No	No
Oxcarbazepine	Yes	Yes	No	No	Yes
Tiagabine	Yes	No	No	No	No
Topiramate	Yes	Yes	Yes	Yes	Yes
Zonisamide	Yes	No	No	No	No

Abbreviations: CAE = childhood absence epilepsy

Table e-2. Mechanism of action of the eight newly approved antiepileptic drugs

Antiepleptic drug	Mechanism of action
Clobazam	Binding to benzodiazepine at the GABAA ligand–gated chloride channel complex
Eslicarbazepine	Use-dependent blockage of voltage-sensitive sodium channels
Ezogabine	Positive allosteric modulator of KCNQ2-5 Positive allosteric modulator of GABAA receptors
Lacosamide	Slow inactivation of voltage-gated sodium channels Binds to CRMP-2
Perampanel	AMPA receptor antagonist
Pregabalin	Binding to the α2-δ protein subunit of voltage-gated calcium channels
Rufinamide	Use-dependent blockage of voltage-sensitive sodium channels
Vigabatrin	Inactivation of GABA transaminase

Table e-3. Common, clinically relevant and serious adverse events of third-generation of antiepileptic drugs in addition to vigabatrin and clobazam (Data based on studies cited in the guideline and post-marketing reports)

Antiepleptic drug	Common adverse events	Dose dependent?	Serious adverse events
Pregabalin	Dizziness, ataxia, sedation, tremor, abnormal coordination, blurred vision, diplopia, weight gain, vomiting, constipation, increased appetite pedal edema, decreased libido and erectile dysfunction. Rare: myoclonus, dyskenisia	Yes	Hypersensitivity syndrome (rare) Neutropenia (rare) A-V block (rare)
Lacosamide	Dizziness, fatigue, nausea, ataxia, nystagmus, headache, abnormal coordination and somnolence, diplopia, blurred vision, depression	Yes	Increased PR interval (special caution should be taken in patients with 2nd and 3rd degree A-V block.
Rufinamide	Dizziness, diplopia, fatigue, somnolence, nausea, ataxia, confusion and impaired concentration.	Yes	Hypersensitivity syndrome Decreased QT_c interval (Investigate history and /or family history of short QT interval).

Ezogabine	Dizziness, somnolence, headache, fatigue, ataxia, dysarthria, confusion, tremor, weight gain, anxiety.	Yes	Retinal and cutaneous blue discoloration, psychotic symptoms urinary retention QT interval prolongation
Perampanel	Dizziness, somnolence, headache, ataxia, diplopia, blurred vision, nausea, confusion, irritability, depression	Yes	Homicidal ideation and aggressive behavior, suicidal ideation and behavior
Eslicarbazepine	Dizziness, sedation, fatigue, headache, diplopia, nausea and vomiting, hiccups, hyponatremia. Rare: dyskenisias	Yes	Reversible granulocytopenia (dose-dependent), pancytopenia, thrombocytopenia Stevens Johnson syndrome (rare)
Vigabatrin	Fatigue, drowsiness, dizziness, ataxia, headache, irritability, depression, weight gain, rash	Yes	Psychosis Retinopathy
Clobazam	Sedation, fatigue, dizziness, irritability, depression and disinhibition, loss of appetite, dry mouth, constipation	Yes	Severe aggressive outbursts Stevens-Johnson syndrome and toxic epidermal necrosis

Table e-4A. Clinically relevant pharmacokinetic properties

AED	Protein binding %	$T_{1/2}$ (hours)	Metabolism/ Elimination	Clinical notes
Pregabalin	0	5–7	renal	Food co-ingestion: -↓ absorption by 25 – 30% - delayed absorption by ~ 2.5 hours Adjust dose in case of renal failure
Lacosamide	<15%	13	Hepatic / renal	Adjust dose in case of moderate to severe renal failure
Rufinamide	35%	6–10	Hepatic / Renal (minimal)	Food co-ingestion: -↑absorption by 40 – 45% -↑Cmax by 100% Bioavailability decreases with increased doses (in a dose-dependent manner)

Ezogabine	80%	7	Hepatic	
Perampanel	95%	100 (53 to 136)	Hepatic/ renal (minimal)	Food co-ingestion: -↓ absorption by 28 – 30% - delayed absorption by ~ 3 hours Adjust dose in case of hepatic failure
Eslicarbazepine	30%	20–24	Hepatic /renal	Adjust dose in case of renal failure
Vigabatrin	0%	10–30	Not metabolized/100% renal excretion	Adjust dose in case of renal failure
Clobazam	85%	CLB: 10–30 N-desmethyl-CLB: 36–46	Hepatic / renal (minimal)	CLB is metabolized into an active metabolite N-desmethyl-CLB

Table e-4B. Clinically relevant interactions with antiepileptic and other drugs

AED	Enzyme induction	Interaction with other AEDs	Interaction with other drugs	Interaction with oral contraceptives
Pregabalin	No	None	none	none
Lacosamide	No	-EIAEDs on LCM: modest ↓ in serum concentrations	none	none
Rufinamide	Modest induction of CYP3A4	-EIAEDs on RFN: ↓serum concentration -VPA on RFN: ↑serum concentration -RFN on AEDs: ↓CBZ and LTG serum concentration ↑PB and PHT serum concentrations	RFN ↓serum concentration of triazolam	↑ metabolism and renders them less effective
Ezogabine	No	-EIAEDs (CBZ and PHT only) on EZG: ↓serum concentration EZG on AEDs: ↓LTG serum concentrations	none	none
Perampanel		EIAEDs on PER: ↓serum concentration PER on AEDs: ↑TPM and OXC serum concentrations	Strong inhibitors of CYP3A4 ↑PER serum concentrations	At doses of 12 mg/day, PER ↑ metabolism and renders them less effective
Eslicarbazepine	No	EIAEDs on ESL: ↓serum concentration ESL on AEDs: ↓LTG and TPM serum concentrations ↑PHT serum concentrations	ESL↓ warfarin serum concentration	↑ metabolism and renders them less effective
Vigabatrin	No	VGB on AEDs: ↑PHT serum concentrations	none	none
Clobazam	No	EIAEDs on CLB↑: ↓serum concentration ↑ N-desmethyl-CLB serum concentration	Cymetidine ↑ CLB serum concentrations	none

		FBM and STP on CLB: ↑ CLB + N-desmethyl-CLB serum concentrations CBM on AEDs: ↑PHT, PRM, VPA serum concentrations		

TABLE e-5. Evidence table: Efficacy of LTG, OXC, LEV, VGB, PGB, LCM, RFN, EZG, PER, ELS, and CLB in treatment-resistant focal and generalized epilepsy and in LGS

Reference	Class	Design	Group Size	Completion rate	Treatment (technique, dose)	Study duration	Outcomes	Drop outs	Adverse events/ comments
Treatment of adults with treatment-resistant focal epilepsy									
Pregabalin									
French, 2003[e5]	I	R-DB-PC Parallel, multiple-dose	453	89%	PGB @: 50 mg/d n = 88 150 mg/d n = 86 300 mg/d n = 90 600 mg/d n = 89 Placebo n = 100	20 weeks (8 week titration)	Seizure reduction and responder rate [95% CI in %] 50 mg/d 12% 15% [8-24%] 150 mg/d 34% 31% [22-41%] 300 mg/d 44% 40% [30-51%] 600 mg/d 54% 51% [40-63%] Placebo 7% 14% [8-22%] p < 0.0001 0.006	N = 46, Pcbo, n = 5 50 mg, n = 6 150 mg, n = 1 300 mg, n=13 600 mg, n=21	33 patients (7.2%) had SAEs
Arroyo, 2004 [e6]	I	R-DB-PC Parallel, multiple - dose	288	88.5%	PGB@ 150 mg/d, n = 99 600 mg/d, n = 92 Placebo, n = 97	20 weeks (8 week titration)	Seizure reduction and responder rate [95% CI in %] 150 mg/d 20.6% 14.1% [9-24] 600 mg/d 47.8% 43.5%* [33-55] Placebo 1.8% 6.2%* [3-14] P < 0.0001 <0.0001*	N = 33, 600 mg n = 17 150 mg, n = 10 Placebo, n = 7	11 (3.8%) patients had SAEs

Elger, 2005 [e8]	II	R-DB-PC Parallel, Single dose different schedule	341	66.2% [class of evidence downgraded by <80% completion rate]	PGB 600 BID, n = 137 Flexible dose (150 to 600 mg/d), n = 131 Placebo, n = 73	18 weeks (6 week titration)	Seizure reduction and responder rate [95% CI in %] 600 mg/d 49.3% 41.3% [31-52] Flexible dose 35.4% 34% [25-44] Placebo 10.6% 10.7% [5-22] P 0.0091 <0.01	600 mg, n = 57 Flexible dose, n = 31 Pcbo, n = 17	Discontinuation rates due to adverse events" 600 mg: 32.8% Flexible dose: 12.2% Pcbo: 6.8%
Beydoun, 2005[e7]	II	R-DB-PC Parallel, Single dose different schedule	313	75.7% [class of evidence downgraded by <80% completion rate]	PGB 600 mg/d 600 BID, n = 104 600 TID, n = 111 Placebo, n = 98	20 weeks (8 week titration)	Seizure reduction and responder rate [95% CI in %] BID 44% 43% [32-51] TID 53% 49%* [39-58] Placebo +1% 9%* [4-15] P <0.0001 <0.001	BID: n = 32 TID: n = 26 Pcbo, n = 17	55 patients withdrew because of adverse events BID: n = 27 TID, n = 21 Pcbo, n = 7
Pregabalin CR									
French, 2014[e9]	I	R-DB-PC Parallel, Single dose	330	88.9% completed the trial	PGB CR 165 mg /day, n = 113 330 mg/day, n = 100 Placebo, n = 110	23 weeks (2 week titration)	28-day % seizure reduction relative to placebo: *165 mg:1.1% **330 mg: 13.1% *p = 0.98; **p = 0.09 Responder rate: Placebo: 35.8% *165 mg: 37.8% **330 mg: 45.9%	Placebo: 2.7% 165 mg: 3% 330 mg:7.1%	Placebo: 2.7% 165 mg: 3% 330 mg:7.1%

							*P = 0.54 **P = 0.07		
Lacosamide									
Halász, 2009[e10]	I	R-DB-PC Parallel, multiple dose vs. placebo	485	82.3%	LCM 200 mg/d, n = 163 LCM 400 mg/d, n = 159 Pcbo, n = 163	16 week (4 week titration)	Seizure reduction and responder rate [95% CI in %] 200 mg/d 35.3%* 35%* [28-42] 400 mg/d 36.4%** 40.5%** [33-48] Placebo 20.5% 25.8% [19-32] P =0.02* 0.07* = 0.03** 0.01**	86 patients d/c the trial 44 due to adverse events	42 patients (8.7%) withdrew because of serious adverse events 200 mg, n = 10 (6.1%) 400 mg, n = 24 (15.1%) Pcbo, n = 8 (4.9%)
Chung, 2010[e11]	II	R-DB-PC Parallel Multiple dose	405	78% [class of evidence downgraded by <80% completion rate]	LCM, 600 mg/d, n = 97 LCM, 400 mg/d, n = 204 Placebo, n = 104	18 week (6 week titration)	Seizure reduction and responder rate [95% Ci in %] 400 mg/d 37.3%* 38.3%* [32-45] 600 mg/d 37.8%** 41.2%** [31-51] Placebo 20.8% 8.3% [3-14] P =0.008* <0.001* ** =0.006**	66 (16.5%) pts d/c because of AEs.	61 of the 66 patients who withdrew because of AE did so during the titration phase.
Ben-Menachem, 2007 [e12]	II	R-DB-PC Parallel Multiple dose	418	74.6% [class of evidence	LCM, 600 mg/d, n = 106 LCM, 400 mg/d, n = 108	18 week (6 week titration)	Seizure reduction and responder rate [95% CI in %] 400 mg/d 37.3%* 38.3%* [29-47]	69 (17%) pts d/c because of AEs.	d/c because of AEs LCM, 600 mg/d, n = 32

				downgraded by <80% completion rate]	LCM 200 mg/d, n = 107 Placebo, n = 97		600 mg/d 37.8%** 41.2%** [32-51] Placebo 20.8% 18.3% [11-26] P =0.008* <0.001* ** =0.006**		LCM, 400 mg/d, n = 20 LCM 200 mg/d, n = 12 Placebo, n = 5
Krauss, 2010 [e13]	III	R-OP Parallel Multiple infusion rates	160	98.2%	LCM 30 min, n = 40 LCM 15 min, n = 100 LCM 10 min, n = 20 200 to 800 mg dose	n/a	No difference in tolerability among infusion rates	No d/c because of AE	
Rufinamide									
Brodie, 2009 [e15]	I	R-DB-P single dose vs placebo	312	82.4%	RFN, 3200 mg/d, n = 156 Placebo, n = 157	13 weeks (2 weeks titration)	Seizure reduction and responder rate [95% CI in %] RFN -20.4% 28.2% [21-35] Placebo +1.6% 18.6% [12-24] P 0.002 0.04	26 (16.7%) patients d/c because of adverse events	d/c because of AE RFN = 21 (13.5%) Placebo 5 (3.2%)
Elger, 2010 [e15]	I	R-DB-P Parallrl Multiple dose	647	85.5%	RFN 1600 mg/d, n = 133 RFN 800 mg/d, n = 129 RFN,400 mg/d, n = 125 RFN 200 mg/d, n = 127 Placebo, n = 133	12 weeks maintenance (no titration)	The median frequency /28 days demonstrated a dose dependent efficacy vs. Placebo for all doses except 200 mg/d (p = 0.003) Responder rate [95% CI in %]: 1600 mg = 14.3% [8-20]	62 (9.4%) discontinued because of AEs	d/c because of AE RFN n = 53 Placebo, n = 9

							800 mg = 11.6% [6-17] 400 mg = 16% [10-22] 200 mg = 4.7% [1-8] Placebo = 9% [3-10] p = 0.0019		
Biton, 2011[e17]	I	R-DB-P Parallel	357	82.8%	RFN 3200 mg/d, n = 176 Placebo, n = 181	96 days (12 days titration)	Seizure reduction and responder rate [95% CI in %] RFN -23.25% 32.5% [26-39] Placebo -9.6% 14.3% [9-20] P 0.007 <0.0001	38 (10.6%) patients d/c because of adverse events	d/c because of Aes RFN, n = 27 (15.3%) Placebo, n = 11 (6.1%)
Ezogagabine									
Brodie, 2010 [e18]	II	R-DB-P Parallel Multiple doses	538	76% [class of evidence downgraded by <80% completion rate]	EZG 900 mg/d, n = 179 EZG 600 mg/d, n = 181 Placebo, n = 179	16 weeks (4 weeks titration)	Seizure reduction and responder rate [95% CI in %] 900mg 27.9%* 38.6%* [31-46] 600 mg 39.9%** 47%** [40-54] Placebo 15.9% 18.9% [13-25] P <0.001* ** <0.0001* ** (each dose vs. Placebo)	d/c because of AE: 86 (15.9%) patients	d/c because of AEs 900mg 26%* 600 mg 17%** Placebo 8%
Porter, 2007 [e19]	II	R-DB-P Parallel Multiple doses	399	69.9% [class of evidence	EZG 600 mg/d, n = 100 EZG 900 mg/d, n =95	24 weeks (8 weeks titration)	Seizure reduction and responder rate [95% CI in %] 600 mg/d: 23% 23% [8-18]	d/c because of AE: 79	d/c because of AEs 600mg 17% 900 mg 20% 1200 mg 29.2%

				downgraded by <80% completion rate]	EZG 1200 mg/d, n =106 Placebo, n = 96		900 mg/d: 29% 32%*[22.2-41] 1,200 mg/d: 35% 33%** [26-44] Placebo: 13% 16% [8-21.6] P <0.0001+ 0.021* 0.016** +all vs. placebo	(19.8%) patients	Placebo 12.5%
French, 2011[e20]	II	R-DB-P Parallel Single dose	305	73.2% [class of evidence downgraded by <80% completion rate]	EZG, 1200 mg/d, n = 153 Placebo, n = 152	18 weeks (6 weeks titration)	Seizure reduction and responder rate [95% CI in %] EZG 44.3% 44.4% [37-52] Placebo 17.5% 17.8% [12-24] P <,0.001 <0.001	d/c because of AE: 54 (17.7%) patients	d/c because of Aes EZG, n = 41 (26.8%) Placebo, n = 13 (8.6%)
Vigabatrin									
French, 1996[e22]	I	R-DB-P Parallel Single dose	182	93%	VGB, 3000 mg/d, n = 92 Placebo, n = 90	16 weeks (4 weeks titration)	Responder rate [95% CI in %] p VGB 43% [33-54] <0.001 Placebo 19% [11-27] Monthly reduction in seizure frequency VGB -3.0 0.0002 Placebo - 0.8	d/c because of AEs: 10 patients	d/d because of AEs VGB: 8% Placebo: 2%

Dean, 1999[e23]	I	R-DB-P Parallel Multiple doses	174	86%	VGB 1 g/d VGB, 3 g/d VGB, 6 g/d Placebo	18 weeks (6 weeks titration)	Responder rate p VGB 1g 24% <0.0001 VGB 3g 51% VGB 6g 54% Placebo 7% Monthly reduction in seizure frequency VGB 1g VGB 3g 4.3 0.0001 VGB 6g 4.5 Placebo 0.2	d/c because of Aes: 17 patients	d/c because of AE VGB 1 g: 6.5% VGB 3 g: 11.4% VGB 6 g: 18.2% Placebo: 2.2%
Clobazam									
Koeppen, 1987[e26]	III	R-DB-P Cross-Over	129	83.7%	CLB 10 to 40 mg/day	3 months CLB then Pcbo, n = 63 3 months Pcbo then CLB, n = 60 1 month wash-out	Difference between seizure frequency on CLB and placebo: Lower seizure frequency on CLB ($p<0.05$)	d/c because of Aes: 4	CLB: n = 3 Pcebo, n = 1 Withdrawal symptoms CLB:
Schmidt, 1986[e27]	III	R-DB-P Cross-Over	20	100%	CLB 40 mg/day	CLB: 4 months Placebo: 4 months	Mean number of seizures/ month: CLB: 10.4 Placebo: 20.3 p <0.01	No d/c because of AEs	AEs CLB: 17 (85%) Placebo: 12 (60%)

						1 month wash-out			
Allen, 1938[e28]	III	R-DB-P Cross-Over	26	77% [class of evidence downgraded in part by <80% completion rate]	CLB 30 mg/day	CLB: 9 weeks Placebo: 9 weeks 8 weeks wash-out	Responder rate: CLB: 12/26 (46%) [no data for placebo) Seizure-free: 3 (11.5%) vs. 0 for placebo	n/a	AEs CLB: 6 (23%) Placebo: 2 (7.7%)
Perampanel									
French, 2012[e29]	I	R-DB-P Parallel Multiple doses	386	83.2%	PER 12 mg/d, n = 121 PER 8 mg/d, n = 129 Placebo, n = 136 Single daily dose.	Titration: 6 weeks Maintenance: 13 week	Seizure reduction and responder rate 12mg 17.6%* 33.9%* [26-42] 8 mg 30.5%** 33.3%** [25-42] Placebo 9.7% 14.7% [9-21] P <0.001* <0.0001* 0.01** <0.0002** (each dose vs. Placebo)	d/c because of AEs: n = 35 (14%)	AEs leading to discontinuation per treatment group 12 mg/d, n=23 (19%) 8 mg, n=12 (9.3%) Placebo, n=6 (4.4%) Common AEs leading to dose reduction / interruption 12 mg/d, n=34 (28.1%)

									8 mg, n=27 (20.9%) Placebo, n=5 (3.7%)
French, 2012[e30]	I	R-DB-P Parallel Multiple doses	390	99.2%	PER 12 mg/d, n = 133 PER 8 mg/d, n = 133 Placebo, n = 121 BID dosing.	Titration: 6 weeks Maintenance: 13 week	Median % change and responder rate [95% CI in %] 12mg -34.5%* 36.1%* [28-44] 8 mg -26.3%** 37.6%** [29-46] Placebo -21.0% 26.4% [19-34] P <0.016* ns* 0.026** ns** (each dose vs. Placebo)	d/c because of AEs: n = 40 (10.2%)	AEs leading to discontinuation per treatment group 12 mg/d, n=24 (18%) 8 mg, n=9 (7%) Placebo, n=7 (6%) Common AEs leading to dose reduction / interruption 12 mg/d, n=45 (33.2%) 8 mg, n=30 (22.6%) Placebo, n=6 (5%)
Krauss, 2012[e31]	I	R-DB-C Parallel Multiple doses	623	88%	PER 8 mg/d, n = 169 PER 4 mg/d, n = 172 PER 2 mg/d, n = 180 Placebo, n = 184 Q day dosing	Titration: 6 weeks Maintenance: 13 week	Median % change and responder rate [95% CI in %] 8 mg -30.8%* 34.9%* [28-42] 4 mg -23.3%** 28%** [21-35] 2 mg -13.6% 20.6% [15-26]	d/c because of AEs: n = 40 (10.2%)	AEs leading to discontinuation per treatment group 8 mg/d, n=12 (7.1%) 4 mg, n=5 (3%) 2 mg, n = 12 (6.7%)

							Placebo -21.0% 17.9% [12-24] P <0.0001* 0.0003* 0.0026** 0.013** (each dose vs. Placebo)		Placebo, n=7 (3.8%) Common AEs leading to dose reduction / interruption 8 mg/d, n= 29 (17.2%) 4 mg, n=12 (7%) 2 mg, n = 3 (1.72%) Placebo, n=7 (3.8%)
Eslicarbazepine									
Elger, 2009[e32]	I	R-DB-C Parallel Multiple doses	402	82%	ESL 400 mg, n = 100 ESL 800 mg, n = 98 ESL 1200 mg, n = 102 Placebo, n = 102	8 weeks baseline (single blind) Titration period: 2 weeks (double blind) Maintenance: 10 weeks (double blind)	Median % change and responder rate for the maintenance period [95% CI in %] 400 mg -26% 23% [15-31] 800 mg -36%* 34%* [24-43] 1200 mg -45%** 43%** [34-53] Placebo -160% 20% [12-27] P <0.0028* <0.05* 0.003** <0.001**	d/c because of AEs: n = 36 (8.9%)	AEs leading to discontinuation per treatment group 400 mg/d, n=4 (4%) 800 mg, n=8 (8.2%) 1200 mg, n = 20 (19.6%) Placebo, n=4 (3.9%)

							(each dose vs. Placebo)		
Gil-Nagel, 2009[e33]	II	R-DB-C Parallel Multiple doses	252	77% [class of evidence downgraded by <80% completion rate]	ESL 800, n = 85 ESL 1200, n = 80 Placebo, n = 87	Titration: 2 weeks Maintenance: 12 weeks	Median % change and responder rate [95% CI in %] 800 mg -37.9%* 34.5%* [24-44] 1200 mg -41.9%** 37.5%** [27-48] Placebo -21.0% 22.6% [14-32] P <0.048* n.s.* 0.021** 0.02** (each dose vs. Placebo)	d/c because of AEs: n = 22 (8.7%)	AEs leading to discontinuation per treatment group 800 mg, n = 7 (8.2%) 1200 mg, n = 11.3% Placebo, n = 6 (6.9%)
Ben-Menachem, 2010[e34]	III	R-DB-C Parallel Multiple doses	395	70.9% [class of evidence downgraded in part by <80% completion rate]	ESL 400 mg, n = 96 ESL 800 mg, n = 101 ESL 1200 mg, n = 98 Placebo, n = 100	8 weeks baseline Titration period: 2 weeks Maintenance: 14 weeks	Median % change and responder rate [95% CI in %] 400 mg - 8.7% 16.7% [9-24] 800 mg -32.6%* 40%* [30-49] 1200 mg -32.8%** 37.1%** [27-46] Placebo -0.8% 13% [6-20] P <0.001* <0.001* <0.001** <0.001** (each dose vs. Placebo)	d/c because of AEs: n = 60 (15.2%)	AEs leading to discontinuation per treatment group 400 mg, n = 12 (12.5%) 800 mg, n = 19 (18.8%) 1200 mg, n = 26 (26.6%) Placebo, n = 3 (3%)
Monotherapy for treatment-resistant focal epilepsy									
Levetiracetam XR									

Chung, 2012[e37]	III	R-DB-Conversion to monotherapy with historic control	228	83.3%	LEV-XR 2000 mg, n = 171 LEV-XR 1000, n = 57	8 weeks baseline Titration period: 2 weeks Baseline AED tapering : 6 weeks LEV-XR monotherapy10 weeks	Completed monotherapy trial LEV-XR 2000 mg: 82% LEV-XR 1000 mg: 87.7% Cumulative exit rate by day 112: LEV-XR-2000: 0.375 [CI:0.297-0.453] Historic control: 0.653 Exit because of: -two-fold increase in sz frequency: n = 34 (21.5%) - in highest 2 day consecutive sz frequency: n = 23 (14.6%) - de-novo GTC sz, n = 12 (7.6%) - status epilepticus or worsening of sz, n = 11 (7%)	d/c because of AE: n = 9 (3.9%)	Psychiatric AEs: n = 34 (14.9%)
Pregabalin									
French, 2014[e38]	III	R-DB-Conversion to monotherapy with historic control	161	92% However study stopped after interim analysis of 125 patients for positive efficacy	PGB 600 mg, n = 129 N = 100 completed study PGB, 150 n = 32 N = 25 completed study	8 weeks baseline Titration period: 2 weeks Baseline AED tapering : 6 weeks PGB monotherapy12 weeks	Completed monotherapy trial: PGB 600 mg: 54.3% PGB 150 mg: 46.9% Cumulative exit rate: PGB-600: 0.275 [CI:0.178-0.372] Historic control: 0.74 and 0.68, P <0.001 for both N = 30 (25%) met one exit criteria	d/c because of AEs: n = 25 600 mg, n =22 (17%) 150 mg, n = 3 (9.4%)	

							PGB-150: 0.377 [CI:0.154-0.6] Historic control: 0.74 and 0.68, P <0.001 for both		
Lacosamide									
Wechsler, 2014[e39]	III	R-DB-Conversion to monotherapy with historic control	425	See outcome	LCM 400 mg, n = 319 LCM 300 mg, n = 106	8 weeks baseline Titration period: 3 weeks Baseline AED tapering: 6 weeks LCM monotherapy10 weeks	Completion of monotherapy trial: n = 271 (63.8%) Cumulative exit rate by day 112: LCM-400: 0.30 [CI:0.246-0.355] Historic control: 0.653 Exit because of: -two-fold increase in sz frequency: n = 50 (17.6%) - in highest 2 day consecutive sz frequency: n = 34 (12%) - de-novo GTC sz, n = 9 (3.2%) Worsening of seizure disorder: 23 (8.1%) - status epilepticus or worsening of sz, n = 5 (1.8%)	d/c because of AEs: n = 69 (16.2%) 400 mg, n =54 (16.9%) 300 mg, n = 15 (14.2%)	
Eslicarbazepine									
Jacobson, 2015[e41]	III	R-DB-Conversion to monotherapy with	172	See outcome	ESL 1200 mg / day, n = 58 ESL 1600 mg /day, n = 114	8 weeks baseline Titration period: 2 weeks	Completion of monotherapy trial: n = 121 (70%) Cumulative exit rate by day 112: ESL-1200: 0.15 [CI:0.08-0.28]	d/c because of AEs: n = 16 (9%)	

		historic control				Baseline AED tapering: 6 weeks ESL monotherapy10 weeks	ESL 1600:0.128[CI: 0.07-0.21] Historic control: 0.653 Exit because of meeting exit criteria ESL 1200 mg: n =7 ESL 1600 mg, n = 12	1200 mg, (3%) 1600 (12%)	
Sperling, 2015[e40]	III	R-DB-Conversion to monotherapy with historic control	193	See outcome	ESL 1200 mg / day, n = 65 ESL 1600 mg /day, n = 128	8 weeks baseline Titration period: 2 weeks Baseline AED tapering: 6 weeks ESL monotherapy10 weeks	Completion of monotherapy trial: n = 271 (63.8%) Cumulative exit rate by day 112: LCM-400: 0.30 [CI:0.246-0.355] Historic control: 0.653 Exit because of: -two-fold increase in sz frequency in consecutive 28 day: n = 11 (6.2%) - in highest 2 day consecutive sz frequency: n = 11 (6.2%) - de-novo GTC sz, n = 5 (2.8%) Worsening of seizure disorder: 12 (6.7%) - status epilepticus, n = 1 (0.6%)	d/c because of AEs: n = 31 (16%) 1200 mg, (12%) 1600 (18%)	
Extended-release formulations in adults with TR focal epilepsy									
Topiramate XR									
Chung, 2014[e36]	I	DB-PC-RCT	249	87.1%	TPM-XR 200 mg/day: n = 124 Placebo: n = 125	Titration: 3 weeks	Median percentage reduction in seizure frequency per week:	d/c because of AEs	

						Maintenance: 11 weeks	TPM-XR: 39.5% Placebo: 21.6%; *p* <0.001. >50% responder rate: TPM: 37.9% Placebo: 23.2% P= 0.013	TPM: 9.7% Placebo: 3.2%	
Extended-release oxcarbazepine									
French, 2014[e35]	II	DB-PC-RCT	366	67.8%	OXC-XR 2400 mg /day, n = 123 1200 mg/ day, n = 122 Placebo, n = 121	Baseline: 8 weeks Titration: 4 weeks Maintenance: 12 weeks	Median percentage reduction in seizure frequency per 28 dayperiod: Placebo: 28.7%; *1200 mg/day: 38.3% Difference over placebo: 1200 mg: -10.3% [CI:-22.3, 1.2] **2400 mg /day: 42.9% Difference over placebo: -18.3% [CI: -30.4, -5.8] *p= 0.08. ** p = 0.003 >50% responder rate: Placebo: 28.1% 1200 mg /day: 36.1% 2400 mg / day: 40.7% *p= 0.08. ** p = 0.02	d/c because of AEs Placebo: 8.3% 1200 mg: 14.8% 2400 mg:30.1%	French JA, Acta Neurol Scand, 2014
Treatment-resistant Generalized Epilepsy									
Lamotrigine									

Biton, 2005[e43]	II	R-DB-PC Parallel Dose adjusted according to age and type of concommitant AED Pediatric, adolescents and adult patients	117	74.5% [class of evidence downgraded by <80% completion rate]	LTG, n = 58 Placebo, n = 59	For patients >12 years old 19 weeks (7 weeks titration, 12 weeks maintenance) < 12 weeks 24 weeks (12 weeks titration, 12 weeks maintenance)	Median % seizure reduction <u>GTC seizures</u>: LTG: 66.5% Placebo: 34.2% $p = 0.006$ <u>All generalized seizures</u> LTG: 46.8% Placebo: 15.9% $p = 0.004$ Responder rate [95% CI in %] <u>GTC seizures</u> LTG: 64% (72% [61-84]during maintenance) Placebo: 39% (49% [36-62]during maintenance) p<0.05 All generalized seizures LTG: 48% (60% [48-73]during maintenance)* Placebo: 38% (39% [27-51]during maintenance)* *p<0.05 (only for comparison during maintenance)	d/c because of AE: 7 (6%) patients	LTG: 8.6% Placebo: 3.3%
Trevathan, 2006[e44]	I	R-DB- PC Parallel	45	91%	LTG, n = 21 Placebo, n = 24	7 weeks titration and 12 weeks maintenance	Median decrease sz. Frequency: LTG: 77% Placebo: 40% P = 0.044	2 patients LTG, n = 1 Placebo, n = 1	Adverse events: LTG: 10% Placebo: 25%
Biton, 2010[e45]	I	R-DB-PC Parallel	146	92.5%	LTG-XR, n = 72 Placebo, n = 74	19 weeks (7 week titration	Median % seizure reduction LTG: 75.4% Placebo: 32.5% $p < 0.0001$	d/c because of AE: 3	LTG: 0.6% Placebo: 1.4%

		Dose adjusted according to type of concommitant AED Adolescents and adults				and 12 week observation)	Responder rate [95% CI in %] LTG: 69.6% [59-80] Placebo: 31.9% [21-43] p<0.0001	(2%) patients	
Levetiracetam									
Berkovic, 2007[e46]	I	R-DB-PC Parallel Single dose Adults and pediatric patients	164	85.4%	LEV, n = 84 3000 mg/d or 60 mg/kg in children Placebo, n = 80	24 weeks (4 weeks titration)	Median % seizure reduction LEV: 56.5% Placebo: 28.2% $p = 0.004$ Responder rate [95% CI in %] LEV: 72.2% [63-82] Placebo: 45.2% [34-56] p = 0.001 Seizure-free – GTC seizures LEV: 34.2% [24-44] Placebo: 10.7% [4-18] p <0.001 Seizure-free – all seizures LEV: 24.1% [14.7-33] Placebo: 8.3%[3-14.9] p = 0.009	d/c because of AE: 5 (3%) patients	LEV: 1.2% Placebo: 5%
Noachtar, 2008[e47]	I	R-DB-PC Parallel	121	88.4%	LEV, n = 61 Placebo, n = 60	16 weeks (4 weeks titration)	Reduction of ≥50% in number of days/week with	d/c because of AE: 3	LEV: 3.2% Placebo: 1.7%

		Single dose Adolescents (> age 13) and adults			JME: 93.4% JAE: 6.6%		myoclonic seizures [95% CI in %] LEV: 58.3% [47-71] Placebo: 23.3% [13-34] p<0.001 All seizures: LEV: 56.7% [45-70] Placebo: 21.7% [11-32] p<0.001 Seizure –freedom Myoclonic seizures LEV: 16.7% [7-26] Placebo: 3.3% [0-8] p =0.03 All seizures LEV: 13.3% [5-22] Placebo: 0 [0-6] p =0.006	(2.5%) patients	
Lennox Gastaut Syndrome									
Clobazam									
Conry, 2009[e48]	II	R-DB-C Parallel Low vs. high dose Children and adults	68	85.3%	Low dose: 0.25mg/kg, n = 32 High dose:1 mg/kg, n = 36	7weeks (3 weeks titration)	Weekly reduction in drop seizure frequency relative to baseline: Mean (SD) Low dose: from 141 ± 188 to 91 ± 122 High dose: from 207 ± 229 to 32 ± 57 Percentage change [95% CI in %]:	d/c because of AEs: 9 (13.2%)	d/c because of AEs Low dose: 9.3% High dose: 16.7%

							Low dose: 12 ± 122%, [0-52] p = 0.0162 High dose: 85 ± 16.8% [80-91], p < 0.0001 High vs. low dose: p<0.0001		
Ng, 2011[e49]	II	R-DB-C Parallel Placebo vs. Low (0.25 mg/kg/d) vs. medium (0.5 mg/kg/d) vs. high dose (1 mg/kg/d) Children and adults	238	74.4% [class of evidence downgraded by <80% completion rate]	Placebo, n = 59 Low dose: 0.25 mg/kg, n = 58 Medium dose: 0.5 mg/kg, n = 62 High dose: 1 mg/kg, N = 59	22 weeks (4 week baseline, 3 weeks titration, 12 weeks maintenance, 2 to 3 weeks tapering	Average weekly drop in seizure rate 0.25 mg/kg/d : 41.2% (p = 0.012) 0.5mg/ kg /d: 49.4% (p = 0.0015) 1.0 mg/kg/day: 68.3% (p <0.0001) Placebo: 12.1% Responder rate [95% CI in %] 0.25 mg/kg/d : 43.4% [30-56] (p = n.s) 0.5mg/ kg /d: 58.6% [46-70] (p = 0.015) 1.0 mg/kg/day: 77.6% [67-88] (p <0.0001) Placebo: 31.6% [20-44] *p values compare each dose to placebo	AEs associated with d/c: Somnolence, lethargy, aggression, ataxia, insomnia and fatigue	d/a because of AEs: 0.25 mg/kg/d : n = 4 0.5mg/ kg /d: n = 8 1.0 mg/kg/d: n = 13 Placebo: n = 2
Rufinamide									

Glauser, 2008[e50]	I	R-DB-PC Parallel Children and adults	138	89.1%	RFN 45 mg/kg RFN = 74 Placebo, n = 64	12 weeks (2 weeks titration)	Median % seizure reduction All seizures: RFN: 32.7% Placebo: 11.7% p = 0.0015 Tonic/atonic seizures RFN: 42.5% Placebo: +1.4% p< 0.0001 50% responder rate/28 days [95% CI in %] RFN: 31.1% [20-42] Placebo: 10.9% [3-19] p = 0.0045	d/c because of AEs: n = 6 (4.3%)	RFN: 8.1% Placebo: 0
Ohtsuka, 2014[e51]	I	R-DB-PC Children and adults	59	91.5%	RFN target dose by weight: 15- 30 Kg: 1000 mg/d 30.1-50Kg: 1800 mg/d 50.1-70kg: :2400mg/d >70.1 kg;3200 mg/d	Baseline: 4 week Titration: 2 week Maintenance: 10 week	Median % seizure reduction All seizures: RFN: 32.9% Placebo: 3.1% p < 0.001 Tonic/atonic seizures RFN: 24.2% Placebo: 3.3% p< 0.0001 50% responder rate RFN: 25% [20-42] Placebo: 7.6% p = 0.07 Odds ratio: 4.67[CI:1.15-18.95]	d/c because of AEs: RFN: n = 4(13.8%) Placebo: n = 1 (3.3%)	
Treatment-resistant focal epilepsy in pediatric patients									
Levetiracetam									

Glauser, 2006[e52]	I	R-DB-PC Parallel	198	89.4%	LEV: 60 mg/kg (could lower dose to 40 mg/kg in case of adverse events) LEV: n = 107 Placebo: n = 91	14 weeks (4 weeks titration)	50% responder rate: LEV: 44.6% Placebo 19.6% p = 0.0002 Percent reduction of seizures frequency over placebo during the treatment period: 26.8% (*p* = 0.0002; 95% CI 14% to 37.6%). Seizure-free: 6.9% Placebo: 1%	d/c because of AEs: n =14 (7%)	LEV:5% Placebo: 9.3%
Pina-Garza, 2009[e53]	I	R-DB-PC Parallel Infants 1 months old up to 4 year old	116	95.7%	< 6 months old: LEV: 40 mg/kg >6 months old: 50 mg/kg LEV, n = 60 Placebo, n = 56	Baseline: 48 hr V-EEG Treatment : 5 days Titration: 1 day Evaluation period: last 48 hours with V-EEG	Responder rate average daily seizure frequency: LEV: 43% Placebo: 19.6% p 0.0013 Median % reduction from baseline in average seizure frequency LEV: 43.6% Placebo: 7.1% Median difference between LEV and placebo: 39.2% (95% CI: 17.5-62.2) p <0.0001	d/c because of AEs: n =2 (1.7%)	LEV:3.3% Placebo: 0
Oxcarbazepine									

Pina-Garza, 2005[e54]	I	R-Rater B Parallel High dose vs. Low dose Infants 1 months old up to 4 year old	128	89.8%	OXC: High dose: 60 mg/kg (can lower to 40 mg/kg in case of Aes), n = 64 Low dose: 10 mg/kg, n =64	High dose: Titration: 26 days Maintenance: 9 days Low dose: no titration Maintenance: 9 days	Median absolute change in seizure frequency per 24 hours: high-dose:−2.00 low-dose:−1.37; p = 0.043. Median percentage reduction in seizure frequency per 24 hours: high-dose: 83.33% low-dose: 46.18%; p = 0.047. Data is not provided where we can calculate the confidence interval of the median reduction.	d/c because of AEs: n =5 (3.9%)	Low dose: 3% High dose: 4.7%
Zonisamide									
Guerrini, 2013[e55]	I	DB-PC-RCT	207	88.4%	ZNS: 8 mg /kg/day n =	Titration: 8 weeks Maintenance: 12 weeks	>50% responder rate: ZNS: 50% Placebo: 31% P= 0.0044	d/c because of AEs ZNS:0.9 % Placebo: 3%	

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