Bilaga till rapport

Diagnos och behandling av epilepsi / Diagnosis and treatment of epilepsy, rapport [281] (2018)

Bilaga 5 – Tabeller över inkluderade studier/Appendix 5 Table of included studies (*reviderad/revised 181128*)

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Diagnos/Diagnosis

Tabell 1.1 EEG vid sömndeprivering/EEG with sleep deprivation

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
DeRoos 2009 [1] USA	RCT	198 patients (5 months to 18 years old) with ≥1 epileptic seizure or suspicious but diagnostically uncertain events.	Sleep deprived EEG (SD-EEG) n=99 patients	Standard EEG n=99 patients	**Epileptiform activity:** I: 37 patients (37.4%) C: 28 patients (28.3%). Nonsignificant statistical difference between groups.	
van Donselaar 1992 [2] The Netherlands	Prospective study	157 patients (≥15 years old) with a clinically presumed idiopathic first seizure. Follow-up 1-2 years.	Sleep deprived EEG (SD-EEG) n=134 patients SD-EEG was obtained in 134 of the 138 patients in whom the standard EEG did not show epileptiform activity.	Standard EEG n=157 patients	**Epileptiform activity:** I: 19 additional patients n=134 (14.2%). C:19 patients n=157 (12.1%). Total (Intervention+ control) =38 of 157 patients (24.2%). **Seizure recurrence at follow-up:** I: 12 of 19 patients (64%, 95% CI, 42% to 87%). C:18 of 19 patients. **Sensitivity**: C: showed epileptic discharges in 18 of 63 patients who suffered a recurrence (sensitivity, 29%). Sensitivity of the combined EEGs was 48%.	A sleep-deprivation EEG, obtained in 11 patients in whom the standard EEG showed epileptic discharges, duplicated these findings in 10 patients.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
					Specificity: C: In 93 of the 94 seizure-free patients, no epileptiform was shown (specificity, 99%). Specificity of the combined EEGs was 91%.	
King 1998 [3] Australia	Prospective study	300 patients (≥5 years old) with unexplained seizures	Sleep deprived EEG (SD-EEG) n=158 patients SD-EEG was obtained in patients in whom the standard EEG did not show epileptiform activity	Standard EEG n=300 patients	**Epileptiform activity:** I: 55 additional patients n=158 (35%). C: 129 of 300 patients (43%). Total (Intervention+ control) =184 of 300 patients (61%).	
Leach 2006 [4] UK	Prospective study	85 patients (>35 years old) with possible new epilepsy	Sleep deprived EEG (SD-EEG) n=85 patients All patients received both standard and SD-EEG	Standard EEG n=85 patients All patients received both standard and SD-EEG.	**Epileptiform activity:** I: 44 of 85 patients (51.8%). C: 22 of 85 patients (25.9%). Difference in proportions=25.9% (95% CI 10.5 to 40.0) p=0.0006	
Rowan 1982 [5] The Netherlands	Prospective study	43 patients (5 to 55 years old) with doubt concerning the clinical diagnosis of epilepsy, or uncertainty regarding the type of epilepsy present in those with known seizures.	Sleep deprived EEG (SD-EEG) n=43 patients 41 patients received both standard and SD-EEG, 2 patients only SD-EEG.	Standard EEG n=41 patients 41 patients received both standard and SD-EEG.	**Epileptiform activity:** I:25 of 43 patients (58%). C:8 of 41 patients (20%). Difference in proportions=38% (95% CI 15.8 to 56.4) p=0.0004	
Sadleir 2010	Prospective study	92 children	Sleep deprived EEG (SD-EEG)	Standard EEG n=92 patients	**Epileptiform activity:** I: 56 patients (61%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
[6] Australia		(2 to 16 years old) with new-onset seizures.	n=92 patients All patients received both standard and SD-EEG.	All patients received both standard and SD-EEG.	C: 52 patients (57%) Nonsignificant statistical difference between groups.	
Schreiner 2003 [7] Canada	Prospective study	157 patients (≥16 years old) with a first unprovoked seizure. Follow up 3–88 months.	Sleep deprived EEG (SD-EEG) n=60 patients SD-EEG were performed in 60 patients whose initial EEG was normal or inconclusive.	Standard EEG n=157 patients	**Epileptiform activity:** I:17 additional patients n=60 (28.4%). C:42 of 157 patients (26.8%). Total (Intervention+ control) =59 of 157 patients (37.5%). Intervention (SD-EEG) detected epileptiform EEG in 8 additional patients in comparison to control (standard EEG). Intervention (SD-EEG) did not detect epileptiform EEG in 5 patients with epileptiform detected in standard EEG (control).	

C= control; CI=confidence interval; EEG= electroencephalography; I= intervention; n= number; p= probability value; RCT= randomized controlled study; SD-EEG= sleep deprived EEG

Tabell 1.2 – EEG före, respektive efter 24 timmar av ett misstänkt epilepsianfall/EEG before and after 24 hours respectively of a suspected epileptic seizure

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
King 1998 [3] Australia	Prospective	300 children and adults (age 5 to 83 years) with unexplained seizures. Patients with previous seizures without previous diagnosis or treatment were included.	EEG within 24h. n=156 patients	EEG after 24h. n=144 patients	**Epileptiform dischargers:** I:51% (80 of 156 patients) C:34% (49 of 144 patients) Difference=17% 95% CI for difference in proportions 6%–28%. p=0.003	
Sofat 2016 [8] USA	Retrospective chart review study	270 patients (age ≥1 years) with new onset unprovoked seizure.	EEG within 6 to >96h. n=270 patients. n ≤12h=32 patients (23 pediatrics (≤18 years) and 9 adults (≥18 years)).	EEG within 6 to >96h. n=270 patients. n≥12h=238 patients (146 pediatrics (≤18 years) and 92 adults (≥18 years))	**Epileptiform dischargers:** ≤6h=67% 6–12h=52% 12–24h=24% ≤24h=31% 12–48h=22.9% 24–48h=25% 48–72h=22% 72–96h=18% >96h=27% 12h v. 12–48h p=0.001 12h v. >48h p=0.002 12–48h v. >48h p=0.70 ≤12h v. >12h OR=3.599 95% CI=1.691–7.660 p=0.001	Pediatric patients had higher incidence of having an EEG showing epileptiform discharges comparing to adult patients (p=0.006). Most of the patients who had EEGs done within the first 12 hours fell into the pediatric group.

CI=confidence interval; EEG=electroencephalography; h=hours; n=number; p=probability value

Tabell 1.2 Ambulatorisk EEG/Ambulatory EEG

First Author Year Reference Country	Study Design	Population	Index test	Referens test	Outcome	Comments
Nousiainen 1992 [9] Finland	All patients received both examinations	62 patients (32 men, 32 women) with intractable seizures (mean age = 30, range = 4-82; mean duration of disease = 14.7, range = 1-72)	8-channel ambulatory EEG in hospitalized conditions (A/EEG; n = 45 with seizures during both tests)	8-channel or 16-channel intensive videomonitoring EEG (IVM; n= 45 with seizures during both tests)	Clinical question answered by EEG (diagnosis, seizure classification, pre-surgical evaluation, epilepsy and psychogenic attacks, pseudo-epileptic attacks; n = 45) Ictal A/EEG = 36 (80%) Ictal IVM = 40 (89%) Calculated results for A/EEG with IVM as gold standard: Sensitivity (95 % CI) = 0.9 (0.76, 0.97) Specificity (95 % CI) = 1 (0.48, 1)	- inpatient recordings of A/EEG

Tabell 1.3. Misstänkt epilepsy – MRT/Suspect epilepsy – Magnetic resonance tomography (MRT)

First author Year Reference Country	Study Design	Population	Reference test	Index test	Outcome	Comments
Dzienis 2007 [10] Poland	Participants received both examinations.	85 patients (43 women; mean age =31, age range =6–73) with partial epileptic attacks under epilepsy treatment	MR scans (1.5 T) with epilepsy sequences (T1, T2, FLAIR)	CT scans	Confirmed lesions, n (%): MR =51 (60 %) CT =33 (39 %) MR & CT =28 (33%) Calculated results based on the above numbers: Sensitivity (CI 95%) =0.55 (0.40; 0.69) Specificity (CI 95%) =0.85 (0.69; 0.95)	Sub-cohort with partial epileptic attacks
Nikodijevic 2016 [11] Macedonia	Participants received both examinations.	37 patients (23 females) diagnosed with refractory epilepsy	MR scans with standard sequences (T1, T2, FLAIR).	CT scans	Pathological findings n (%): MR =28 (76 %) CT =11 (30 %)	
Olszewska & Costello 2014 [12] Ireland	Participants received both examinations	91 patients (50 females; age range =18–81; mean age = 41.8) with MR scans within 48h of seizure (provoked seizures were excluded)	MR scans (1.5T; n = 59) with epilepsy sequences (T1, T2, FLAIR, diffusion weighted, gradient echo)	CT scans (n =59)	Abnormal findings n (%): MR=27 (46%) CT=23 (39%) MR only=7 (12 %) CT only=3 (5 %) MR and CT=20 (34 %) Neither CT nor MR = 29 (49 %) Calculated results based on the above numbers: Sensitivity (CI 95%) =0.74 (0.54, 0.89) Specificity (CI 95%) =0.91 (0.75, 0.98)	The same epileptologist reviewed both MR and CT. CT was always done before MR

CI= confidence interval; CT= computerized tomography; FLAIR= Fluid attenuation inversion recovery; MR: Magnetic Resonance imaging, n=number; T=time

Läkemedel/Drugs

Tabell 2.1. AED

First author Year Reference Country	Study design	Population (time from first seizure to randomization)	Intervention	Control	Outcome	Comments
Assarzadegan 2015 [13] Iran	RCT	A first seizure, generalized tonic-clonic, mean age=35, female=44%, N=101	Multivitamins as a placebo, n_2=51		**Seizure recurrence** 0–6 months: AED 0% Placebo 16%	
Beghi 1993 Italy [14] = Leone 2006 (FIRST) [15]	RCT	First unprovoked generalized tonic-clonic seizure (with or without partial onset) age ≥ 2 years N=419	Carbamazepine, phenobarbital, valproate or phenytoin, physicians target dose, time to treatment ≤ 1 week, n_1=215,	No treatment until recurrence, delayed treatment, n_2=204	**Seizure recurrence** *see Leone 2006* Adverse events: AED 7%; No AED 0%	
Camfield 1989 [16] Canada	RCT	Children, first afebrile unprovoked partial or generalized tonic-clonic seizure, female=55%, N=31	Carbamazepine 10 to 20 mg/kg/day, time to treatment ≤ 1 month, n_1=14	No anticonvulsant treatment, n_2=17	**Seizure recurrence** 0–12 months: AED 14%; No AED 53% Adverse events AED 29%; No AED 0%	
Chandra 1992 [17] Indonesia	RCT	Age ≥ 16 years, single partial or generalized unprovoked seizure, N=228	Valproate 1200 mg/day, time to treatment ≤ 2 week, n_1=113	Placebo, n_2=115	**Seizure recurrence** 9–12 months: AED 4%; Placebo 56% Adverse events AED 9%; No AED 2%	
Das 2000 [18] India	RCT	A single unprovoked idiopathic generalized seizure, N=76	Antiepileptic drugs, time to treatment unknown, n_1=36	No treatment, n_2=40	**Seizure recurrence** 12–24 months: AED 11%; No AED 45%	
Gilad 1996 Israel [19]	RCT	A generalized unprovoked seizure, N=91	Carbamazepine or valproate time to treatment ≤ 24 hours, n_1=46	No treatment, n_2=45	**Seizure recurrence** 0–12 months: AED 13%; No AED 57%	

					12–24 months: AED 20%; No AED 57% 24–36 months: AED 22%; No AED 69% Adverse events AED 20%; No AED 0%	
Leone 2006 [15] Italy = Beghi 1993 (FIRST) [14]	RCT	*See Beghi 1993*	*See Beghi 1993*	*See Beghi 1993*	**Seizure recurrence** 0–12 months: AED19%; No AED 22%, 2-year remission: Immediate AED 81%; Deferred AED 78%	
Marson 2005 [20] United Kingdom	RCT	A single partial or generalised unprovoked seizure, for, with at least one follow-up visit, N=812 (404+408) age ≥ 1 month	Carbamazepine or valproate, clinician in equipoise, n_1=404, 30% ≤ 1 week, 55% ≤ 1 month, 81% ≤ 3 month	No treatment, n_2=408	**Seizure recurrence** 0–24 months: AED 32%; No AED 39% 2–year remission: immediate AED 69%; Deferred AED 61%, at ≈ 3,5 years both groups have approximately the same percentage in remission Adverse events AED 39%; No AED 31%	

AED= anti-epileptic drugs; N= number; RCT= randomized controlled study

Tabell 2.2 Personer med epilepsy i remission/Persons with epilepsy in remission.

First author Year Reference Country	Design	Population	Intervention (A)	Control (B)	Outcome	Comments
Gebremariam 1999 [21] Ethiopia	RCT	Seizure free for 18 months, mean age≈6 years, female= 31% N=80	Withdrawal of AED after 18 seizure free months. N_1=41	Withdrawal of AED after 24 seizure free months. N_2=39	**Seizure recurrence** A: n_1=12 (34%), N_1=35 B: n_2=14 (41%), N_2=34 Largest difference at 6–12 months	Follow up data after withdrawal:[1] A=30 months B=24 months
Peters 1998 [22] Netherlands	RCT	Seizure free for 2 months, median age ≈ 6 (0–16) years, female 50%, N=161	Withdrawal of AED after 6 seizure free months. N_1=78	Withdrawal of AED after 12 months, N_2=83	**Seizure recurrence** [2] A: n_1=37 (47%), N_1=78 B: n_2=39 (48%), N_2=82 Largest difference at 3–12 months	Follow up data after withdrawal: A: 18 months B: 18 months
Tennison 1994 [23] USA	RCT	Children with no seizures past 18 months, mean age = 11 (3–21) years, female 41%, N=133	Withdrawal of AED after 24 seizure free months, N_1=72	Withdrawal of AED after 48 months, N_2=61	**Seizure recurrence**[3] A: n_1=34 (47%), N_1=72 B: n_2=19 (31%), N_2=61 Difference increasing after 24 months	Follow up data after randomization: A: 24 months B: 24 months
Verrotti 2000 [24] Italy	RCT	Children & adolescents, partial epilepsy, mean age = 11 (8–15) years, female 55%, N=89	Withdrawal of AED after 12 seizure free months, N_1=45	Withdrawal of AED after 24 seizure free months, N_2=44	**Seizure recurrence**[4]**:** A: n_1=13 (29%), N_1=45 B: n_2=11 (25%), N_2=44	Follow up after withdrawal: A: 72 months B: 72 months

AED=anti-epileptic drugs; N=number; RCT=randomised controlled study

[1] A: 48-18=30, B: 48-24= 24

[2] Table 1, p. 726. A: 100-52,6=47%, B: 100-52,3=48%

[3] Text p. 1 409, length of follow up Figure 2, p. 1 049

[4] Table 1, p. 1 394, length of follow up, figure p. 1 394.

Tabell 2.3. Koncentrationsbestämning/Therapeutic drug monitoring, TDM

First author Year Reference Country	Study Design	Population (lost to follow up not included)	Intervention	Control	Outcome	Comments
Fröscher 1981 [25] Germany	RCT	Diagnosed epilepsy, ≤ 3 seizures of one seizure type preceding 12 months, no gross evidence of non-compliance, no abuse of alcohol, no pregnancy. Grand mal 21, grand mal + psychomotor seizures 53, grand mal + absences 31. Age 11–74 years. N=105	*Therapeutic Drug Monitoring* (TDM). AED: Carbamazepine, Ethosuximide, Phenobarbital, Phenytoin, Primidone, Valproic acid n_1=53	*No Therapeutic Drug Monitoring* (TDM) AED: Carbamazepine, Ethosuximide, Pheno-barbital, Phenytoin, Primidone, Valproic acid n_2=52	*No improvements or worse in seizure recurrence at 12 months:* TDM: 30% No TDM 38%; *Side effects*: presumed to be related to the anti-epileptic treatment. No data.	
Jannuzzi 2000 [26] Italy	RCT	Diagnosed untreated partial or idiopathic generalized epilepsy, ≥ 2 seizures past 4 months N=116	*Therapeutic Drug Monitoring* (TDM). *AED*: carbamazepine, phenobarbital, phenytoin, sodium valproate n_1=58	*No Therapeutic Drug Monitoring* (TDM) *AED*: carbamazepine, phenobarbital, phenytoin, sodium valproate n_2=58	*Patients in remission at 12 months:* TDM: 60% No TDM: 61% Adverse events: TDM: 76% No TDM: 71%	No adverse events were considered serious.
Sivasankari 2012 [27] India	RCT	Diagnosed partial or idiopathic generalized epilepsy on phenytoin monotherapy, for at least six, ≥ 2 seizure episodes past 4 months N=51	*Therapeutic Drug Monitoring* (TDM). *AED*: phenytoin n_1=25	*No Therapeutic Drug Monitoring* (TDM) *AED*: phenytoin n_2=26	*Seizure frequency* during month sixth: TDM: m_1=0.6, sd_1=0.5 No TDM: m_2=1.62, sd_2=0.64 Adverse events: TDM: 15% No TDM: 4%	Headache, drowsiness, somnolence

N=; n= number; RCT=randomized controlled study; TDM= therapeutic drug monitoring

Tabell 2.4 AED som tillägg/AED as Add-on

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Biton 2014 [28] USA	RCT (Multicentre: 85 centres in five countries: Australia, Brazil, Canada, Mexico, and the USA)	400 patients (age 16 to 70 years) diagnosed with two or more partial-onset seizures/month during the 3 months prior to screening and eight or more partial-onset seizures during the 8-week prospective baseline period. Patients were uncontrolled on one to two concomitants AEDs at optimal stable dosages.	AED+ brivaracetam (BRV: 5, 20, 50 mg/day target dose), n=298 5 mg/day, (I-5), n=97 20 mg/day, (I-20), n=100 50 mg/day, (I-50), n=101 Baseline: 8 weeks Titration: 0 weeks Maintenance: 12 weeks	AED+ Placebo n=98	**≥50% reduction in total partial seizure frequency (mITT)**: I-5: 21/97 (21.6%), p=0.353 I-20: 23/100 (23.0%), p=0.239 I-50: 33/101 (32.7%), p=0.008 C: 16/98(16.3%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency (mITT)**: I-5: 14/34 (41.2%) I-20: 19/37 (51.4%) I-50: 24/33 (72.7%) C: 13/32 (40.6%) **Seizure free (mITT):** I-5: 1/97 (1.0%) I-20: 1/100 (1.0%) I-50: 4/101 (4.0%), C: 0/98 (0.0%) **Discontinuation due to adverse events:** I-5: 8/97 (8%) I-20: 5/100 (5%), I-50: 6/101 (6%), C: 2/98 (2%)	mITT: 4 participants were excluded from published analyses due to failure to take the study medication and randomization issues. Group affiliation not reported.
French 2010 [29] USA	RCT (Multicentre: 41 centres in four countries: Brazil, India, Mexico, and the USA)	210 patients (age 16 to 65 years) diagnosed at least four partial-onset seizures/month during the 4-week prospective baseline period.	AED+ brivaracetam (BRV: 5, 20, 50 mg/day target dose), n=154 5 mg/day, (I-5), n=50 20 mg/day, (I-20), n=52 50 mg/day, (I-50), n=52	AED+ Placebo, n=54	**≥50% reduction in seizure frequency (mITT)**: I-5: 16/50 (32.0%), p=0.047 I-20: 23/52 (42.2%), p<0.002 I-50: 29/52 (55.8%), p<0.001 C: 9/54 (16.7%)	mITT: 2 participants were excluded from published analyses due to lost to follow-up before first drug intake. Group affiliation not reported.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Patients were taking one to two concomitants AEDs at optimal stable dosages.	Baseline: 4 weeks Titration: 0 weeks Maintenance: 7 weeks		**Seizure free (mITT):** I-5: 4/50 (8.0%) I-20: 4/52 (7.7%) I-50: 4/52 (7.7%), C: 1/54 (1.9%) **Discontinuation due to adverse events:** I-5: 2/50 (4.0%) I-20: 1/52 (1.9%), I-50: 1/52 (1.9%), C: 3/54 (5.6%)	
Klein 2015 [30] USA	RCT (Multicentre: 147centres in 27 countries: North America, Western Europe, Eastern Europe, Latin America, and Asia)	768 patients (age 16 to 80 years) with well-characterized focal epilepsy or epileptic syndrome, uncontrolled with one or two concomitant AEDs at stable dosage for at least 1 month before first visit.	AED+ brivaracetam (BRV: 100, 200 mg/day target dose), n=505 100 mg/day, (I-100), n=254 200 mg/day, (I-200), n=251 Baseline: 8 weeks Titration: 0 weeks Maintenance: 12 weeks concomitant	AED+Placebo, n=263	**≥50% reduction in seizure frequency (ITT)**: I-100: 98/254 (38.6%), p<0.001 I-200: 94/251 (37.5%), p<0.001 C: 56/263 (21.3%) **Seizure free (ITT):** I-100: 13/254 (5.1%), p=0.003 I-200: 10/251 (4.0%), p=0.019 C: 2/263 (0.8%) **Discontinuation due to adverse events:** I-100: 21/254 (8.3%), I-200: 17/251 (6.8%), C: 10/263 (3.8%)	
Kwan 2014 [31] Australia	RCT (Multicentre: 74 centres in 15 countries:	480 patients (age 16 to 70 years) with ≥2 focal seizures/month (with or without secondary	AED+ brivaracetam (BRV: 20–150 mg/day individualize target dose), n= 359	AED+Placebo, n=121 Focal seizures: n=108	**≥50% reduction in seizure frequency (ITT)**: *Focal seizures* I: 110/323 (34.1%), p=0.056	Discontinuation due to adverse events was not reported separately for patient groups with focal and generalized seizures.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	Austria, Belgium, Czech Republic, Germany, Hong Kong, India, Italy, Norway, Republic of South Africa, Russian Federation, Singapore, South Korea, Sweden, Taiwan, and Ukraine)	generalization) or ≥2 days with primary generalized seizures/month in the 3 months prior to screening, and ≥4 focal seizures or generalized seizure (any type) days during baseline. Focal epilepsy: n=431 Generalized epilepsy: n=49 Patients were uncontrolled on one to three concomitant AEDs.	Focal seizures: n=323 Generalized seizures: n=36 Titration: During the dose-finding period, BRV was initiated at 20 mg/day and up-titrated in a stepwise manner to 50, 100, or 150 mg/day, at 2-week intervals based on the investigator's assessment of efficacy and tolerability. Patients remained on the dose received at the end of the dose-finding period during the maintenance period. Baseline: 4 weeks Titration: 8 weeks Maintenance: 8 weeks	Generalized seizures: n=13	C: 26/108 (24.1%) *Primarily generalized seizures* I: 18/36 (50.0%), C: 4/13 (30.8%) **Seizure free (ITT):** Focal seizures I: 5/323(1%), C: 0/108 (0%) **Discontinuation due to adverse events:** *Focal+ generalized seizures* I: 23/359 (6.4%), C: 7/121 (5.8%)	
Ryvlin 2014 [32] France	RCT (Multicentre: 88 centres in 12 countries: Poland, India, France, Germany, Spain, Italy, Switzerland, Hungary, Finland, The Netherlands, Belgium, and the UK)	399 patients (age 16 to 70 years) with focal epilepsy with a history of focal seizures with or without secondary generalization, and two or more focal seizures/ month for 3 months prior to screening and eight or more focal seizures during the	AED+ brivaracetam (BRV: 20, 50, 100 mg/day target dose), n=298 20mg/day, (I-20), n=99 50mg/day, (I-50), n=99 100mg/day, (I-100), n=100 During the treatment period, the dose of study medication could be reduced once using the	AED+Placebo, n=100	**≥50% reduction in seizure frequency (mITT)**: I-20: 27/99 (27.3%), p=0.339 I-50: 27/99 (27.3%), p=0.372 I-100: 36/100 (36.0%), p=0.023 C: 20/100 (20.0%) **Seizure free (mITT):** I-20: 2/99 (2.0%) I-50: 0/99 (0.0%) I-100: 4/100 (4.0%), C: 0/100 (0.0%)	mITT: 1 participant was excluded from published analyses due to failure to take the study medication. Group affiliation not reported.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		8-week prospective baseline period. Patients were receiving one or two concomitants AEDs.	fallback option at the discretion of the investigator. Baseline: 8 weeks Titration: 0 weeks Maintenance: 12 weeks		**≥50% reduction in focal to bilateral tonic-clonic seizure frequency (mITT)**: I-20: 15/36 (41.7%) I-50: 18/40 (45.0%) I-100: 19/39 (48.7%) C: 11/37 (29.7%) **Discontinuation due to adverse events:** I-20: 4/99 (4.0%) I-50: 6/99 (6.0%), I-100: 5/100 (5.0%), C: 4/100 (4.0%)	
Van Paesschen 2013 [33] Belgium	RCT (Multicentre: 42 centres in 9 European countries: Belgium, Czech Republic, Finland, France, Germany, The Netherlands, Poland, Spain and the United Kingdom)	157 patients (age 16 to 65 years) with partial-onset seizures. All study participants were required to have wellcharacterized focal epilepsy or epileptic syndrome, two or more partial-onset seizures per month during the 3 months prior to study entry, four or more partial-onset seizures during the baseline period. Patients were receiving one or two concomitants AEDs.	AED+ brivaracetam (BRV: 50, 150 mg/day target dose), n=105 50mg/day, (I-50), n=53 200mg/day, (I-150), n=52 Titration: Patients randomized to BRV 50 mg/day started at a dose of 25 mg/day and were up-titrated to 50 mg/day after 1 week. Patients randomized to BRV 150 mg/day started at a dose of 50 mg/day and were up-titrated to 100 mg/day after 1 week	AED+Placebo, n=52	**≥50% reduction in seizure frequency (ITT)**: I-50: 21/53 (39.7%), p=0.077 I-150: 17/52 (33.3%), p=0.261 C: 12/52 (23.1%) **Seizure free (ITT)[5]:** I-50: 5/53 (9.4%) I-150: 3/52 (5.8%), p=0.019 C: 1/52 (1.9%) **Discontinuation due to adverse events:** I-50: 2/53 (3.8%), I-150: 3/52 (5.8%), C: 2/52 (3.8%)	

[5] only reported for the entire 10-weeks treatment period

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			and 150 mg/day after 2 weeks. Baseline: 4 weeks Titration: 3 weeks Maintenance: 7 weeks			

AED= anti-epileptic drug; C=Control; ITT=Intention-To-Treat; mITT= modified Intention-To-Treat; ns= non-significant; I=Intervention, RCT= randomized controlled study

Tabell 2.5 Eslikarbazepinacetat.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Ben-Menachem 2010 [34] Sweden	RCT (Multi-centre, 45 centres in 13 European countries: Argentina, Australia, Belgium, Brazil, Denmark, Germany, the Netherlands, Portugal, Romania, South Africa, Spain, Sweden, and UK)	395 patients (age 18 to 69 years) diagnosed with simple or complex partial-onset who experienced at least 4 partial-onset seizures and treated with 1 to 3 concomitant AEDs in a stable dose regimen.	AED+ eslicarbazepine acetate (ESL), n= 295 400 mg/day (I-400), n=96 800 mg/day (I-800), n=101 1200 mg/day (I-1200), n=98 Titration: All patients started at their full maintenance dose except for I-1200, who started at 800 mg once-daily for a 2-week titration period before reaching target dose. Baseline: 8 weeks Titration: only I-1200 had a 2 weeks titration period Maintenance: 14 weeks	AED+ Placebo, n=100	**≥50% reduction in seizure frequency (ITT)**: I-400: 16/96 (13%) ns I-800: 40/101 (40%) p<0.001 I-1200: 36/98(37%) p<0.01 C: 13/100 **Seizure free (ITT):** I-400: 1/96 (1%) ns I-800: 8/101 (8%) p<0.05 I-1200: 4/98 (4%) ns C: 1/100 (1%) **Discontinuation due to adverse events (ITT):** I-400: 12/96 (13%) I-800: 19/101 (19%) I-1200: 26/98 (27%) C: 3/100 (3%)	
Elger 2007 [35] Germany	RCT (Multi-centre, 19 centres in five European countries: Croatia, Czech Republic, Germany, Lithuania, and Poland)	144 patients (age 18 to 65 years) with at least four partial-onset seizures per month in spite of treatment with one or two AEDs during at least 2 months prior to randomization.	AED+ eslicarbazepine acetate (ESL), n=96 1200 mg once daily (I-1200), n=50 600 mg twice daily, (I-2*600), n=46 Titration: 400 mg/day increase at 4-week-	AED+ Placebo, n=47	**≥50% reduction in seizure frequency (mITT)**: I-1200: 27/50 (54%) p=0.008 I-2*600: 19/46 (41%) p=0.12 C: 13/47 (28%) **Seizure free (mITT):** I-1200: 12/50 (9%)	mITT: 1 participant withdrew from published results before taking any medication. Group affiliation not reported.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			intervals week until target dose. Baseline: 2 months Titration: 8 weeks Maintenance: 4 weeks		I-2*600: 11/46 (24%) C: 4/47 (24%) **Discontinuation due to adverse events (ITT):** I-1200: 3/50 (6%) I-2*600: 4/46 (9%) C: 4/47 (9%)	
Elger 2009 [36] Germany	RCT (Multicentre, 40 centres in 11 countries Austria, Croatia, Czech Republic, Germany, Hungary, Lithuania, Poland, Romania, Russia, Switzerland, and Ukraine)	402 patients (age 18 to 76 years) with partial seizures for at least 12 months before screening, who were receiving one to two AEDs in a stable dose regimen for at least 2 months before screening.	AED+ eslicarbazepine acetate (ESL) n=300 400 mg/day (I-400), n=100 800 mg/day (I-800), n=98 1200 mg/day (I-1200), n=102 Titration: Patients had their dose increased with 400 mg at weekly intervals until reaching the assigned dose. Baseline: 8 weeks Titration: 2 weeks Maintenance: 12 weeks	AED+ Placebo, n=102	**≥50% reduction in seizure frequency (ITT)**: I-400: 23/100 (23%) p=ns I-800: 33/98 (34%) p=0.0359 I-1200: 42/102(43%) p=0.0009 C: 20/102 (20%) **Seizure free (ITT):** I-400: 2/100 (2%) p=ns I-800: 4/98 (4%) p=ns I-1200: 8/102 (8%) p<0.05 C: 2/102 (2%) **Discontinuation due to adverse events (ITT):** I-400: 4/100 (4%) I-800: 8/98 (8%) I-1200: 20/102 (20%) C: 4/102 (4%)	
Gil-Nagel 2009 [37] Spain	RCT (Multicentre, 39 centres in Mexico, Portugal, and Spain)	253 patients (age 17 to 77) years diagnosed with simple or complex partial seizures treated with one to	AED+ eslicarbazepine acetate (ESL) n=165 800 mg/day (I-800), n=85	AED+ Placebo, n=87	**≥50% reduction in seizure frequency (ITT)**: I-800: 28/85 (35%), ns	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		two concomitant AEDs in a stable dose regimen	1200 mg/day (I-1200), n=80 Titration: All patients were treated with half their assigned dose before being titrated to their full dose (800 or 1200 mg) Baseline: 8 weeks Titration: 2 weeks Maintenance: 12 weeks		I-1200: 30/80 (38%) p=0.020 C: 19/87 (23%) **Seizure free (ITT):** I-800: 4/85 (5%) ns I-1200: 3/80 (4%) ns C: 1/87 (1%) **Discontinuation due to adverse events (ITT):** I-800: 7/85 (9%) I-1200: 9/80 (11%) C: 5/87 (8%)	
Sperling 2015 [38] USA	RCT (Multicentre, 173 centres in Argentina, Australia, Brazil, Belgium, Canada, Cyprus, France, Germany, Greece, Hungary, India, Italy, Poland, Turkey, South Korea, Romania, South Africa, Ukraine, and the USA)	650 patients (age 16 to 71) with a documented diagnosis of epilepsy and had ≥4 simple or complex partial onset seizures and treated with a stable dose of one to two AEDs	AED+ eslicarbazepine acetate (ESL) n=426 800 mg/day (I-800), n=216 1200 mg/day (I-1200), n=210 Titration: Patients in the ESL 800 mg group started treatment at 400 mg, and those in the ESL 1,200 mg group started at 800 mg. The dose was increased by 400 mg at the end of the first week Baseline: 8 weeks Titration: 2 weeks Maintenance: 12 weeks	AED+ Placebo, n=224	**50% reduction in seizure frequency (ITT)**: I-800: 66/216 (31%) p=0.07 I-1200: 87/210 (41%) p<0.001 C: 51/224 (23%) **Seizure free (ITT):** I-800: 4/216 (2%) I-1200: 4/210 (2%) C: 2/224 (1%) **Discontinuation due to adverse events (ITT):** I-800: 26/216 (12%) I-1200: 54/210 (26%) C: 18/224 (8%)	

C=Control; I=Intervention, ITT=Intention-To-Treat, mITT=modified Intention-To-Treat, n=number; ns= non-significant; RCT=randomized controlled study

Tabell 2.6 Gabapentin

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Anhut 1994 [39] Germany	RCT, multicentre (24 centres in Europe, Canada, South Africa, and Australia)	272 adults (age 12 to 67 years) with refractory partial epilepsy Patients received 1–2 AEDs Male/female: 152/120 (56/44%)	AED+ gabapentin, (900 or 1200 mg/day target dose) n=163 900 mg/day, (I-900) n=111 1200 mg/day (I-1200), n=52 Titration: "Medication was introduced in a 2-day period at the beginning of the double-blind phase" (no further information). Decreasing the dosage was permitted if toxicity occurred. Baseline: 12 weeks Double-blind phase: 12 weeks (no information on titration)	AED+ placebo, n=109	**≥50% reduction in partial seizure frequency**: I-900: 22/111 (20%) I-1200: 14/52 (27%) C: 11/109[6] (10%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency**[7]: I-900: 45.5% I-1200: 45.0% C: 33.3% **Seizure-free:** not reported **Discontinuation due to adverse events:** I-900: 9/111 (8%) I-1200: 2/52 (4%) C: 4/109 (4%)	ITT data were calculated from PP percentages, excluded patients assumed to be non-responders. ("ITT analysis" in study not true ITT)
Appleton 1999 [40] UK	RCT, multicentre (54 centres in Europe, South Africa and USA)	247 children (age 3 to 12 years) with refractory partial epilepsy Patients received 1–3 AEDs	AED+ gabapentin (target dose 600 to 1800 mg/day, equivalent to 23.2 to 35.3 mg/kg/day)) n=119	AED+ placebo n=128	**≥50% reduction in partial seizure frequency**: I: 25/119 (21%) C: 23/128 (18%) (ns)	ITT data calculated from ITT percentages in publication

6 Data was imputed from Al Bachari et al [39], who had requested additional unpublished data for excluded patients
7 Percentages refer to “evaluable population”, N=245. Not possible to calculate n/N.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Male/female: 134/113 (54/46%)	Baseline: 6 weeks Titration: "by the third day of the double-blind phase" (no further information) Maintenance: 12 weeks		**Seizure-free during double-blind phase:** I: 3/119 (3%) C: 1/128 (1%) **Discontinuation due to adverse events, ITT:** I: 6/119 (5%) C: 3/128 (2%)	
Sivenius 1991 [41] Finland	RCT, single-centre	45 adults (age 16 to 59 years) with refractory partial epilepsy Patients received 1–2 AEDs Male/female: 47/53%	AED+ gabapentin (target dose 900 or 1200 mg/day) n=27 900 mg/day (I-900), n=18 1200 mg/day (I-1200), n=9 Titration: increase from half of the final dose the first day to final dose the second day Baseline: 12 weeks Titration: 2 days Maintenance phase: 3 months	AED+ placebo n=18	**≥50% reduction in partial seizure frequency**: I-900: 2/18 (11%) I-1200: 3/9 (33%) C: 3/18 (17%) **Seizure-free:** Not reported **Discontinuation due to adverse events:** Not reported	2 patients were excluded after randomization in I-900 group, reasons not stated. ITT data reported in table (excluded patients assumed to be non-responders)
UK gabapentin study group 1990 [42] UK	RCT, multicentre (centres in UK and Germany)	127 patients (age 14 to 73 years) with refractory partial epilepsy Patients received 1–3 other AEDs	AED+ gabapentin, (1200 mg/day target dose) n=61 Titration: 600 mg/day first 2 weeks and 1200 mg/day the following weeks	AED+ placebo, n=66	**≥50% reduction in monthly partial seizure frequency**: I: 13/61 (21%) C: 6/66 (9%) **Seizure-free:** not reported **Discontinuation due to adverse events:** I: 7/61 (11%)	ITT data were calculated from PP percentages, (excluded patients were assumed to be non-responders)

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Male/female: I: 39/61% C: 44/56%	Baseline: 3 months Titration: 2 weeks Maintenance: 12 weeks		C: 4/66 (6%)	
US gabapentin study group, 1993 [43] USA	RCT, multicentre (15 centres in USA)	306 adults (age 16 to 70 years) with refractory partial epilepsy Patients received 1–2 AEDs (one patient received 3 AEDs) Male/female: 202/34	AED+ gabapentin (600, 1200 or 1800 mg/day target dose), n=208 600 mg/day (I-600), n=53 1200 mg/day (I-1200), n=101 1800 mg/day (I-1800), n=54 Titration: increase from 300 or 600 mg/day to target dose or maximum tolerated dose over 2 or 3 days Baseline: 12 weeks Titration: 2–3 days Maintenance: 12 weeks	AED+ placebo n=98	**≥50% reduction in monthly partial seizure frequency**: I-600: 9/53 (17%) I-1200: 16/101 (16%) I-1800: 14/54 (26%) C: 8/98 (8%) **Seizure-free:** not reported **Discontinuation due to adverse events:** I: 7/208 (3%) C: 1/98 (1%)	ITT data were calculated from PP percentages (excluded patients were assumed to be non-responders)
Yamauchi, 2006 [44] Japan	RCT, multicentre (54 centres, phase III study)	209 (age ≥16, mean age 31 to 33 years) with refractory partial epilepsy Patients received 1–2 AEDs Male/female: 101/108 (48/52%)	AED+ gabapentin (target dose 1200 or 1800 mg/day) n=127 1200 mg/day (I-1200), n=86 1800 mg/day (I-1800): 41 Titration: 600 mg/day at first day, 1200 mg/day at second day and 1800	AED+ placebo n=82	**≥50% reduction in monthly partial seizure frequency, (ITT)**: I-1200: 13/86 (15%) I-1800: 7/41 (17%) C: 5/82 (6%) **Seizure-free (partial seizure frequency), (ITT):** I-1200: 0/86 (0%) I-1800: 0/41 (0%) C: 0/82 (0%)	ITT data were calculated from PP data reported in study, excluded patients were assumed to be non-responders.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			mg/day (for I-1800) at third day Baseline: 12 weeks Titration: 3 days Maintenance: 12 weeks		**Discontinuation due to adverse events or laboratory test abnormalities:** I: 7/127 (6%) C: 1/82 (1%) (not reported for I-1200 and I-1800 separately)	

C=control, I=intervention, ITT=intention to treat, ns=non-significant, RCT=randomized clinical trial, POS=partial-onset seizures, TPM=topiramate

Tabell 2.7 Lakosamid

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Ben-Menachem, 2007 [45] Sweden and USA	RCT (Multicentre: 68 centres in Germany, Hungary, Lithuania, Poland, Sweden, Switzerland, U.K., and the U.S.A.)	421 (418) patients (age 18 to 65 years) with refractory partial seizures. Patients received at least 2 AEDs.	AED+ lacosamide (200, 400, 600 mg/day target dose), n=321 200 mg/day, (I-200), n=107 400 mg/day, (I-400), n=108 600 mg/day, (I-600), n=106 Titration: I-600; 100 mg/day increase each week until target dose. I-200, I-400 received placebo during the first 2 or 4 weeks of titration, respectively, started on lacosamide 100 mg/day at week 3 or 5, respectively, 100 mg/day increase each week until target dose. Baseline: 8 weeks Titration: 6 weeks Maintenance: 12 weeks	AED+ placebo n=97	**≥50% reduction in seizure frequency (mITT)**: I-200: 35/107 (32.7%), p=0.09 I-400: 44/108 (41.1%), p=0.004 I-600: 40/106 (38.1%), p=0.01 I-T: 119/321 (37%) C: 21/97 (21.9%) **Seizure free during maintenance phase (mITT):** I-200: 1/107 (0.9%) I-400: 5/108 (4.6%) I-600: 1/106 (0.9%) I-T: 7/321 (2%) C: 0/97 (0%) **Discontinuation due to adverse events (mITT):** I-200: 12/107 (15%) I-400: 20/108 (18.5%) I-600: 32/106 (30%) I-T: 64/321 (21%) C: 5/97 (5%)	One down-titration of 100 mg/day was allowed at the end of the titration period, after achieving the randomized dose, if the patient experienced an intolerable adverse event (AE). Once the dose was reduced, it could not be increased. Patients who required a second down-titration were discontinued from the trial. Defined as all randomized patients who received at least one dose of study medication. Treatment allocation was only indicated for 418 out of 421 randomized patients. p-values equals I versus C.

Chung 2010 [46] USA	RCT (Multicentre: 72 sites in USA)	405 patients (age 16 to 70 years) with	AED+ lacosamide (400, 600 mg/day target dose), n=301	AED+ placebo n=104	**≥50% reduction in seizure frequency (ITT)**: I-400: 77/204 (38.3%), p<0.001	One dose reduction (100 mg/day) was permitted at the end of titration (week 6) for patients experiencing intolerable adverse events. Patients who were

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		refractory partial seizures. Patients received at least 2 AEDs.	400mg/day, (I-400), n=204 600mg/day, (I-600), n=97 Titration: 100 mg/day and titrated in 100-mg increments per week until the target dose was met. Baseline: 8 weeks Titration: 6 weeks Maintenance: 12 weeks		I-600: 40/97 (41.2%), p<0.001 I-T: 117/301 (39.2%) C: 19/104 (18.3%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency**[8]: I-400: 47/84 (56.0%) I-600: 33/47 (70.2%) C: 15/45 (33.3%) I-T: 80/131 (61.1%) **Seizure free during maintenance phase (ITT):** I-400: 4/204 (2%) I-600: 5/97 (5.2%) I-T: 9/301 (3%) C: 0/104 (0%) **Discontinuation due to adverse events (ITT):** I-400: 37/204 (18%) I-600: 26/97 (27%) I-T: 63/301 (17.6%) C: 5/104 (5%)	unable to tolerate trial medication earlier during titration, and those unable to tolerate the reduced dose, were to discontinue treatment. ITT defined as all randomized patients. ITT was calculated from reported data (percentages) in the article (excluded patients, 3 in I-400 group, were assumed to be non-responders). p-values equals I versus C.
Halász 2009 [46] Hungary	RCT (Multicentre; Australia, Croatia, Czech Republic,	485 patients (age 16 to 70 years) with	AED+ lacosamide (200, 400 mg/day target dose), n=322	AED+ placebo n=163	**≥50% reduction in seizure frequency (ITT)**: I-200: 56/163 (34%), p=0.07 I-400: 64/159 (40%), p=0.01	One-step dose reduction of 100 mg/day was allowed at the end of the titration period at the fourth week for patients experiencing intolerable AEs. If the dose was reduced, it could not

[8] Possibly ITT (no information on seizure types for the 3 patients in I-400 group that were excluded after randomization)

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	Finland, France, Germany, Hungary, Lithuania, Poland, Russia, Spain, Sweden, and the United Kingdom.	refractory partial seizures.	200mg/day, (I-200), n=163 400mg/day, (I-400), n=159 Titration: I-400; the dose was increased by 100 mg/day each week. I-200 received placebo during the first 2 weeks of titration, 100 mg/day lacosamide at week 3, and the dose was increased to 200 mg/day at the beginning of week 4. Baseline: 8 weeks Titration: 4 weeks Maintenance: 12 weeks		I-T: 120/322 (37%) C: 41/163 (25%) **Seizure free during maintenance phase (ITT):** I-200: 5/163 (3.1%) I-400: 3/159 (1.9%) I-T: 8/322 (2.5%) C: 3/163 (1.8%) **Discontinuation due to adverse events (ITT):** I-200: 10/163 (6%) I-400: 24/159 (15.7%) I-T: 34/322 (11%) C: 8/163 (5.5%)	be increased again during this trial. Patients who required a second dose reduction were discontinued from the trial. ITT. Defined as all randomized patients. ITT was calculated from reported data in the article. p-values equals I versus C.
Hong 2016 [47] China	RCT (Multicentre: 72 sites in China and Japan)	548 patients age 16 to 70 years) with refractory partial seizures. Patients received 1–3 AEDs at baseline	AED + lacosamide (200, 400 mg/day target dose), n= 364 200 mg/day, (I-200), n=183 400 mg/day, (I-400), n=181 Titration: Start at 100 mg/day and titrated in 100-mg increments per	AED+ placebo, n= 184	**≥50% reduction in seizure frequency, maintenance phase (ITT)**: I-200: 70/183 (38%) I-400: 88/181 (49%) C: 36/184 (20%) **Seizure free during maintenance phase (ITT):** I-200: 8/183 (4%) I-400: 8/181 (4%) C: 0/184 (0%)	ITT was calculated from reported data (percentages) in the article, excluded patients were assumed to be non-responders.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			week until the tar-get dose was met. Baseline: 8 weeks Titration: 4 weeks Maintenance: 12 weeks		**Discontinuation due to adverse events (ITT):** I-200: 8/183 (4%) I-400: 28/181 (15%) C: 14/184 (8%)	

C=control, I=intervention, ITT=intention to treat, ns=non-significant; mITT=modified Intention-To-Treat; RCT=randomized clinical trial

Tabell 2.8 Lamotrigin

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Duchowny 1999 [48] USA and France	RCT (Multicentre: 40 sites in USA and France)	199 patients (age 2 to 16 years) with refractory partial seizures. Patients received up to 2 AEDs.	AED+ lamotrigine (1–15 mg/kg/day target dose depending on concurrent therapy), n=98 Titration: Depending on concurrent therapy. Baseline: 8 weeks Titration: 6 weeks Maintenance: 12 weeks	AED+ placebo n=101	**≥50% reduction in seizure frequency (ITT)**: **All partial seizures:** I: 44/98 (45%), p=0.004 C: 25/101 (25%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency (ITT):** I: 26/46 (57%), p=0.023 C: 12/40 (30%) **Seizure free (ITT):** Not reported. **Discontinuation due to adverse events (ITT):** I: 5/98 (5.1%)	ITT=Intention-To-Treat. Defined as all randomized patients p-values equals I versus C.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
					C: 6/101 (5.9%)	
Matsuo 1993 [49] USA	RCT (Multicentre: 15 centres in USA).	216 patients (age 18 to 65 years) with refractory partial-onset seizures. Patients received up to 3 AEDs.	AED+ lamotrigine (300, 500 mg/day target dose), n=143 300 mg/day, (I-300), n=71 500 mg/day, (I-500), n=72 Titration: Patients received 50 mg BID and increased by 100mg/day at weekly intervals until target dose. Baseline: 12 weeks Titration and Maintenance: 24 weeks	AED+ placebo n=73	**≥50% reduction in seizure frequency (ITT)**: **All partial seizures:** I-300: 13/71 (18%) I-500: 20/72 (28%) I-T: 33/143 (23%) C: 12/73 (16%) **Seizure free (ITT):** Not reported. **Discontinuation due to adverse events (ITT):** I-300: 3/71 (4%) I-500: 10/72 (14%) I-T: 13/143 (9%) C: 1/73 (1.4%)	The target dose could be reduced by 100 mg. ITT Defined as all randomized patients. ITT was calculated from reported data in the article.
Naritoku, 2007 [50] USA	RCT (Multicentre; sites in North and South America, Europe and Asia).	243 patients (age >12 years) with refractory partial-onset seizures. Patients received 1 to 2 AEDs.	AED+ lamotrigine XR (200–500 mg/day target dose depending on concurrent therapy), n=121 Titration: Depending on concurrent therapy.	AED+ placebo n=122	**≥50% reduction in seizure frequency, maintenance phase (ITT)**: I: 65/121 (54%) C: 39/122 (32%)	Modified Intention-To-Treat. Defined as all randomized patients. ITT was calculated from reported data in the study.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			Baseline: 8 weeks Titration: 7 weeks Maintenance: 12 weeks		**≥50% reduction in focal to bilateral tonic-clonic seizure frequency (mITT)[9]:** I: 52.2% C: 25.5% **Seizure freedom during maintenance phase (ITT):** I: 20/121 (16.5%) C: 6/122 (4.9%) **Discontinuation due to adverse events (ITT):** I: 12/121 (9.9%) C: 2/122 (1.6%)	

BID=twice/day; C=control, I=intervention; I-T=Intervention total; ITT=intention to treat, ns=non-significant, P= probability value; PS=partial seizures; RCT=randomized clinical trial; XR=extended release;

[9] Not possible to calculate n/N from reported data

Tabell 2.9 Levetiracetam

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Cereghino 2000 [51] USA	RCT (Multicentre: 41 centres in the United States)	294 patients (age 16 to 70 years) with partial-onset seizures for at least two years. Patients had to have a minimum of 12 partial seizures within 12 weeks before study selection, with a minimum of two partial seizures during the baseline period. Patients received at least 1 AEDs.	AED+ levetiracetam (1000, 3000 mg/day target dose), n=199 1000 mg/day, (I-1000), n=98 3000mg/day, (I-3000), n=101 Titration: Dosage was escalated at 2-week intervals until reaching target dose. Dosages of levetiracetam were 333 mg/day for 2 weeks, then 666 mg/day for 2 weeks and 1000 mg/day started on the first visit of the observation period, or 1000 mg/day, 2000 mg/day, then 3000 mg/day. Baseline: 12 weeks Titration: 4 weeks Maintenance: 14 weeks	AED+ placebo n=95	**≥50% reduction in seizure frequency (ITT)**: I-1000: 31/98 (31.6%), p<0.001 I-3000: 39/101 (38.6%), p<0.001 C: 10/95 (10.5%) **Seizure free (ITT):** I-1000: 3/98 (3.1%), ns I-3000: 8/101 (7.9%), p=0.01 C: 0/95 (0.0%) **Discontinuation due to adverse events:** I-1000: 6/98 (6.1%) I-3000: 7/101 (6.9%) C: 5/95 (5.3%)	
Glauser 2006 [52] US	RCT (Multicentre: 60 centres in the United States and Canada)	216 (age 4 to 16 years) with partial seizures and at least four partial seizures during the 4 weeks preceding the screening visit and to have at least four partial seizures during each 4-week interval of the 8-week baseline period. Patients received one or two AEDs.	AED+ levetiracetam (60 mg/kg/day target dose), n=101 Titration: an initial dose of 20 mg/kg/day then increasing every 2 weeks to a final target dose. Baseline: 8 weeks Titration: 4 weeks Maintenance: 10 weeks	AED+ placebo n=97	**≥50% reduction in seizure frequency (mITT)**: I: 45/101 (44.6%), p=0.0002 C: 19/97 (19.6%) **Seizure free (mITT):** I: 7/101 (6.9%) C: 1/97 (1.0%) **Discontinuation due to adverse events:** I: 5/101 (5.0%) C: 9/97 (9.3%)	mITT: Before breaking the blind, 18 patients were excluded from ITT, including all 16 patients at one site who were excluded because of extensive violation of the protocol and consequent unreliability of the data, and 2 patients

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
						because they discontinued before taking any study medication. It is unclear to which groups the 16 patients were assigned.
Inoue 2015 [53] Japan	RCT (Multicentre: 56 centres in Japan)	352 patients (age 16 to 65) with a history of partial-onset seizures for more than 2 years, and who experienced partial-onset seizures 12 times or more during the baseline and at least twice every 4 weeks. Patients received one to three AEDs.	AED+ levetiracetam (LEV: 500, 1000, 2000, 3000), n=281 500mg/day, (l-500), n=71 1000mg/day, (l-1000), n=70 2000mg/day, (l-2000), n=70 3000mg/day, (l-3000), n=70 Titration: The dosage for patients assigned to LEV 500 or 1000 mg/day was not up-titrated. Patients randomized to LEV 2000 or 3000 mg/day received LEV 1000 mg/day and had their dosage increased by 1000 mg/day every 2 weeks until the target dose was reached. Baseline: 12 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=70	**≥50% reduction in seizure frequency (mITT)**: I-500: 13/71 (18.3%), ns I-1000: 12/70 (17.1%), ns I-2000: 11/70 (15.7%), ns I-3000: 23/70 (32.8%), p=0.003 C: 8/70 (11.4%) **Seizure free (mITT):** I-500: 0/71 (0%) I-1000: 2/70 (2.9%) I-2000: 2/70 (2.9%) I-3000: 2/70 (2.9%) C: 0/70 (0%) **Discontinuation due to adverse events:** I-500: 2/71 (2.8%) I-1000: 1/70 (1.4%) I-2000: 4/70 (5.7%) I-3000: 6/70 (8.6%) C: 1/70 (1.4%)	mITT: One randomized patient was excluded due to a study drug dispensing error during baseline. Group affiliation unknown.
Peltola 2009 [54] Finland	RCT (Multicentre: 34 centres in 7 countries: Brazil,	158 patients (age 12–70 years) with a confirmed diagnosis of partial-onset seizures for at least 6	AED+ levetiracetam (1000 mg/day target dose), n=79	AED+ placebo n=79	**≥50% reduction in seizure frequency (ITT)**: I: 34/79 (43.0%), ns C: 23/79 (29.1%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	Finland, India, Mexico, Russia, South Africa, and Ukraine)	months preceding the screening visit. During the 8-week baseline period, patients were required to have at least eight partial seizures, and at least two partial seizures in each 4-week interval of the baseline period. Patients received one up to three AEDs.	Baseline: 8 weeks Titration: 0 weeks Maintenance: 12 weeks		**Seizure free (ITT):** I: 8/79 (10.1%) C: 1/79 (1.3%) **Discontinuation due to adverse events:** I: 5/79 (6.3%) C: 2/79 (2.5%)	
Shorvon 2004 [55] UK	RCT (Multicentre: 61 centres in 6 countries: Belgium, France, Germany, Luxembourg, Switzerland, and the UK)	324 patients (age 16 to 65 years) with refractory epilepsy. All patients had seizures that had persisted for at least the previous 2 years and had to at least four partial seizures during each 4-week interval in the 8- or 12-week baseline period Patients received one to two AEDs.	AED+ levetiracetam (LEV: 1000, 2000), n=212 1000 mg/day, (I-1000), n=106 2000 mg/day, (I-2000), n=106 Titration: LEV was titrated upward in twice-daily increments of 500 mg at 2-week intervals until patients were stabilized on their assigned dosages. The 1000-mg group received placebo for 2 weeks before initiation of active drug. Baseline: 8 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=112	**≥50% reduction in seizure frequency (ITT)**: I-1000: 23/106 (21.7%), p=0.019 I-2000: 30/106 (28.3%), P<0.001 C: 11/112 (10.4%) **Seizure free (mITT):** I-1000: 5/106 (5.0%) I-2000: 2/106 (2.0%) C: 1/112 (0.9%) **Discontinuation due to adverse events:** I-1000: 8/106 (7.5%) I-2000: 15/106 (14.2%) C: 6/112 (5.4%)	
Tsai 2006	RCT Multicentre: 5 centres 94 patients (age 16	AED+ levetiracetam (2000 mg/day target dose), n=47	Baseline: 8 weeks Titration: 2 weeks Maintenance: 12 weeks	AED+ placebo n=47	C: 5/47 (10.6%) **Seizure free (ITT):** I: 4/47 (8.5%)	

[56] Taiwan	to 60 years) diagnosed as having epilepsy for ≥6 months before the study. Partial seizures were treatment resistant in all cases, and, during an 8-week baseline period, all patients had at least four complex or secondarily generalized partial seizures. Patients received one up to three AEDs.	Titration: The initial dosage was 500 mg twice daily, which was increased to 1,000 mg twice daily after 2 weeks.			C: 0/47 (0%) **Discontinuation due to adverse events:** I: 3/47 (6.3%) C: 1/47 (2.1%)	
Wu 2009 [57] China	RCT Multicentre: 6 centres 206 patients (age 16 to 70 years) with treatment-refractory partial-onset seizures and experiencing at least eight partial-onset seizures during the 8-week historical baseline period. Patients received one or two AEDs	AED+ levetiracetam (3000 mg/day target dose), n=103 Titration: treatment was started with 500 mg twice daily and was up-titrated in twice-daily increments of 500 mg at 2-week intervals; the dose was increased to 2000 mg/day after 2 weeks and to 3000 mg/day after an additional 2 weeks.	Baseline: 8 weeks Titration: 2 weeks Maintenance: 12 weeks	AED+ placebo n=103	**≥50% reduction in seizure frequency (ITT)**: I: 57/103 (55.3%), p<0.001 C: 26/103 (25.2%) **Seizure free (ITT):** I: 11/103 (10.8%), p=0.012 C: 2/103 (2.0%) **Discontinuation due to adverse events:** I: 0/103 (0%) C: 1/103 (1.0%)	
Xiao 2009 [58] China	56 patients (age 16 to 70 years) diagnosed with partial seizures, were refractory to current antiepileptic therapy,	AED+ levetiracetam (3000 mg/day target dose), n=28 Titration: Patients initially received 1000 mg/day and increased to 2000 mg/day after 2 weeks,	Baseline: 8 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=28	**≥50% reduction in seizure frequency (ITT)**: I: 13/28 (46.4%), ns C: 11/28 (39.3%) **Seizure free (ITT):** I: 3/28 (10.7%), C: 2/28 (7.1%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	and had experienced at least 4 seizures per month. Patients received one or two AEDs	and to 3000 mg/day after another 2 weeks.			**Discontinuation due to adverse events:** I: 0/28 (0%) C: 0/28 (0%)	

C=Control; I= intervention; ITT=Intention-To-Treat, mITT=modified Intention-To-Treat, ns= non-significant, I=Intervention

Tabell 2.10. Oxkarbazepin

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Glauser, 2000 [59] USA	RCT (Multicentre: 47 centres in 8 countries: Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel, USA.)	267 patients (age 3 to 17 years) with refractory partial seizures. Patients received 1 or 2 AEDs.	AED+ oxcarbazepine (30-46 mg/kg/day target dose), n=138 Titration: Day 1-2; 10mg/kg, day 3-6; 20 mg/kg, day 7-10; 30mg/kg, day 11-14; target dose. Baseline: 56 days Titration: 14 days Maintenance: 98 days	AED+ placebo n=129	**≥50% reduction in partial seizure frequency (ITT)**: I: 55/138 (40%) C: 28/129 (22%) **Seizure free (ITT):** I: 5/138 (3.6%) C: 1/129 (0.8%) **Discontinuation due to adverse events (ITT):** I: 14/138 (10%) C: 4/129 (3%)	ITT=Intention-To-Treat. Defined as all randomized patients. ITT was calculated from reported data in the article.
French 2014 [60] USA	RCT (Multicentre: 88 sites in 8 countries in North America (United States, n=25; Mexico, n=13; Canada, n=2) and Eastern Europe/ Russia (Poland, n=18; Russia, n=16; Bulgaria, n=10; Croatia, n=6; Romania, n=5)	366 patients (age 18 to 65 years) with refractory partial-onset seizures. Patients received 1 to 3 AEDs.	AED+ oxcarbazepine XR (1200, 2400 mg/day target dose), n=245 1200 mg/day, (I-1200), n=122 2400 mg/day, (I-2400), n=123 Titration: The dose was increased weekly in 600 mg increments. Baseline: 8 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=121	**≥50% reduction in seizure frequency (ITT)**: *All seizures:* I-1200: 44/122 (36.1%), p=0.08 I-2400: 50/123 (40.7%), p=0.02 I-T: 94/245 (38%) C: 34/121 (28.1%) **Seizure free (ITT):** I-1200: 6/122 (4.9%), p=0.53 I-2400: 14/123 (11.4%), p=0.008 I-T: 20/245 (8%) C: 4/121 (3.3%) **Discontinuation due to adverse events (ITT):** I-1200: 18/122 (15%) I-2400: 37/123 (30%) I-T: 55/245 (22%) C: 10/121 (8%)	ITT defined as all randomized patients. p-values equals I versus C.

AED= anti-epileptic drugs; C=Control; n= number; I=Intervention; I-T=Intervention total; ITT=Intention-To-Treat; RCT=randomised controlled trial (study); XR=extended release

Tabell 2.11 Perampanel

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
French 2012 [61] USA	RCT (Multicentre: 68 centres in 5 countries: Argentina, Canada, Chile, Mexico, and the United States)	390 patients (age 12 to 77 years) diagnosed with partial-onset seizures with or without secondary generalization, had failed ≥2 AEDs, had ≥5 partial seizures during baseline. Patients received at least 3 AEDs.	AED+ perampanel (8, 12 mg/day target dose), n=267 8mg/day, (I-8), n=133 12mg/day, (I-12), n=134 Titration: patients had weekly 2 mg increments up to the randomized dose. Patients experiencing intolerable adverse events (AEs) could defer up-titration or have their dose reduced. Consecutive 2 mg down-titration was discouraged and doses could be increased when tolerability improved. Baseline: 6 weeks Titration: 6 weeks Maintenance: 13 weeks	AED+ placebo n=121	**≥50% reduction in seizure frequency (mITT)**: I-8: 50/133 (37.6%), ns I-12: 48/134 (35.8%), ns C: 32/121 (26.4%) **Seizure free (mITT):** I-8: 3/133 (2.2%) I-12: 2/134 (1.5%) C: 0/121 (0.0%) **Discontinuation due to adverse events:** I-8: 9/133 (7%) I-12: 24/134 (18%) C: 7/121 (6%)	mITT: 2 Patients were excluded after randomization due to screen failures and, thus, not included in the published data. Group affiliation unknown.
French 2013 [62] USA	RCT (Multicentre: 78 centres in 16 countries: Australia, Austria, Belgium, Germany, Finland, France, United Kingdom, Greece, India, Israel, Italy, The Netherlands, Russia, Sweden, United States,	386 patients (age 12 years and older) with a diagnosis of simple or complex partial seizures, and that had at least five partial seizures in the 6-week baseline phase without a 25-day seizure-free period. Patients received at least 3 AEDs.	AED+ perampanel (8, 12 mg/day target dose), n=250 8 mg/day, (I-8), n=129 12 mg/day, (I-12), n=121 Titration: perampanel treatment was increased in increments of 2mg/day each week until target dose. Baseline: 6 weeks Titration: 6 weeks Maintenance: 13 weeks	AED+ placebo n=136	**≥50% reduction in seizure frequency (ITT)**: I-8: 43/129 (33.3%), p=0.002 I-12: 41/121 (33.9%), p<0.001 C: 20/136 (14.7%) **Seizure free (ITT):** I-8: 3/129 (2.3%) I-12: 6/121 (5.0%) C: 2/136 (1.5%) **Discontinuation due to adverse events:**	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	and South Africa)				I-8: 11/129 (8.5%) I-12: 23/121 (19.0%) C: 4/136 (2.9%)	
Krauss et al 2012 [63] USA	RCT (Multicentre: 116 centres in 24 countries in Europe, Asia, and Australia)	706 patients (age 12 years and older) with a diagnosis of simple or complex partial seizures, at least five partial seizures in the 6-week baseline phase without a 25-day seizure-free period. Patients received at least 3 AEDs.	AED+ perampanel (2, 4, 8 mg/day target dose), n=521 2 mg/day, (I-2), n=180 4 mg/day, (I-4), n=172 8 mg/day, (I-8), n=169 Titration: perampanel treatment was increased in increments of 2mg/day each week until target dose. Baseline: 6 weeks Titration: 6 weeks Maintenance: 13 weeks	AED+ placebo n=185	**≥50% reduction in seizure frequency (ITT)**: I-2: 37/180 (20.6%), ns I-4: 49/172 (28.5%), p=0.013 I-8: 59/169(34.9%), p<0.001 C: 33/185 (17.9%) **Seizure free (ITT):** I-2: 3/180 (1.9%) I-4: 8/172 (4.4%) I-8: 8/169(4.8%) C: 2/185 (1.2%) **Discontinuation due to adverse events:** I-2: 10/180 (6%) I-4: 5/172 (3%) I-8: 11/169(7%) C: 6/185 (3%)	
Lagae 2016 [64] Belgium	RCT (Multicentre: 39 centres in 11 countries: India, Hungary, Latvia, United States, Thailand, Spain, Australia, Belgium, Czech Republic, Poland, and	133 patients (age 12 to 17 years old) with epilepsy with partial-onset seizures and at least one partial-onset seizure during the 4-week period. Patients received at least 3 AEDs.	AED+ perampanel (target dose: range of 8–12 mg/day), n=85 Titration: Patients received perampanel 2 mg/day or matching placebo and were uptitrated weekly in 2-mg increments to the target dose. Baseline: weeks Titration: 6 weeks	AED+ placebo n=48	**≥50% reduction in seizure frequency (ITT)**: I: 49/85 (59.0%), p=0.0144 C: 17/48 (37.0%) **Seizure free (ITT):** I: 18/85 (23.7%) C: 7/48 (16.3%) **Discontinuation due to adverse events:** I: 3/85 (3.5%) C: 0/48 (0.0%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	Republic of Korea)		Maintenance: 13 weeks			

AED= anti-epileptic drugs; C=Control; I=Intervention; ITT=Intention-To-Treat, mITT=modified Intention-To-Treat, ns= non-significant; RCT= randomized control study

Tabell 2.12 Pregabalin

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Beydoun 2005 [65] USA	RCT (Multicentre: 43 centres in USA and Canada)	313 patients (age 17 to 82 years) with medically refractory partial epilepsy. Patients received 1 to 3 AEDs.	AED+ pregabalin (600 mg/day target dose, BID or TID), n=215 600mg/day BID, (I-600B), n=104 600mg/day TID, (I-600T), n=111 Titration: 50 or 75 mg/day. Dosing was escalated incrementally every 2 days to reach 600 mg/day by day 8. Baseline: 8 weeks Titration: 8 days Maintenance: 11 weeks	AED+ placebo n=98	**≥50% reduction in partial seizure frequency (ITT)**: I-600B: 44/104 (42%), p≤0.001 I-600T: 54/111 (49%), p≤0.001 I-T: 98/215 (45.6%) C: 9/98 (9%) **Seizure free during maintenance phase (ITT):** I-T: 6/215 C: 0/98 **Discontinuation due to adverse events (ITT):** I-600B: 27/104 (26%) I-600T: 21/111 (19%) I-T: 48/215 (22%) C: 7/98 (7%)	ITT was defined as all randomized patients p-values equals I versus C. Data on seizure freedom was collected from Pulman et al. 2014 [66].

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Elger 2005 [67] USA	RCT (Multicentre: 53 centres in Canada and Europe; Austria, France, Germany, Italy, Lithuania, Spain, and the United Kingdom)	341patients (age 18 to 78 years) with a diagnosis of epilepsy with partial seizures. Patients received 1 to 3 AEDs.	AED+ pregabalin (600 mg/day BID or flexible 150-600 mg/day target dose), n=268 600 mg/day, (I-600), n=137 150-600 mg/day, (I-150-600), n=131 Titration: I-600 received 600	AED+ placebo n=73	**≥50% reduction in partial seizure frequency (ITT)**: I-600: 62/137 (45.3%), p=0.001 I-150-600: 41/131 (31.3%), p=0.001 I-T: 103/268 (38%) C: 8/73 (11%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency**: **Seizure free during last 4 weeks (ITT):** I-600: 17/137 (12.4%)	Patients who experienced intolerable adverse events could reduce their daily dose (e.g., the number of capsules taken daily) to the previous level (e.g., 450 to 300 mg/day, or 600 to 450 mg/day) for the remainder of the treatment period. While all patients could reduce the number of capsules of study medication, only those in the I-flexible 150-600 group received an actual dose reduction. ITT was defined as all randomized patients. p-values equals I versus C.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			mg/day (300 mg BID) on day 1 and for the entire treatment period. I-150-600 started on the lowest therapeutic dose of 150 mg/day (75 mg BID) for the first 2 weeks, and then increased to 300 mg/day for the next 2 weeks. Seizure-free patients during these first 4 weeks remained on 300 mg/day for the remainder of the study, patients experiencing seizures increased their dose to 450 mg/day for the next 4 weeks. At week 8, patients who had been seizure-free for the preceding 4 weeks remained on 450 mg/day for the remainder of the study, while those still experiencing seizures increased their		I-150-600: 16/131 (12.2%) I-T: 33/268 (12%) C: 6/73 (8.2%) **Seizure free during entire double-blind phase (ITT):** I-600: 4/137 (2.9%) I-150-600: 4/131 (3.1%) I-T: 8/268 (3.0%) C: 1/73 (0%) **Discontinuation due to adverse events (ITT):** I-600: 45/137 (32.8%) I-150-600: 16/131 (12.2%) I-T: 61/268 (23%) C: 5/73 (6.8%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			dose to 600 mg/day. Baseline: 6 weeks Titration: I-600; 0 weeks I-150-600; 0-8 weeks Maintenance: I-600; 12 weeks I-150-600; 4-12 weeks			
French 2003 [68] USA	RCT (Multicentre: 76 centres in the USA and Canada)	4555 patients (age 12 to 75 years) with refractory partial seizures. Patients received 1 to 3 AEDs.	AED+ pregabalin (50, 150, 300, 600 mg/day target dose), n=355 50 mg/day, (I-50), n=88 150 mg/day, (I-150), n=88 300 mg/day, (I-300), n=90 600 mg/day, (I-600), n=89 Baseline: 8 weeks Titration: 0 Maintenance: 12 weeks	AED+ placebo n=100	**≥50% reduction in partial seizure frequency (ITT):** I-50: 13/88 I-150: 27/88 I-300: 36/90 I-600: 45/89 I-T: 121/355 (34%) C: 14/100 (14%) **Seizure free (ITT):** I-50: 1/88 I-150: 0/88 I-300: 0/90 I-600: 1/89 I-T: 2/355 (0.6%) C: 0/100 (0%) **Discontinuation due to adverse events (ITT):** I-50: 6/88 (6.8%), p=ns I-150: 1/86 (1.2%), p=0.006 I-300: 13/90 (14.4%), p≤0.001 I-600: 21/89 (23.6%), p≤0.001	ITT= All randomized patients. Data on ≥50% reduction in seizure frequency and seizure freedom were collected from Pulman et al. 2014 [64]. p-values equals I versus C.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
					C: 5/100 (5%)	
French 2014 [69] USA	RCT (Multicentre; 66 centres in 18 countries: United States, Bulgaria, Czech Republic, Germany, Hungary, Poland, Romania, Hong Kong, India, Malaysia, Singapore, Thailand, Argentina, Bosnia and Herzegovina, Mexico, Puerto Rico, Russian Federation, Serbia.	325 patients (age 18 to 75 years) with treatment resistant partial seizures. Patients received 1 to 3 AEDs.	AED+ pregabalin (165, 330 mg/day target dose), n=215 165 mg/day, (I-165), n=101 330 mg/day, (I-330), n=114 Titration: 82.5 mg for 3 days followed by 165 mg dose escalation. I-330 patients were escalated on day 14. Baseline: 8 weeks Titration: 2 weeks Maintenance: 12 weeks	AED+ placebo n=110	**≥50% reduction in partial seizure frequency (ITT)**: I-165: 37/101 (37%) I-330: 51/114 (45%) I-T: 88/215 (41%) C: 39/110 (35%) **Seizure free (ITT):** Not reported. **Discontinuation due to adverse events (ITT):** I-165: 3/101 (3%) I-330: 8/114 (7%) I-T: 11/215 (5%) C: 3/110 (2.7%)	No dosage reductions were permitted at any time. ITT was defined as all randomized patients. ITT was calculated from reported data in the article.

BID=twice/day; C=Control; I=Intervention; I-T=Intervention total; ITT=Intention-To-Treat; ns=non-significant; TID=three times/day

Tabell 2.13. Topiramat

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Ben-Menachem, 1996 [70] Sweden	RCT, multicentre (4 centres in Sweden, Norway, Denmark and Germany)	56 adults (age 18-65 years) with refractory partial epilepsy Patients received 1-2 background AEDs Male/female: 84/16%	AED+ topiramate (800 mg/day target dose) n=28 Titration= increase from 100 mg/day to target dose or maximal tolerated dose, increments 100-200 mg/week Baseline: 8 weeks Titration: 5 weeks Maintenance: 8 weeks	AED+ placebo, n= 28	**≥50% reduction in monthly partial seizure frequency**: I: 12/28 (43%) C: 0/28 (0%) p=0.001 **Seizure-free:** not reported **Discontinuation due to adverse events:** I: 6/28 (2%) C: 0/28 (0%)	ITT analysis
Chung, 2014 [71] USA	RCT, multicentre phase III study (66 centres in 16 countries: Argentina, Australia, Belgium, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, and the United States)	249 adults (age 18-75 years) with refractory partial epilepsy Patients received 1-3 background AEDs Male/female: 132/117	AED+ topiramate (200 mg/day target dose) n=124 Titration=increase from 50 mg/day to target dose, increments 50 mg/week Baseline: 8 weeks Titration: 3 weeks Maintenance: 8 weeks	AED+ placebo n=125	**≥50% reduction in weekly partial seizure frequency**: I: 47/124 (38%) C: 29/125 (23%) p=0.013 **Seizure-free during double-blind phase:** I: 4/124 (3%) C: 2/125 (2%) (ns) **Discontinuation due to adverse events:** I: 12/124 (10%) C: 4/125 (3%)	ITT analysis

Elterman 1999 [72] USA	RCT, multi-centre (16 centres in USA and Costa Rica)	86 children and adolescents (age 2-16 years) with refractory partial epilepsy	AED+ topiramate, (125-400 mg/day target dose, dependent on patient weight)	AED+ placebo, n=45	**≥50% reduction in partial seizure frequency**: I: 16/41 (39%) C: 9/45 (20%) p=0.080	ITT analysis

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Patients received 1-2 background AEDs Male/female: 56/44%	n=41 Titration: Increase from 25 mg/day to target dose at 4 2-week intervals Baseline: 4 weeks Titration: 8 weeks, Maintenance: 8 weeks		**≥50% reduction in focal to bilateral tonic-clonic seizure frequency**: I: 9/20 (45%) C: 6/20 (30%) **Seizure-free during maintenance phase:** I: 4/41 (10%) C: 2/45 (4%) **Discontinuation due to adverse events:** I: 0/41 (0%) C: 1/45 (2%)	
Faught, 1996 [73] USA	RCT, multicentre (17 centres)	181 adults (age 18-68 years) with refractory partial epilepsy Patients received 1-2 background AEDs Male/female: 143/38	AED+ topiramate (200, 400 or 600 target dose) N=136 200 mg/day, n=45 (I-200) 400 mg/day, n=45 (I-400) 600 mg/day, n=46 (I-600) Titration: Increase from 100 mg/day to target dose or maximum tolerated dose, increment 100-200 mg/ week Baseline: 12 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=45	**≥50% reduction in partial seizure frequency**: I-200: 12/45 (27%) p=0.620 I-400: 21/45 (47%) p=0.013 I-600: 21/46 (46%) p=0.027 C: 8/45 (18%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency (mITT)**: I-200: 10/14 (21%) I-400: 13/15 (71%) I-600: 10/13 (77%) C: 3/14 (21%) **Seizure-free, total partial seizures:** not reported **Free from focal to bilateral tonic-clonic seizure:** I-200: 3/14 (21%)	ITT analysis

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
					I-400: 8/15 (53%) I-600: 4/13 (31%) C: 0/14 (0%) **Discontinuation due to adverse events:** I-200: 4/45 (9%) I-400: 9/45 (20%) I-600: 13/46 (28%) C: 7/45 (16%)	
Guberman, 2002 [74] USA	RCT, multicentre (centres in Hungary, Poland, Israel, Canada, Russia, Czech Republic)	263 adults (age 18-67 years) with refractory partial epilepsy Patients received 1-2 background AEDs (carbamazepine with or without another AED) Male/female: 52/48%	AED+ topiramate (200 mg/day target dose) n=171 Two different titration strategies: Group I (TPM 25/25): 200 mg／day over 8 weeks (increase from 25 mg／day to target dose, 25 mg／day weekly increments) n=75 patients Group II (TPM 50/50): 200 mg／day over 4 weeks (increase from 50 mg／day to target dose, 50 mg／day weekly increments) n=73 patients Baseline: 4 weeks Titration: 4/8 weeks	AED+ placebo n=92	**≥50% reduction in monthly partial seizure frequency**: I: 77/171 (45%) C: 22/92 (24%) p<0.001 **≥50% reduction in focal to bilateral tonic-clonic seizure frequency (mITT)**: I: 28/55 (50%) C: 12/36 (34%) **Seizure-free:** I: 10/171 (6%) C: 2/92 (2%) **Discontinuation due to adverse event:** I: 13/171 (8%) C: 2/92 (2%)	Two different titration strategies were tested. Results from both titration groups are pooled in the table (I) ITT data

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			Stabilization: 4/8 weeks			
Korean Topiramate study group, 1999 [75] Korea	RCT, multicentre	177 adults (age 16-65 years) with refractory partial epilepsy Patients received 1-2 background AEDs Male/female: 95/82	AED+ topiramate (600 mg/day target dose) n=91 Titration: increase from 50 mg/day to target dose or maximum tolerated dose, increment 50-100 mg/week Baseline: 12 weeks Titration: 10 weeks, Maintenance: 8 weeks	AED+ placebo n=86	**≥50% reduction in monthly partial seizure frequency:** I: 45/91 (49%) C: 11/86 (13%) **Seizure-free during double-blind phase:** I: 7/91 (8%) C: 1/86 (1%) **Discontinuation due to adverse events:** I: 7/91 (8%) C: 3/86 (3%)	ITT data, patients not reported were assumed to be non-responders
Privitera 1996 [76] USA	RCT, multicentre (17 centres)	190 adults (age 18-68 years) with refractory partial epilepsy Patients received 1-2 background AEDs Male/female: 152/38	AED+ topiramate (600, 800 or 1000 mg/day target dose) n=143 600 mg/day (I-600) n=48 800 mg/day (I-800) n=48 1000 mg/day (I-1000) n=47 Titration: increase from 100 mg/day to target dose or maximum tolerated dose, incre-ment100 mg/week	AED+ placebo n=47	**≥50% reduction in partial seizure frequency:** I-600: 21/48 (44% p<0.001 I-800: 19/48 (40%) p=0.001 I-1000: 18/47 (38%) p=0.001 C: 4/47 (9%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency**: I-600: 8/12 (67%) I-800: 8/17 (47%) I-1000: 6/11 (55%) C: 6/17 (35%) **Seizure-free:** not reported	ITT analysis

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			Baseline: 12 weeks Titration: 6 weeks Maintenance: 12 weeks		**Discontinuation due to adverse events:** I-600: 10/48 (21%) I-800: 5/48 (10%) I-1000: 8/47 (17%) C: 1/47 (2%)	
Sharief, 1996 [77] UK	RCT, multicentre (4 sites in Sweden, Spain, UK and France)	47 adults (age 15-65 years) with refractory partial epilepsy Patients received 1-2 background AEDs Male/female: 40/7	AED+ topiramate (400 mg/day target dose) n=23 Titration: 100 mg/day first week, 200 mg/day second week, 400 mg/day third week, or maximum tolerated dose Baseline: 8 weeks, titration: 3 weeks, maintenance: 8 weeks	AED+ placebo n=24	≥50% reduction in monthly partial seizure frequency: I: 8/23 (35%) C: 2/24 (8%) p=0.033 ≥50% reduction in focal to bilateral tonic-clonic seizure frequency: I: 10/14 (71%) C: 3/8 (38%) Seizure-free during double-blind phase: I: 2/23 (9%) C: 0/24 (0%) Free from focal to bilateral tonic-clonic seizure: I: 6/14 (43%) C: 2/8 (25%) Discontinuation due to adverse events: I: 6/23 (26%) C: 1/24 (4%)	ITT analysis
Tassinari 1996 [78] Italy	RCT, multicentre (6 sites in UK, Italy, France, Norway and Denmark)	60 adults (18-65 years) with refractory partial epilepsy Patients received 1-2 background AEDs	AED+ topiramate (600 mg/day target dose) n=30 Titration: increase from 100 mg/day to target dose or maximum tolerated	AED+ placebo n=30	**≥50% reduction in monthly partial seizure frequency:** I: 14/30 (47%) C: 3/30 (10%) p=0.001 **Seizure-free during double-blind phase:** I: 0/30 (0%) C: 0/30 (0%)	ITT analysis

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Male/female: 47/13	dose, increment 100-200 mg/week Baseline: 8 weeks, ´ Titration: 4 weeks Maintenance: 8 weeks		**Discontinuation due to adverse events:** I: 4/30 (13%) C: 1/30 (3%)	
Yen 2000 [79] China	RCT, single-centre	46 adults (age 18-54 years) with refractory partial epilepsy Patients received 1-4 background AEDs Male/female: 19/27	AED+ topiramate (300 mg/day target dose) n=23 Titration: increase from 50 mg/day to target dose or maximum tolerated dose, increment 50 mg/week Baseline: 8 weeks, ´ Titration: 6 weeks Maintenance: 8 weeks	AED+ placebo, n=23	**≥50% reduction in monthly partial seizure frequency:** I: 11/23 (48%) C: 3/23 (13%) p=0.01 Seizure-free: not reported **Discontinuation due to adverse events:** I: 2/23 (9%) C: 2/23 (9%)	ITT analysis
Zhang, 2011 [80] China	RCT, single-centre	86 adults (age ≥65 years) with refractory partial epilepsy Patients received 1-3 background AEDs Male/female: 49/37	AED+ topiramate (200 mg/day target dose). n=46 patients Titration: increase from 25 mg/day to target dose, increment 25 mg/week Baseline: 8 weeks, Titration: 8 weeks	AED+ placebo n=40	**≥50% reduction in partial seizure frequency**: I: 22/46 (47.8%) C: 3/40 (7.5%) p<0.05 **Seizure-free:** not reported **Discontinuation due to adverse events:** not reported	ITT analysis

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			Maintenance: 12 weeks			

AED= anti-epileptic drugs; C=control, I=intervention, ITT=intention to treat, ns=non-significant, RCT=randomized clinical study; TPM=topiramate

Tabell 2.14. Vigabatrin

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Bruni 2000 [81] Canada	RCT (Multicentre: 10 centres in Canada)	111 patients (age 18 to 50 years) with a diagnosis of complex partial seizures or partial seizures with secondary generalization, Patients were required to have a minimum of six complex partial seizures or partial seizures secondarily generalized over the eight-week period preceding entry. Patients received at least 2 AEDs.	AED+ vigabatrin (VGB: 1 to 4 g/day), n=58 Titration: A starting dose of 500 mg b.i.d. At eight-week intervals thereafter the daily dose was increased by 1 gram (500 mg b.i.d.) up to a maximum of 4 grams. Patients not having experienced any seizures during the last 6 weeks of any of these eight-week intervals had their dose increased by one gram and if complete seizure control was maintained, that dose was continued throughout the remainder of the segment. If, at the next visit additional seizures had ocurred, the patient continued dose escalation. Baseline: 12 weeks Titration: 32 weeks Maintenance: 4 weeks	AED+ placebo, n=53	**≥50% reduction in seizure frequency (ITT)**: I: 28/58 (48.3%), p=0.022 C: 14/53 (26.4%) **Seizure free (ITT):** I: 5/58 (9%), C: 2/53 (4%) **Discontinuation due to adverse events:** I: 6/58 (10.3%) C: 4/53 (7.5%)	
Dean 1999 [82] USA	RCT (Multicentre: 14 centres in USA)	174 patients (age 18 to 60 years) with documented, uncontrolled complex partial seizures or partial seizures with secondary generalization. Lack of adequate seizure control was defined as at least six seizures plus a seizure-free interval of <28 days during the last 8	AED+ vigabatrin (VGB: 1, 3, 6 g/day target dose), n=129 1 g/day, (I-1), n=45 3 g/day, (I-3), n=43 6 g/day, (I-6), n=41 Titration: the initial VGB dosage of 1 g/day was increased by 0.5 g/day each week on days 1 and *5* until the assigned target dose.	AED+ placebo, n=45	**≥50% reduction in seizure frequency (ITT):** I-1: 11/45 (24%), p=0.025 I-3: 22/43 (51%), p<0.001 I-6: 22/41 (54%), p>0.001 C: 3/45 (7%) **Seizure free (ITT):** I-1: 0/45 (0.0%) I-3: 4/43 (9.3%) I-6: 5/41 (12.2%) C: 0/45 (0.0%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		weeks of the pretreatment evaluation period. Patients received 1 to 2 AEDs	 Baseline: 12 weeks Titration: 6 weeks Maintenance: 12 weeks		**Discontinuation due to adverse events:** I-1: 3/45 (6.5%) I-3: 5/43 (11.4%) I-6: 8/41 (18.2%) C: 1/45 (2.2%)	
French 1996 [83] USA	RCT (Multicentre)	182 patients (age 18 to 60) diagnosed with complex partial seizures. All patients studied had at least six documented complex partial seizures during the last 8 weeks of baseline period. Patients received 1 to 2 AEDs	AED+ vigabatrin (3 g/day target dose), n=92 Titration: The dose of vigabatrin was increased as follows: week 1, one tablet twice daily (1 g/day); week 2, one tablet in the morning and two tablets at night (1.5 g/day); week 3, two tablets twice daily (2 g/day); and week 4, two tablets in the morning and three tablets at night (2.5 g/day). The dose of vigabatrin was increased to three tablets twice a day (3 g/day) at the start of week 1 during maintenace. Baseline: 12 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo, n=90	**≥50% reduction in seizure frequency (ITT)**: I: 40/92 (43.5%), p<0.001 C: 17/90 (18.9%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency**: I: 15/31 (52%) C: 15/29 (48%) **Seizure free (ITT):** I: 5/92 (4.5%) C: 0/90 (0.0%) **Free from focal to bilateral tonic-clonic seizures**: I: 7/31 (23%) C: 7/29 (24%) **Discontinuation due to adverse events:** I: 7/92 (7.6%) C: 2/90 (2.2%)	
Grünewald 1994 [84]	RCT	45 patients (age 15 to 61 years) with partial seizures	AED+ vigabatrin (3 g/day target dose), n=22 Titration: 1 g	AED+ placebo, n=23	**≥50% reduction in seizure frequency (ITT)**: I: 10/22 (45.5%), p=0.016 C: 3/23 (13.0%)	

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
United Kingdom		refractory to optimal antiepileptic drug treatment. Patients received 1 to 2 AEDs	twice daily increasing after 14 days to 1.5 g twice daily Baseline: 8 weeks Titration: 2 weeks Maintenance: 18 weeks		**Seizure free (ITT):** I: 1/22 (4.5%) C: 0/23 (0.0%) **Discontinuation due to adverse events:** I: 2/22 (9.1%) C: 0/23 (0.0%)	

C=Control; I=Intervention; ITT=Intention-To-Treat, ns= non-significant; p= probability value; RCT= randomized controlled study

Tabell 2.15 Zonisamide

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Brodie 2005 [85] UK	RCT (Multicentre: 54 centres across 18 European countries (49 centres) and South Africa (five centres).)	351 patients (age 12 to 77 years) with refractory partial seizures. Patients received 1 to 3 AEDs.	AED+ zonisamide (100, 300, 500 mg/day target dose), n=231 100 mg/day, (I-100), n=57 300 mg/day, (I-300), n=56 500 mg/day, (I-500), n=118 Titration: I-100, I-300, I-500; 25 mg (a.m.) + 25 mg (p.m.) on days 1–3, increasing to 50 mg + 50 mg on days 4–7. I-300; the dose was increased at weekly intervals, reaching 100 mg + 200 mg daily in week 16. I-500; dose increments were continued for patients in the 500mg/day group,	AED+ placebo n=120	**≥50% reduction in seizure frequency (ITT)**: *SP+CP seizures:* I-100: 17/57 (30%), p=ns I-300: 19/56 (34%), p=ns I-500: 52/118 (44.3%), p<0.001 I-T: 88/231 (38%) C: 24/120 (20%) *All seizures:* I-100: 17/57 (30%), p=ns I-300: 19/56 (34%), p=ns I-500: 55/118 (46.6%), p<0.001 I-T: 91/231 C: 21/120 (17.5%) **Seizure free (ITT):** I-500: 6/118 (5%), C: 2/120 (1.7%) **Discontinuation due to adverse events (ITT):** I-100: 0/57 (0%) I-300: 7/56 (12.5%) I-500: 29/118 (24.6%) C: 8/120 (6.7%)	ITT defined as all randomized patients. ITT was calculated from reported data in the article. p-values equals I versus C.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			reaching 200 mg + 300 mg daily in week 18. Baseline: 12 weeks Titration: 6 weeks Maintenance: 18 weeks			
Faught 2001 [86] USA	RCT (Multicentre: 20 centres in USA).	203 patients (age 13 to 68 years) with refractory partial-onset seizures. Patients received 1 to 2 AEDs.	AED+ zonisamide (400 mg/day target dose), n=118 Titration: Patients received either 100 mg/d of zonisamide for weeks 1 through 5, 200 mg during week 6, 300 mg during week 7, and 400 mg weeks 8 through 12. Or patients received 100 mg/d of zonisamide for the first week, 200 mg/d over weeks 2	AED+ placebo n=85	**≥50% reduction in seizure frequency (ITT)**: I: 41/118 (35%) C: 16/85 (19%) **Seizure free (ITT):** I: 6/118 (5%) C: 2/85 (2.4%) **Discontinuation due to adverse events (ITT):** I: 19/118 (16%) C: 7/85 (8.2%)	ITT defined as all randomized patients. ITT was calculated from reported data in the article.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			through 6, 300 mg/d for week 7, and 400 mg/d for weeks 8 through 12. Baseline: 4 weeks Titration: 7 weeks Maintenance: 5 weeks			
Guerrini 2013 [87] Italy	RCT (Multicentre; 41 sites in Europe and India).	207 patients (age 6 to 17 years) with refractory partial-onset seizures. Patients received 1 to 2 AEDs.	AED+ zonisamide (500 mg/day target dose), n=107 Titration: 1 mg/kg/day and titrated in weekly increments of 1 mg/kg over 8 weeks to a target dose of 8 mg/kg/day (maximum 500 mg/day). Baseline: 8 weeks Titration: 8 weeks Maintenance: 12 weeks	AED+ placebo n=100	**≥50% reduction in seizure frequency (ITT)**: I: 53/107 (50%), p=0.0044 C: 31/100 (31%) **Seizure free (ITT):** I: 15/107 (14%), p=0.0049 C: 3/100 (3%) **Discontinuation due to adverse events (ITT):** I: 1/107 (0.9%) C: 3/100 (3%)	In the event of dose-limiting adverse events (AEs) during titration, one down-titration to a lower dose was permitted, which was titrated up again when tolerability improved. Patients not titrating up following a dose reduction continued unchanged on the lower dose during the maintenance period. ITT defined as all randomized patients. p-values equals I versus C.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Lu 2011 [88] China	RCT	104 patients (age 18 to 70 years) with refractory partial seizures. Patients received 1 to 2 AEDs.	AED+ zonisamide (300, 400 mg/day target dose), n=53 Titration: zonisamide was supplied by Eisai Co. Ltd, Tokyo, Japan (ZJ) or by Shenzhen Zifu Co. Ltd, China (ZC). ZJ; 100 mg/day for 2 weeks, 200 mg/day at week 3, target dose of 300 mg/day at week 4. ZC; 100 mg/day, weekly increment of 100 mg to target dose of 400 mg/day at week 4. Baseline: 12 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=51	**≥50% reduction in seizure frequency (ITT)**: I: 29/53 (54.7%) C: 18/51 (35.3%) **≥50% reduction in focal to bilateral tonic-clonic seizure frequency (ITT)**: I: 18/36 (50%) C: 12/32 (34%) **Seizure free (ITT):** I: 3/53 (5.7%) C: 1/51 (2%) **Discontinuation due to adverse events (ITT):** I: 0/53 (0%) C: 0/51 (0%)	ITT defined as all randomized patients.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Sackellares 2004 [89] USA	RCT (Multicentre; 4 centres in USA).	152 patients (age 18 to 70 years) with refractory partial seizures. Patients had to receive at least one, but no more than two, of either phenytoin, carbamazepine, phenobarbital or primidone.	AED+ zonisamide (7 mg/kg/day=400-600 mg/day target dose), n=78 Titration: 100 mg/day (1.5 mg/kg/d) for one week, 200 mg/day (3 mg/kg/d) at week 2, 400 mg/day (6 mg/kg/d) at week 3, until target dose was reached. Baseline: 8-12 weeks Titration: 4 weeks Maintenance: 12 weeks	AED+ placebo n=74	**≥50% reduction in seizure frequency (ITT)**: *Complex partial seizures:* I: 24/78 (30.8%) C: 10/74 (13.5%) p=0.0159 *All seizures:* I: 22/78 (28.2%) C: 12/74 (16.2%) p=0.0796 **Seizure free (ITT):** Not reported. **Discontinuation due to adverse events (ITT):** I: 12/78 (15.4%) C: 1/74 (1.4%)	ITT defined as all randomized patients. p-values equals I versus C.
Schmidt 1993 [90] Germany	RCT (Multicentre; 9 centres in Europe).	139 patients (age 18 to 59 years) with refractory partial seizures. Patients received up to 3 AEDs.	AED+ zonisamide (20 mg/kg/day maximum target dose), n=71 Titration: 1.5 mg/kg/day, increased on day 8 to 3.0	AED+ placebo n=68	**≥50% reduction in seizure frequency (ITT)**: *Generalized and partial seizures:* I: 21/71 (29.9%) C: 6/68 (9.4%) p<0.05 **Seizure free (ITT):** Not reported.	ITT defined as all randomized patients. p-values equals I versus C.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			mg/kg/day and on day 15 to 6.0 mg/kg/day. Baseline: 8-12 weeks Titration: 4 weeks Maintenance: 12 weeks		**Discontinuation due to adverse events (ITT):** I: 2/71 (2.8%) C: 0/68 (0%)	

C=Control; CP=complex partial seizures; I=Intervention; I-T=Intervention total; ITT=Intention-To-Treat; ns=non-significant; SP=simple partial seizures

Tabell 2.16. AED som tillägg, generaliserade tonisk-kloniska anfall, terapiresistent/AED as add-on, generalized tonic-clonic seizures, pharmaco-resistant

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Berkovic 2007 [91] Australia	RCT (Multicenter, 50 centers in Europe, North America, Mexico, Australia, New Zealand)	164 patients (age 4 to 65 years) with refractory generalized tonic-clonic seizures. Patients received 1 to 2 AEDs.	AED+ levetiracetam n=80 Target dose: Adults: 3000 mg/day Pediatric and adolescent: 60 mg/kg/day Titration: Week 4 and 5, 1000 mg or 20 mg/kg. Week 6 and 7, 2000 mg or 40 mg/kg. Baseline: 8 weeks (4-week historical and 4-week prospective, placebo). Titration: 4 weeks Maintenance: 20 weeks	AED+ placebo n=84 patients	**Maintenance phase:** **≥50% reduction in seizure frequency (ITT)**: *GTC seizures:* I: 55/80 (68.4%) C: 37/84 (44%) p=0.004 **Seizure freedom (ITT)**: *GTC seizures:* I: 27/80 (34.2%) C: 9/84 (10.7%) p<0.001 *All seizures:* I: 19/80 (24.1%) C: 7/84 (8.3%) p=0.009 **Discontinuation due to adverse event (ITT):** I: 1/80 (1.3%) C: 4/84 (4.8%)	ITT defined as all randomized patients. p-values equals I versus C.
Biton 1999 [92] USA	RCT (Multicenter, 17 US and 1 Costa Rican center).	79 patients (age >4 years) with refractory generalized tonic-clonic seizures.	AED+ topiramate n=39 patients Target dose: <34 kg=175 mg/day	AED+ placebo n=40 patients	**Titration+ Maintenance phase:**	ITT is defined as all randomized patients. One patient in the placebo group did not experience PGTC seizures and was not included in

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Patients received 1 to 2 AEDs.	34 to 42.9 kg = 225mg/day ≥43 kg=400 mg/day Titration: Week 1 to 4, 50mg/day. Week 5 to 6, 50-75 mg BID. Week 7 to 8, 75–150 mg BID. Baseline: 8 weeks Titration: 8 weeks Maintenance: 12 weeks		**≥50% reduction in seizure frequency (ITT)**: *GTC seizures:* I: 22/39 (56%) C: 8/40 (20%) p=0.001 *All seizures:* I: 18/39 (46%) C: 7/41 (17%) p=0.003 **Seizure freedom (ITT):** *GTC seizures:* I: 5/39 (13%) C: 2/40 (5%) p=0.225 *All seizures:* I: 2/39 (5%) C: 0/41 (0%) p=0.173 **Discontinuation due to adverse event:** I: 1/39 (2.5%) C: 1/41 (2.4%)	the analyses of PGTC seizures (n=40) but included in analyses of all generalized seizures (n=41).
Biton 2005 [93] USA	RCT (Multicenter, 38 international study sites).	117 patients (age ≥2 years) with refractory generalized tonic-clonic (GTC) seizures.	AED+ lamotrigine n=58 patients <u>Target dose:</u> 200 mg/day for patients on valproate, 400	AED+ placebo n=59 patients	**Maintenance phase:** **≥50% reduction in seizure frequency (mITT)**:	mITT is defined as all randomized patients who received at least one dose of study medication.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		Patients received 1 to 2 AEDs.	mg/day for patients on an enzyme-inducing AED other than valproate, 300 mg/day for patients on an AED other than valproate and enzyme-inducing AEDs. Titration: Patients 2 to 12 years: Week 1 to 2; 0.15–0.3 mg/day depending on concurrent therapy. Week 3 to 12; double dose every second week. Patients ≥12 years: Week 1 to 2; 12.5–50 mg/day depending on concurrent therapy. Week 3 to 7; double dose every second week. Baseline: 8 weeks Escalation: 7 to12 weeks Maintenance: 12 weeks		*GTC seizures:* I: 42/58 (72%) C: 29/59 (49%) p<0.05 *All seizures:* I: 35/58 (60%) C: 23/59 (39%) p<0.05 **Seizure freedom (mITT):** *GTC seizures:* I: 22/58 (38%) C: 14/59 (24%) p=ns *All seizures:* I: 16/58 (28%) C: 10/59 (17%) p=ns **Discontinuation due to adverse event (mITT):** I: 5/58 (9%) C: 2/59 (3%)	
Biton 2010 [94] USA	RCT (Multicenter, North and South America, Europe and Asia).	153 patients (age ≥13 years) with refractory generalized tonic-clonic (GTC) seizures. Patients received 1 to 2 AEDs.	AED+ lamotrigine XR (extended release). n=76 patients <u>Target dose:</u> 200 mg/day for patients on valproate, 500	AED+ placebo n=77 patients	**Maintenance phase:** **≥50% reduction in seizure frequency (ITT)**:	ITT is defined as all randomized patients. ITT was calculated from reported data in the article.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			mg/day for patients on an enzyme-inducing AED other than valproate, 300 mg/day for patients on an AED other than valproate and enzyme-inducing AEDs. Titration: Week 1 to 2; 25–50 mg/day depending on concurrent therapy. Week 3 to 4; 25–100 mg/day. Week 5; 50–200 mg/day. Week 6; 100–300 mg/day. Week 7; 150–400 mg/day. Baseline: 8 weeks Escalation: 7 weeks Maintenance: 12 weeks		*GTC seizures:* I: 53/76 (70%) C: 30/77 (39%) **Seizure freedom (ITT):** *GTC seizures:* I: 32/76 (42%) C: 10/77 (13%) **Discontinuation due to adverse event (ITT):** I: 1/76 (1.3%) C: 2/77 (2.6%)	
French 2015 [95] USA	RCT (Multicenter, 78 sites in 16 countries; Australia, Austria, China, Czech Republic, France, Germany, Greece, India, Israel, Japan, Latvia, Lithuania,	163 patients (age ≥12 years) with refractory generalized tonic-clonic (GTC) seizures. Patients received 1 to 3 AEDs.	AED+ perampanel n=81 patients <u>Target dose:</u> 8 mg/day Titration: 2 mg initial dose, up titration in weekly 2 mg increments to target dose.	AED+ placebo n=82 patients	**Maintenance phase:** **≥50% reduction in seizure frequency (mITT)**: *GTC seizures:* I: 52/81 (64.2%) C: 32/82 (39%) p=0.0019	mITT defined as all randomized patients who received at least one dose of study medication. In the control group n=81 patients were reported. Numbers in the table were recalculated to ITT (n=82).

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
	Poland, Serbia, South Korea, United States).		Baseline: 4 or 8 weeks Titration: 4 weeks Maintenance: 12 weeks		**Seizure freedom m(ITT):** *GTC seizures:* I: 25/81 (30.9%) C: 10/82 (12.2%) *All seizures:* I: 19/81 (23.5%) C: 4/82 (4.9%) **Discontinuation due to adverse event (mITT):** I: 9/81(11.1%) C: 5/82 (6.1%)	

AED= antiepileptic drug; BID=twice/day; C=Control; GTC= generalized tonic-clonic seizures; I=Intervention; ITT=Intention-To-Treat; mTT=modified Intention-To-Treat; ns=non-significant; RCT= randomized controlled study

Kirurgi/Surgery

Tabell 3.1. Resektiv kirurgi/Resective surgery

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Dwivedi, 2017 [96] India	RCT	116 patients, ≤18 years, with pharmaco-resistant epilepsy Population representative of paediatric epilepsy surgery candidates Female/male: 74/42	Epilepsy surgery (TLR, extratemporal resection, hemispherotomy, corpus callosotomy, hypothalamic hamartoma disconnection/resection) + AED N=57	AED N=59	Seizure-free at 1-year follow-up, n/N[10]: I: 21/57 C: 0/59 Serious adverse events: I: 19/57 C: 0/59	Primary outcome: seizure freedom Secondary: seizure severity, intelligence quotient, social quotient, behaviour, QoL Definition of seizure-free: ILAE class 1 Follow-up: at 6 and 12 months Lost to follow up: I: 1/57, (ITT data reported) Adverse events: includes both complications and expected adverse events, cf discussion
Engel, 2012 [97] USA	RCT	38 patients, ≥12 years, with pharmacoresistant TLE Candidates for TLR based on presurgical evaluation Male/female: 18/20	TLR + AED N=15	AED, N=23	Seizure-free at 2-year follow-up, n/N: I: 11/15 C: 0/23 OR (95% CI): ∞ (11.8 to ∞), p<0.001 Seizure-free at 1-year follow-up, n/N[11]: I: 10/15 C: 0/23 Serious adverse events: I: 6/15	Primary outcome: seizure freedom Secondary: QoL, cognitive function and ancillary outcomes Definition of seizure-free: free from disabling seizures (Engel class I) during the second (or first*) year of follow-up Follow-up time: every 3 months for 2 years

10 Data from Kaplan-Mayer analysis which represent ILAE 1 outcome.
Other data for seizure freedom at 1-year follow-up are also reported
(I: 44/57 and C: 4/59), but the definition of seizure freedom for these data is not clear.
11 Calculated from reported data in publication

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
					C: 7/23	Adverse events: included both those related to and those unrelated to treatment A sample set of 200 participants was originally planned, but the study was terminated due to recruitment difficulties Lost to follow-up: I: 2/15, C: 8/23 Seven controls were operated prior to the 2-year follow-up. (ITT data reported) QoL: significant effect when PP analysis was performed
Markand, 2000 [98] USA	Cohort study, prospectively followed patients	86 patients, 2.5–48 years, with pharmaco-resistant TLE, who underwent presurgical evaluation 1994–1997 Male/female: 51/39	TLR +AED N=53	Nonsurgical group, AED (not suitable candidates for surgery) N=37	Seizure-free at 1-year follow-up, n/N I: 39/53 C: 0/37	Primary outcome: QoL Definition of seizure freedom: Engel class I Follow-up: 1 year Lost to follow-up: C: 4/37 (ITT data reported) Adverse events: not reported Groups are comparable on demographic data
Mikati, 2008 [99] Lebanon	Cohort study, matched data from medical records	29 children, 4–16 years, with pharmaco-resistant epilepsy who underwent pre-surgical evaluation 1997–2004 Male/female: 16/13	Focal resection (frontal or temporal lobectomy) +AED N=17	Nonsurgical group, AED N=12	Seizure-free at 1-year follow up, n/N: I: 12/17 C: 1/12	Primary outcome: QoL Definition of seizure free: Engel class Ia Cross-sectional follow-up, at least 1 year (Mean: 26±13 vs 33±20 months) Adverse events: not reported

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
						Retrospective review of medical records Groups were matched on demographic and clinical variables
Picot 2016 [100] France	Cohort study, prospectively followed patients	207 patients, 15–60 years, with pharmaco-resistant focal epilepsy who underwent presurgical evaluation 2001–2013 Male/female: 80/127	Focal resection +AED, N=119	Nonsurgical group, AED N=88	Seizure-free at 2-year follow-up, n/N: *ILAE class I:* I: 80/119 C: 10/88 *ILAE class I+II:* I: 86/119 C: 10/88 *Engel class I:* I: 89/119 C: 10/88	Primary outcome: cost effectiveness Definition of seizure-free: ILAE class I, ILAE class I+II and Engel class I (a-b) are reported Follow-up: at 2 and 5 years Adverse events: not reported Groups are comparable on demo-graphic variables Lost to follow-up: I: 3/119, C: 7/88 (ITT data reported)
Reuber 2004 [101] Germany	Cohort study	94 patients, ≥15 years, with pharmaco-resistant TLE who underwent pre-surgical evaluation 1998–2000 Male/female: 42/52	TLR + AED N= 76	Nonsurgical group, AED N=18	Seizure-free at 1-year follow-up, n/N: I: 57/76 C: 1/18	Primary outcome: depression and anxiety Definition of seizure-free: “completely seizure-free” Follow-up: 1 year Adverse events: not reported Retrospective study Groups are comparable on demo-graphic variables
Taft, 2014 [102] Sweden	Population-based prospective cohort study	141 patients, ≥16 years, with pharmaco-resistant epilepsy who underwent pre-surgical evaluation in Sweden 1995–1998 Male/female:	Various epilepsy surgery procedures (83 % TLR) + AED N=96	Non-surgical group who underwent presurgical evaluation during the same period, AED N=45	Seizure-free at last year of follow-up, % (n/N): I: 55 % (53/96) C: 11 % (5/45) Adverse events of surgery, n/N: *Major complications*:	Primary outcome: Health-related QoL (HRQOL) Definition of seizure-free: no seizures, with or without auras (ILAE class I and II) in the last year of follow-up

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
		I: 49/51 C: 38/62			I: 1/96 *Minor (transient) complications:* I: 10/96	Follow-up: Surgery group: 28.5 months, range18–58, Non-surgery group: 45 months, range 23–76 Groups are comparable on demographic variables
Wiebe 2001 [103] Canada	RCT (stratification according to the presence or absence of generalised tonic-clonic seizures)	80 patients ≥16 years, with pharmaco-resistant TLE Male/female: 38/42	TLR + AED N=40 (36 underwent surgery)	AED, N=40	Seizure-free at 1-year follow-up, n/N: I: 23/40 C: 3/40 Log-rank test: P<0.001 Adverse events of surgery, n/N: I: 4/40 C: 0/40	Primary outcome: seizure freedom Secondary: frequency and severity of seizures, QoL, disability, and death. Definition of seizure-free: free from seizures impairing awareness (i.e. complex partial or generalised tonic-clonic seizures) at one year Follow-up: every 3 months for 1 year Adverse events: includes complications but not expected adverse events Data assessment was blinded Lost to follow-up: no patient Patients were randomized prior to presurgical evaluation ITT data reported (4 patients in surgery group did not undergo surgery)

AED= antiepileptic drugs, C=control; I=intervention; cf=confer**;** ITT=intention to trea t; N=number of participants; n=number of events; PP=per protocol; QoL=quality of life; RCT=randomized clinical trial; SD=standard deviation; TLE=temporal lobe epilepsy, TLR=temporal lobe resection

Tabell 3.2 Resektiv epilepsikirurgi duration/Resective epilepsy surgery, duration

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
Asadi-Pooya 2016 [104] USA	Cohort study, data from prospective database	275 patients with pharmaco-resistant TLE (mesial sclerosis) Mean age: 37 years (SD: 11/12) Male/female: 132/143	TLR	Patients with varying durations of epilepsy	Epilepsy duration <20 years compared with >20 years: no significant effect on seizure outcome, p=0.5 (n/N not reported)	Definition of seizure freedom: Engel class IA+B Follow-up: ≥1 year
Bjørnæs, 2004 [105] Norway	Cohort study, data from medical records/data base	31/36 patients with pharmacoresistant focal epilepsy and IQ≤70 (from a cohort of 236 operated patients) Mean age: 28.1 years (range 10.6–54.0) Male/female: 17/14	TLR (n=23) Extratemporal resection (n=8)	Patients with varying durations of epilepsy	Seizure-free, %: Duration ≤12.2 years: 80% N=10 (n/N=8/10*) Duration 12.3–27.2 years: 63 %, N=11 (n/N=7/11*) Duration ≥27.2 years: 10 %, N=10 (n/N=1/10*) OR for group with shortest duration relative to group with longest duration: 36.0 (95% CI: 2.3 to 574.3), p=0.0009	Definition of seizure freedom: Engel class I Follow-up: ≥ 2 years (two patients were only followed for 1 year)
Dalmagro, 2005 [106] Brazil	Cohort study, data from medical records	43/44 patients with pharmacoresistant posterior cortex epilepsy Mean age: seizure free: 20.3 years (SD: 10.9), not seizure free: 26.2 years (SD: 14.4) Male/female: 23/20	Posterior resection	Patients with varying durations of epilepsy	Prediction of seizure freedom for shorter duration of epilepsy: OR (95% CI) = 1.10 (1.00 to 1.21) P= 0.049	Definition of seizure freedom: Engel class I Follow-up: ≥ 1 year (mean 40 months) If not adjusted, OR was nonsignificant

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
Daszkiewicz 2017 [107] Poland	Cohort study, data from medical records	52 children with TLE (neuronal-glial tumours) Mean age: 10.2 years (range 1.5–18) Male/female: 31/21	Epilepsy-associated tumour resection	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <1 y: 12/13 Duration >1 y: 33/39 (p< 0.05)	Definition of seizure freedom: Engel class I Follow-up: mean 2.94 years (range 1–7) after surgery
Edelvik 2013 [108]] Sweden	Cohort study, prospective data from national database (SNESUR)	278 adults and children with pharmacoresistant focal epilepsy Male/female: 133/145	Resective epilepsy surgery	Patients with varying durations of epilepsy	Duration of epilepsy in percent of life length as predictors for seizure freedom, multivariate regression analysis, increment units of 10%: OR (95% CI): 0.91 (0.83 to 1.00)	Definition of seizure freedom: ILAE class I+II Follow-up: 5 or 10 years (mean 7.6 years) Relative epilepsy duration was a negative predictor for seizure free long-term outcome
Elsharkawy 2008 [109] Germany	Cohort study, retrospective	218 adult patients (>16 years) pharmacoresistant extratemporal epilepsy Mean age (SD): 29.6 (11.7) years Male/female: 129/89	Extratemporal resection	Patients with varying durations of epilepsy	Seizure freedom in the group with shorter duration of epilepsy (≤5 years) vs longer duration (>5 years): HR (95 % CI) = 0.631 (0.404 to 0.987), p=0.044 Cox multivariate stepwise regression analysis, prediction of long- and short-term outcome by duration of epilepsy: not significant	Definition of seizure freedom: Engel class I Follow-up: Mean 4.2 years (range 1–5) after surgery (assessed at 6 months, 1, 2 and 5 years)
Fauser 2008 [110] Germany	Cohort study, retrospective data from medical	120 patients (66 adults and 54 children) with pharmaco-resistant	TLR (n=55) Extratemporal resection (n=38)	Patients with varying durations of epilepsy	Multivariate regression analysis, prediction of surgical outcome 1 year postoperatively (seizure freedom vs. incomplete seizure	Definition of seizure freedom: Engel class IA

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
	records/ local database	focal epilepsy (focal cortical dysplasias) Mean age: 20.9 years (range 1–66) (gender distribution not reported)	Multi-lobar resection (n=27)		control) by duration of epilepsy: not significant	Follow up at 3, 6, 12 months and then annually
Hennessy 2001 [111] UK	Cohort study, retrospective data from case notes	80 patients with pharmaco-resistant TLE (lesions) Median age: 19 years, (range 4–48), Male/female: 39/41	TLR	Patients with varying durations of epilepsy	Percentage remission and actuarial probability of achieving 1-year seizure free by 5 years of follow up, %: Duration <10 y: 88 Duration 11–15 y: 63 Duration 16–20 y: 56 Duration >20 y: 57 (p=0.02) Increase in duration of epilepsy from one category to the next was associated with a decrease in the probability of remission by 25%, HR: 0.75, (95% CI: 0.59 to 0.97) p=0.03	Definition of seizure freedom: 12 consecutive months of absolute seizure freedom, with or without auras (corresponding to ILAE class I+II) Follow-up: on annual basis for the first 5 years after surgery Calculations of n/N not possible

Janszky 2005 [112] Germany	Cohort study, description of study design indicates prospectively collected data	171/184 patients with pharmaco-resistant TLE (hippocampal sclerosis) Mean age: 33.1 years (range 16–59) Male/female: 71/100	TLR	Patients with varying durations of epilepsy	Seizure-free, n/N (at 5 years): Duration <10 y: 10/11 Duration 11–20 y: 15/22 Duration 21–30 y: 11/22 Duration >30 y: 5/16 Longer epilepsy duration was a significant negative predictor in univariate and multivariate analysis at 3 and 5 years' outcome, but not at 6 months and 2 years.	Definition of seizure freedom: seizure-free with non-disabling auras from the operation to the last outcome assessment, or for >2 years at the time of outcome assessment Follow-up: 6 months, 2, years, 3 years, and 5 years after surgery (5 years for principal analysis)

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
					ROC analysis revealed that epilepsy duration is a reliable predictor for a poor 5-year outcome (area under the curve: 0.75)	171 of 184 patients had >6 months' follow-up. 71 patients were followed for 5 years. Attrition is reported for each assessment point.
Kanner 2009 [113] USA	Cohort study, retrospective data from medical records/ local database	100 adults with pharmaco-resistant TLE Mean age: 31.2 (SD: 10.7) Male/female: 60/40	TLR	Patients with varying durations of epilepsy	Seizure-free, Engel class IA, per 5-y increase in duration of epilepsy OR (95 % CI): 1.1 (0.9 to 1.4), p=0.46 Seizure-free, Engel class 1A+1B, per 5-years increase in duration of epilepsy OR (95% CI: 1.3 (1.0 to 1.6) p=0.059 Multivariate analysis, duration of seizure disorder: not significant	Definition of seizure freedom: Engel class IA and Engel class IA+IB, respectively Follow-up: 2 years after surgery
Liava, 2016 [114] Italy	Cohort study, data from medical records/local database	208 adults and children (125/83) with pharmaco-resistant posterior cortex epilepsy Mean age: 22.4 y (range 1-60) Male/female: 128 /80	Posterior resection	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <5 y: 38/42 Duration 5–10 y: 27/37 Duration >10 y: 80/129	Definition of seizure freedom: Engel class I Follow-up: mean 9.6 years (range 2.4–19) after surgery
Luyken 2003 [115] Germany	Cohort study, prospectively collected data from registry and database	207/214 patients with pharmco-resistant epilepsy (tumours) Mean age: 28 years (range 5–67)	Epilepsy-associated tumour resection	Patients with varying durations of epilepsy	Stepwise logistic regression: decrease of risk for seizure freedom per year of duration of epilepsy before surgery, OR (95% CI): 0.956 (0.921 to 0.993)	Definition of seizure freedom: Engel class I Follow-up: Median 8 years (range 2–14)

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
		Male/female: 104/103			P=0.0205	
McIntosh 2004 [116] Australia	Cohort study, data from medical records	325/360 patients with pharmaco-resistant TLE Age range: 6.7–58.8 years Male/female: not reported	TLR	Patients with varying durations of epilepsy	Lower risk for recurrence with shorter duration of epilepsy (≤18.5 years) vs longer duration (>18.5 years): HR (95% CI) = 1.5 (1.09 to 2.03) p=0.01 Multivariate regression analysis, prediction of seizure recurrence by duration of epilepsy: not significant	Definition of seizure freedom: Engel class I Follow-up: mean 9.6 years (range 0.7–23). Only five patients had follow-up of <2 years (four deceased and one lost to follow-up)
Patra 2014 [117] USA	Cohort study, retrospective data from medical records	119/120 patients with pharmaco-resistant partial epilepsy of temporal or extratemporal origin Mean age: 39.6 years (range 7–70) Male/female: 64/56	TLR (n=88) Extratemporal resection (n=32)	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration ≤20 y: 37/53 Duration >20 y: 38/66 Outcomes reported by location of surgical resection: Seizure freedom among patients undergoing TLR duration ≤20 y: 86%, duration >20 y: 62%, p= 0.017. Corresponding outcome for patients undergoing extratemporal resection: 39% vs. 39%; p=0.98	Definition of seizure freedom: Engel class I Follow-up: mean 36.1 months (range 1–168)
Pelliccia 2017 [118] Italy	Cohort study, retrospective data from a local database	255 patients (120 children, 135 adults) with pharmaco-resistant	Leisonectomy (n=62) Leisonectomy +	Patients with varying durations of epilepsy	Multivariate stepwise logistic regression analysis, prediction of seizure freedom by shorter duration of epilepsy,	Definition of seizure freedom: Engel class Ia Follow-up, mean (SD):

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
		epilepsy associated tumours Mean age (SD): children: 11.2 (4.7) years, adults: 29.9 (9.9) years Male/female: 155/100	corticectomy (n=193)		OR (95% CI): 0.92 (0.89 to 0.94), p<0.001	Children: 105.0 (54.7) months Adults: 123.6 (55.4) months
Radhakrishnan 2016 [119] India	Cohort study, data from a prospectively collected registry	105 patients with pharmaco-resistant long-term epilepsy associated tumours Mean age: 20 years (range 3–50) Male/female: not reported	TLR (n=82) Extratemporal resection (n=23)	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <5 y: 25/28 Duration 6–10 y: 18/28 Duration 11–16 y: 14/20 Duration >16 y: 20/29 ROC analysis, area under the curve: 0.61 (p -0.05), cut-off: 6.6 years (the most specific and sensitive time frame which predicted seizure recurrence)	Definition of seizure freedom: completely seizure-free from the operation to the last outcome assessment, or for the last >2 years Follow-up: ≥3 years (at 3 and 12 months and then yearly)
Ramantani 2017 [120] Germany	Cohort study, data from a data-base	75 children and adolescents with pharmaco-resistant epilepsy Mean age: 10 years (range 0.3–18) Male/female: 39/36	Frontal lobe resection	Patients with varying durations of epilepsy	Stepwise logistic regression analysis, duration of epilepsy as a predictor of seizure recurrence, OR per year (95% CI): 1.15 (1.03 to 1.31)	Definition of seizure freedom: Engel class I Follow-up: mean 8.1 years (range: 1–14.5)
Ramantani 2017 [121] Germany	Cohort study, data from medical records	50 children and adolescents with pharmaco-resistant posterior cortex epilepsy Mean age: 11.1 years (range 0.6–17.9) Male/female: 30/20	Posterior resection	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration ≤2 y: 7/8 Duration >2 y: 23/42 Logistic regression analysis: longer epilepsy duration was associated with increased risk of seizure recurrence, OR (95% CI) 1.04 (1.01 to 1.06) per year	Definition of seizure freedom: Engel class I Follow-up: mean 8.0 years (range 1.5–18) after surgery

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
Rydenhag 2013 [122] Sweden	Cohort study, prospective data from national database (SNESUR)	156 patients (103 adults and 53 children) with pharmaco-resistant epilepsy (tumours and cavernomas) Median age: 26.0 (IQR: 15.6–37.0) Male/female: 85/71	TLR (n=111) Extratemporal resection (n=45)	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <2,5 years: 31/35 Duration 2.5–5 years: 21/25 Duration 5–10 years: 23/32 Duration 10–20 years: 29/39 Duration ≥20 years: 16/25 Univariate analysis, relation of seizure freedom and duration: z=-2.08, p=0.037 Stepwise multivariate logistic regression analysis: duration not significantly correlated with outcome (when adding seven patients, of whom six were re-operated and one had died, to the non-seizure free group, epilepsy duration was correlated with a seizure free outcome, p=0.047)	Definition of seizure freedom: ILAE class I+II (Engel class IA+B) Follow-up: 2 years after surgery
Salanova 2002 [123] USA	Cohort study, data from medical records	215 patients with pharmaco-resistant TLE Mean age: 30.2 years (range 8–57) Male/female: not reported	TLR	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <10 y: 38/48 Duration >10 y: 110/167 (p=0.08)	Definition of seizure freedom: Engel class I Follow-up: mean 7 years (range 1–15) after surgery Yearly follow-up
Schramm 2012 [124] Germany	Cohort study, data from a prospectively collected local database	92/96 children with pharmaco-resistant epilepsy Mean age: 7.3 years (range 4 months to 18 years) Male/female: 43/49	Hemispherotomy	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <2 years: 21/22 Duration 2–4 years: 19/23 Duration 5–10 years: 22/24 Duration >10 years: 10/13	Definition of seizure freedom: ILAE class I Follow-up: mean 8.25 years (range 1–20) Patients with hemimegalencephaly

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
						(n=10) are excluded from the reported data
Simasathien 2013 [125] USA	Cohort study, data from medical records/ local database	158 patients with pharmaco-resistant frontal lobe epilepsy Mean age: 20.4 years (range 0.1-53) Male/female: 84/74	Frontal lobe resection	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <10 year: 53/89 Duration ≥10 year: 26/69 Prediction of increased seizure recurrence at various cutoffs of epilepsy duration, RR (95% CI), adjusted p-value: <2 years vs ≥2 years: 2.59 (1.21–6.72) p=0.01 <3 years vs ≥3 years: 2.20 (1.22–4.31), p= 0.007 <5 years vs ≥5 years: 2.61 (1.53–4.68), p = 0.0003 <10 years vs ≥10 years: 2.07 (1.31–3.31) p=0.002	Definition of seizure freedom: Engel class IA Follow-up: mean 4.3 years (SD: 0.29) 131/158 had >1-year follow-up
Stavem 2004 [126]] Norway	Cohort study, data from a prospectively collected database	63 adult patients with pharmaco-resistant TLE Mean age: 31.4 years (range 16–55) Male/female: 27/36	TLR	Patients with varying durations of epilepsy	Likelihood of being seizure-free in relation to epilepsy duration, increase of 5 years, OR (95% CI): 1.05 (0.81 to 1.33), p=0.71, n=63	Definition of seizure freedom: Engel class I Follow-up: 2 years after surgery
Sun 2014 [127] China	Cohort study, data from medical records	121/123 patients with pharmaco-resistant TLE Mean age: 27.6 years (range 5–54) Male/female: 63/58	TLR	Patients with varying durations of epilepsy	Seizure-free, n/N: Duration <10 y: 41/64 Duration >10 y: 46/57 (p=0.042) Multiple logistic regression analysis showed a significant relation between duration of <10 years and good outcome at 5	Definition of seizure freedom: Engel class I Follow-up: mean 3.3 years (range 1–5) Conflicting results between univariate analysis and multiple logistic regression

First author Year Reference Country	Study Design	Population	Intervention	Comparison	Outcome	Comments
					years postoperatively, N=16 (P=0.019)	analysis, but regression analysis included data from only 16 of 121 patients, at 5 years postoperatively

HR= hazard ratio;OR=odds ratio TLE=temporal lobe epilepsy; TLR=temporal lobe resection; RR= risk ratio; SNESUR=Swedish national epilepsy surgery register

Tabell 3.3. Anfallskuperande läkemedelsbehandling/ emergency treatment with drugs

First Author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Scott 1999 [128] UK	RCT	18 patients at residential center severe epilepsy, earlier treatment rectal diazepam 5-19 years	Buccal midazolam n=40 episodes (14 patients)	Rectal diazepam n=39 episodes (14 patients)	Response Intervention=75% 30/40 episodes Control=59% 23/39 episodes	Response=cessation of seizure within 10 min of drug administration. Some patients were included in both intervention and control groups due to repeated seizure events.
McIntyre 2005 [129] UK	RCT	177 patients on-going seizures without intravenous access 7 m-15 years, median=3 years female 45%	Buccal midazolam n=109 episodes (92 patients)	Rectal diazepam n=110 episodes (85 patients)	Response Intervention=65% 71/109 episodes Control=41% 45/110 episodes Respiratory depression Intervention=5% 5/109 episodes Control=6% 7/110 episodes	Therapeutic success cessation of seizure within 10 min of drug administration without requiring assisted ventilation and without another seizure within 1 h Respiratory depression need for assisted ventilation

First Author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Baysun 2005 [130] Turkey	RCT	43 patients acute convulsions 2 m-12 years Intracranial hemorrhage, fever, meningitis, hypocalcemia, encephalitis	Buccal midazolam 23 patients epilepsy=12 female=12	Rectal diazepam n=20 patients Epilepsy=6 Female=9	Response Intervention=78% 18/23 Control=85% 17/20 Adverse effects Oxygen saturation decreased 1 patient in intervention group	Treatment success seizure stopped within 10 minutes
Mpimbaza 2008 [130] Uganda	RCT	108 patients prolonged seizures without malaria age 3 m - 12 y	Buccal midazolam 49 patients epilepsy=6	Rectal diazepam 59 patients epilepsy=7	Response Intervention=73% 36/49 Control=44% 26/59 Adverse effects all patients n=330 Pruritus n=1 (midazolam with phenobarbitone) Respiratory depression: Intervention n=2 Control n=2	Treatment success seizure stopped within 10 minutes and did not reoccur within one hour. Calculated from failure Failure Intervention=13/49 Control=33/59 Oxygen saturation <92% Respiratory depression: need for assisted ventilation

First Author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Ashrafi 2010 [131] Iran	RCT	98 patients acute prolonged convulsive seizures >5 min 3 m-12 years	Buccal midazolam 49 patients female=23	Rectal diazepam 49 patients female=17	<u>Stopped seizing</u> ≤4 minutes Intervention 88% 42/49 Control=49% 24/49 ≤5 minutes Intervention=100 % 49/49 Control=82% 40/49 (82%). ≤8 minutes Intervention=100 % 49/49 Control=100% 49/49 <u>Parent satisfaction:</u> Intervention=94% 46/49 Control=14% 7/49 All patients admitted to hospital ≥ 48h. No adverse effects reported	<u>Treatment success</u> seizure stopped ≤ 5 minutes, without respiratory depression and did not reoccur within one hour.

Annan behandling/alternative therapy

Tabell 4.1 Ketogen kost/Ketogenic diet

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Lambrechts 2017 [132] Netherlands	RCT	57 children and adolescents (1–18 years) with pharmaco-resistant epilepsy not eligible for surgery.	Ketogenic diet (KD) n = 29, for 4 months in addition to continued AED treatment. KD group Age (mean) = 7 years 8 months Duration of epilepsy (mean) = 5 years and 4 months	Control group (C) n = 28, continued AED treatment. C group Age (mean) = 8 years 1 months Duration of epilepsy (mean) = 6 years and 2 months	**Responders; n (%) (≥50% reduction in seizure frequency from baseline) at 4 months (ITT):** KD=13 (45%) C=4 (14%) **Calculated results:** RR (CI 95%)= 3.14 (1.16, 8.47) RD (CI 95%)= 0.31 (0.08, 0.53) **>90% reduction in seizure frequency from baseline; n (%)at 4 months (ITT):** KD=6 (21%) C=3 (11%) **Adverse events at 4 months in KD group (n=23):** Gastrointestinal symptoms (p=0.021).	Numbers included in the table are recalculated from reported results to ITT.
Sharma et al 2013 [133] India	RCT	102 children (2–14 years) with pharmaco-resistant epilepsy and with daily seizures.	Modified Atkins diet (MAD); n = 50, for 3 months in addition to continued AED treatment. MAD group Age (mean ± SD) = 4.7 ± 2.8 years Male=41 (82%) Female=9 (18%)	Control group (C); n = 52, continued AED treatment. C group Age (mean ± SD) = 5.2 ± 3.3 years Male=37 (71%) Female=15 (29%)	**Responders; % (>50% reduction in seizure frequency from baseline) at 3 months (ITT):** MAD=52% C=11.5% p=0.001 **Calculated results:** RR (CI 95%)= 4.51(2.03, 10.01) RD (CI 95%)= 0.40 (0.24, 0.57)	

			Duration of epilepsy in years (mean ± SD) = 3.4 ± 2.1	Duration of epilepsy in years (mean ± SD) = 3.3 ± 1.9	**>90% reduction in seizure frequency from baseline; % at 3 months (ITT):** MAD= 30% C=7.7% p=0.001 **Adverse events in MAD group (n=50):** Constipation (46%), anorexia (18%), vomiting (10%), lethargy (6%), lower respiratory tract infections (4%), hyperammonemic encephalopathy (2%).	
Neal 2008 [134] UK	RCT	145 children (2–16 years) with pharmaco-resistant epilepsy and at least daily seizures.	Ketogenic diet (KD), (n = 73) for 3 months in addition to continued AED treatment. <u>KD group</u> 2–6 years of age= 37 (51%) 7–11 years of age= 27 (37%) 12–16 years of age= 9 (12%) Male=38 (52%) Female=35 (48%) Mean duration of epilepsy = not reported	Control group (C), (n =72), continued AED treatment. <u>C group</u> 2–6 years of age= 29 (40%) 7–11 years of age= 32 (44%) 12–16 years of age= 11 (15%) Male=38 (53%) Female=34 (47%) Mean duration of epilepsy = not reported	**Responders; n (%) (≥50% reduction in seizure frequency from baseline) at 3 months (ITT):** KD=28 (38%) C=4 (6%) Calculated results: RR (CI 95%)= 6.90 (2.55, 18.69) RD (CI 95%)= 0.33 (0.20, 0.45) **>90% reduction in seizure frequency from baseline; % at 3 months** KD=7% C=0% **Adverse events at 3 months in KD group (n=55):** Vomiting (24%), diarrhoea (13%), abdominal pain (9%), constipation (33%), lack of energy (24%), hunger (22%).	Numbers included in the table are recalculated from reported results to ITT.
Sharma 2016 [129] India	RCT	81 children (2–14 years) with pharmaco-resistant	Simplified modified Atkins diet (sMAD; n = 41) for 3 months in addition to continued AED treatment.	Control group (C); (n = 40), continued AED treatment.	**Responders; % (>50% reduction in seizure frequency from baseline) at 3 months (ITT):** sMAD=56.1%	

		epilepsy and with daily seizures.	<u>sMAD group</u> Age (mean ± SD) = 5.6 ± 3.4 years Male=34 (81%) Female=7 (19%) Age at onset of epilepsy in months (mean ± SD) = 17 ± 14.5	<u>C group</u> Age (mean ± SD) = 4.8±3 years Male=30 (75%) Female=10 (25%) Age at onset of epilepsy in months (mean ± SD) = 13.1 ± 13.1	C=7.5% p<0.0001 Calculated results: RR (CI 95%)=7.48 [2.44 to 22.96] RD (CI 95%)=0.49 [0.31 to 0.66] **>90% reduction in seizure frequency from baseline; % at 3 months (ITT):** sMAD= 19.5% C=5% p=0.09 <u>Adverse events at 3 months in sMAD (n=36):</u> Constipation (16.6%), lethargy (8.3%), anorexia (8.3%), weight loss (13.8%), intercurrent infections (2.7%).	
Zare 2017 [135] Iran	RCT	66 adults (18–57 years) with pharmaco-resistant epilepsy.	Modified Atkins diet (MAD), (n=34) for 2 months in addition to continued AED treatment. <u>MAD group</u> Age (mean ± SD) = 29.4 ± 8.8 years Male=24 (70.6%) Female=10 (29.4%) Duration of epilepsy in years (mean ± SD) = 17.8 ± 10.6	Control group (C), (n=32), continued AED treatment. <u>C group</u> Age (mean ± SD) = 27.2 ± 7.3 years Male=21 (65.6%) Female=11 (34.4%) Duration of epilepsy in years (mean ± SD) = 14.09 ± 7.5	<u>Responders; % (>50% reduction in seizure frequency from baseline) at 2 months (ITT):</u> MAD=12 (35.3 %) C=0 (0%) p=0.001 Calculated results: RR (CI 95%)=23.57 [1.45, 382.39] RD (CI 95%)=0.35 [0.19, 0.52] <u>Adverse events at 2 months in MAD (n=34):</u> Weight loss, increased cholesterol levels.	

C= control; ITT=Intention-To-Treat; MAD=modified Atkins diet; RCT= randomized controlled study; SD= standard deviation; sMAD=simplified modified Atkins diet; RR= relative risk; RD=risk difference

Tabell 4.2 VNS

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Klinkenberg 2012 [136] Netherlands	RCT	41 children (23 males; 4–18 years old, mean age = 11) with medically refractory epilepsy despite adequate and stable AED concentrations.	High-output stimulation with VNS (n = 21) as an addition to AED therapy for 20 weeks. Age (mean years; months) = 10;11 Male (n)= 11 Female (n) = 10 Duration of epilepsy (mean years; months) = 7;8	Low-output-stimulation with VNS (n=20) as an addition to AED therapy for 20 weeks. Age (mean years; months) = 11;6 Male (n) = 12 Female(n) = 8 Duration of epilepsy (mean years; months) = 9;5	**Reduction in seizure frequency >50% of baseline; at end of blinded phase** Intervention (n = 19): 3 (16%) Control (n = 19): 4 (21%) **Calculated results** RR (CI 95%)= 0.75 (0.19, 2.91)	Only the blinded phase of the study is included here.
Handforth 1998 [137] USA	RCT	20 centers, 254 patients (105 females, 13–60 years) with at least 6 partial-onset seizures over 30 days involving complex partial or secondarily generalised seizures.	High-output stimulation with VNS (n = 94; 49 males; mean age = 32.1 ± 10.8) as an addition to AED therapy for 12 to 16 weeks. Age (mean ± SD) = 34.2 ± 10.1 Male (%) = 42.7 Female (%) = 57.3 Duration of epilepsy (mean years ± SD) = 23.7 ± 10.8	Low-output stimulation with VNS (n = 102; 59 females; mean age = 34.2 ± 10.1) as an addition to AED therapy for 16 weeks. Age (mean ± SD) = 32.1 ± 10.8 Male (%) = 51.6 Female (%) = 48.4 Duration of epilepsy (mean years ± SD) = 22.1 ± 11.5	**Reduction in seizure frequency >50% of baseline; during treatment period** Intervention (n =94): 22 (23.4%) Control (n = 102): 16 (15.7%) **Calculated results** RR (CI 95%)= 1.49 (0.84, 2.66)	
The VNS Study Group 1995 [138] North America and Europe (17 centers)	RCT	114 patients (≥ 12 years)	High-output stimulation with VNS (n =54; male = 61%; mean age = 33.1) as an addition to AED therapy for 14 weeks.	Low-output stimulation with VNS (n = 60; male = 63%; mean age = 33.5) as an addition to AED therapy for 14 weeks.	**Reduction in seizure frequency >50%: during the final 12 weeks** Intervention (n = 54): 17 (31%) Control (n = 60): 8 (13%)	Only the blinded phase of the study is included here.

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
			Age (mean) = 33.1 Male (%) = 61 Duration of epilepsy (mean years) = 23.1	Age (mean) = 33.5 Male (%) = 63 Duration of epilepsy (mean years) = 20.0	Calculated results: RR (CI 95%)= 2.36 (1.11, 5.03)	

C= control; ITT=Intention-To-Treat; MAD=modified Atkins diet; RCT= randomized controlled study; SD= standard deviation; sMAD=simplified modified Atkins diet ;RR= relative risk; RD=risk difference

[1] Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR, Hedges Team. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ 2005;330(7501):1179.

Tabell 4.3 Djup nervstimulering/Deep brain stimulation, DBS

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Fisher 2010 [139] USA	RCT (Multicenter, 17 U.S. Centers).	110 patients (18 to 65 years) with medically refractory seizures.	Bilateral stimulation of the anterior nuclei of the thalamus for localisation-related epilepsy.	No stimulation	Generalised estimation equations model (GEE) for quantitative data using stepwise regression and GLS Overall adjusted relative mean seizure reduction (3rd month of blinded phase) (all included): Intervention vs. control= -29% (p=0.0017).	Effectiveness of therapy depended upon region of seizure origin. Seizure origin in one or both temporal regions (median seizure reduction compared to baseline): I:44.2% (n=33) C:21.8% (n=29) p=0.025. Seizure origin in frontal, parietal, or occipital regions did not demonstrate significant differences in seizure reduction between the intervention and control group. Multifocal or diffuse seizure origin (median seizure reduction compared to baseline): I:35.0% (n=8) C:14.1%, (n=9) p=not significant

C= control; I= intervention; n= number

Tabell 4.4 Anti-depressive drug treatment

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Hovorka 2000 [140] Czech Republic	A single-centre, non-randomised, uncontrolled, prospective before and after study	43 people with focal epilepsy exceeding 15 points on the HAMD-21 scale for depression 35 females and 8 males Age: 21 to 49 years: mean: 33.2 years	Citalopram at a flexible dose; the average dose was 19.3 mg +/- 2.6 mg at the end of the first month, 22.62 mg +/- 8.3 mg at the end of the second month. Treatment period: 8 weeks	Baseline period: 2 months	Seizure frequency Treatment period: m=2.21, sd=1.00 Baseline period: m=2.24, sd=0.76 Change = -0,03 $CI_{95\%}$ = -0,30, 0,24	Baseline values are treated as parameters
Thome-Souza 2007 [141] Brazil	A single-centre, non-randomised, uncontrolled, prospective before and after study	36 children and adolescents with focal epilepsy and diagnosis of depression 19 females and 17 males Aged 5 to 18 years, mean: 12.7 years	Sertraline up to 200 mg per day, mean dose 111.5 mg per day (50 to 200 mg). Fluoxetine up to 80 mg per day, mean dose 45.7 mg per day (20 to 80 mg). Treatment period: Mean 25.8 months (range 12–78)	Baseline period: Not reported	Worsening from baseline 2 of 36 = 0.06 $CI_{95\%}$ = -0.02, 0.13	Baseline values are treated as parameters

CI=confidence interval; M= month; sd= standard deviation

Tabell 4.5 – CNS Treatment with CNS stimulants

First author Year Reference Country	Study Design	Population	Intervention	Control	Outcome	Comments
Feldman 1989 [142] USA	RCT with cross-over design	10 children (age 6 to 11 years) with seizures (single AED treatment) and attention-deficit disorder (ADHD).	Methylphenidate (0.3 mg/kg per dose, twice a day, on school days for 4 weeks) with 2-week washout period before cross-over to placebo.	Placebo (4 weeks) with 2-week washout period before cross-over to methylphenidate.	**Seizure relapse:** None of the patients had seizures during the study period.	None of the five children who continued receiving methylphenidate beyond the study period, had seizures during the extended period (3–12 months).
Gonzalez-Heydrich 2010 [143] USA	RCT with cross-over design	33 children (age 6 to 18 years) diagnosed with epilepsy and ADHD.	Methylphenidate (1–3 weeks) with 1-week washout period before cross-over to placebo. *Group I:* 18mg target dose, 1 week (n=3 patients). *Group II:* 36mg target dose (18 mg first week, 36mg second week, 2 weeks in total) (n=9 patients). *Group III:* 54 mg target dose (18 mg first week, 36 mg second week, 53 mg third week, 3 weeks in total) (n=21 patients). Each group had one-week wash-out before cross-over to placebo.	Placebo	**Seizure relapse:** I: 4 patients C: 3 patients	One child discontinued treatment under placebo but completed the entire active arm, whereas 10 children discontinued that active arm but completed their placebo treatment (p=.01). Preliminary indication of an increase in the daily risk of having a seizure with increasing doses of methylphenidate. It is important to note that the number of seizure events observed in the study is too small to confidently determine whether there is an increase in seizure risk from higher methylphenidate doses.

ADHD= attention deficit hyperactivity disorder; AED= anti-epileptic drug; C= control; I= intervention; n= number; RCT= randomized controlled study

Hälsoekonomi/Health economics

Tabell 5.1: Resektiv kirurgi som tillägg till antiepileptiska läkemedel

Författare År Referens Land	Frågeställning, design	Kostnader	Effektmått	Resultat	Kommentarer
Hinde 2014 [144] Storbritannien Burch 2012 [145] Storbritannien	Vuxna patienter (35 år vid operation) som samtliga genomgått video-EEG och MRT och bedömts lämpliga för utredning för tinninglobskirurgi. Kostnadseffektivitet beräknas för: 1) Inga ytterligare diagnostiska test. Standardbehandling med antiepileptiskt läkemedel 2) Stöd för diagnos med FDG-PET. Kirurgi om positivt. Om negativt eller otydligt, standardbehandling med antiepileptiskt läkemedel. 3) Stöd för diagnos med FDG-PET. Om otydligt, ytterligare diagnostiskt test med invasiv anfallsregistrering. Om positivt, kirurgi. Om negativt, standardbehandling med antiepileptiskt läkemedel. Beslutsträd vid bilddiagnostik för år 1, sedan Markov-baserad modellstudie med livslångt tidsperspektiv. Hälso- och sjukvårdsperspektiv.	Endast hälso- och sjukvårdskostnader. Brittiska pund, 2010 Diskonteringsränta 3,5 % på kostnader. Kostnader för: 1) 23 775 GBP 2) 26 621 GBP 3) 27 696 GBP	Kvalitetsjusterade levnadsår, QALY (skattat i annan studie med standard gamble) Diskonteringsränta 3,5 % på utfall. Utfall QALY: 1) 12,88 2) 14,58 3) 14,91	Kostnad per vunnen kvalitetsjusterat levnadsår, QALY 2 mot 1: 1 679 GBP 3 mot 1: 1 932 GBP Känslighetsanalys med det konservativa antagandet att effekterna av kirurgi är desamma som vid läkemedelsbehandling efter ett år: 2 mot 1: 1 526 GBP 3 mot 1: 13 794 GBP	Studien bedöms ha medelhög kvalitet och överförbarhet. Strategi 3 är det alternativ som stämmer bäst överens med svenska förhållanden, även om PET fram tills nyligen inte använts i lika stor grad i de svenska utredningarna. Studien beaktar endast kostnader inom hälso- och sjukvården och inte eventuell påverkan på produktivitet.

Bowen 2012 [146]Kanada	a) behandling med antiepileptiskt läkemedel b) remiss till regionalt epilepsicenter för kirurgiutredning och följande kirurgi c) kirurgi (diagnostik och utredningskostnader ej inkluderade) Beslutsträd för första året, sedan en Markov-baserad modellstudie med tidsperspektiv på 20 år. Hälso- och sjukvårdsperspektiv. Baserat på bland annat journaldata från Ontario, Kanada.	Endast direkta kostnader. Kanadensiska dollar, 2010 Diskonteringsränta 5% på kostnader. Kostnader för: a) 60 985 CAD b) 68 514 CAD 59 197 CAD	Kvalitetsjusterade levnadsår, QALY (skattat i annan studie med EQ-5D) Diskonteringsränta 5% på utfall. Utfall QALY: a) 10,757 b) 11,058 c) 11,648	a) mot c): Kirurgi dominant Känslighetsanalyser: 1) tidshorisont på 10 år 2) tidshorisont på 40 år 3) 3 % diskonteringsränta på kostnader och utfall. Kostnad per QALY a) mot b) 1) 71 259 CAD 2) 4 884 CAD 3) 13 795 CAD Kostnad per QALY a mot c 1) 28 392 CAD 2) Kirurgi dominerar 3) Kirurgi dominerar	Studien bedöms ha medelhög kvalitet och överförbarhet. Studien beaktar endast direkta kostnader inom sjukvården. Kirurgiutredning omfattade olika undersökningar i varierande utsträckning för olika patienter samt teamkonferenser. Invasiv anfallsregistrering räknas till kostnaderna för kirurgi. Dödlighet vid operation antas vara 1,8 % baserat på deras kanadensiska kohort vilket är högt jämfört med svenska registerstudier. Övrig dödlighet antas vara lika med övriga befolkningen. Samtliga barn som inte opereras har fortsatt svårbehandlad epilepsi under 20-årsperioden (ingen förbättras). Livskvalitetsvikter från vuxna har använts.

CAD= Kanadensisk dollar; EQ-5D = ett standardiserat instrument för att mäta livskvalitet; FDG= fluorodeoxyglukos; GBP= Brittiskt pund; MRT=Magnetisk resonanstomografi PET =Positronemissionstomografi; video-EEG=Video-elektroencefalografi; QALY= kvalitetsjusterade levnadsår (quality adjusted life years)

Tabell 5.2 Ketogen kost som tillägg till antiepileptika

Författare År Referens Land	Frågeställning, design	Kostnader	Effektmått	Resultat	Kommentarer
de Kinderen 2015 [147] Nederländerna	Beräkning av kostnadseffektivitet vid behandling av barn (1–18 års ålder) med behandlingsresistent epilepsi med: a) ketogen kost som tillägg till standardbehandling med antiepileptiskt läkemedel b) endast standardbehandling med antiepileptiskt läkemedel. Markovbaserad modellstudie med ettårigt samt femårigt tidsperspektiv. Hälso- och sjukvårdsperspektiv. Nederländska data. Data hämtades från publicerade studier, expertutlåtanden och priser i Nederländerna.	Kostnader för hälso- och sjukvården inkluderas. Euro, 2013. Diskonteringsränta 4% på kostnader. Kostnader rapporteras för 1 år/ 5 år: a) 14 036 / 30 935 b) 3 306 / 15 029	Kvalitetsjusterade levnadsår, QALY, skattade med livskvalitetsvikter (time-trade-off) från annan studie. Diskonteringsränta 1,5 % på utfall. Utfall QALY vid 1 år/ 5 år: a) 0,693 / 3,34 b) 0,662 / 3,15	Kostnad per vunnen kvalitetsjusterat levnadsår, QALY för analys med 1 års/ 5 års tidsperspektiv: a) vs. b) 346 899 euro/QALY a) vs. b) 86 025 euro/QALY Känslighetsanalys där kostnaderna för sjukhusinläggningar exkluderas och samtliga patienter behandlas med klassisk ketogen kost (lägre kostnad) ger kostnad på 19 032[12] euro/QALY vid tidsperspektiv om 5 år.	Studien bedöms ha medelhög kvalitet och överförbarhet. Studien beaktar inte eventuell påverkan på vårdnadshavares produktion. Livskvaliteten som används är skattad på vuxna.
Wijnen 2017 [148] Nederländerna	Beräkning av kostnadseffektivitet vid behandling av barn (2–18 års ålder) med behandlingsresistent epilesi med: a) ketogen kost som tillägg till standardbehandling med antiepileptiskt läkemedel (n=26)	Beräkning av kostnadseffektivitet vid behandling av barn (2–18 års ålder) med behandlingsresistent epilesi med: a) ketogen kost som tillägg till standardbehandling med antiepileptiskt läkemedel (n=26)	Andel responders (minst 50% minskning i antal epileptiska anfall) vid 4 och 16 månaders.	Andel responders vid 4 /16 månader var a) 50% / 34,6 % b) 18,2 / (18,2 enligt LOCF)	Studien bedöms ha medelhög kvalitet och överförbarhet. Studiens skattning av kvalitetsjusterade levnadsår och kostnadseffektivitetskvoter höll inte tillräckligt hög

[12] Uppgift framräknad från andra presenterade resultat.

Författare År Referens Land	Frågeställning, design	Kostnader	Effektmått	Resultat	Kommentarer
	b) endast standardbehandling med antiepileptiskt läkemedel. (n=22) Randomiserad klinisk studie med ett tidsperspektiv på 16 månader. Jämförelsegruppen saknar data efter 4 månader och antaganden har därför gjorts. Samhällsperspektiv och hälso- och sjukvårdsperspektiv. Nederländska data.	b) endast standardbehandling med antiepileptiskt läkemedel. (n=22) Randomiserad klinisk studie med ett tidsperspektiv på 16 månader. Jämförelsegruppen saknar data efter 4 månader och antaganden har därför gjorts. Samhällsperspektiv och hälso- och sjukvårdsperspektiv. Nederländska data.			kvalitet och återges därför inte.

N= antal; QALY= Quality-Adjusted Life Years

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