Tailoring therapy to optimize care for Epilepsy

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- For discussion only -

Disclosures

- Session (travel expenses) sponsored by Pfizer

Premature mortality in epilepsy

Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study

Seena Fazel, Achim Wolf, Niklas Långström, Charles R Newton, Paul Lichtenstein

Lancet 2013; 382: 1646–54

- Study of **all** people in Sweden diagnosed with epilepsy 1954 -2009 (n=70000), matched to up to 10 age- and sex-matched controls and unaffected siblings, followed up to the age of 56 years old
- Possible due to linkage of several national databases (census, patient register, cause of death register, multi-generation register) through unique national identification number
- Key findings:
- Mortality in people with epilepsy increased >10x after controlling for age, sex, income, marital, and immigration status
- Mortality increased for internal and external causes
- Ratios of psychiatric comorbidities 3-5x elevated in people with epilepsy (depression, alcoholism, substance misuse)
- Very high effect of psychiatric comorbidity on odds ratio for external causes of death

Comorbidities in epilepsy

- Diabetes type I (10 fold increase in NHNN cohort)
- Maternal mortality (11 x increase) + morbidity (preeclampsia, C-section, prolonged stay, 1-2 x increase)

Keezer M, in preparation
McDonald et al, JAMA Neurology 2015

Personal Impact of Epilepsy Scale

Category "Seizures"
1 Seizure recency
2 Severe seizure recency
3 Seizure severity
4 Seizures with lost awareness
5 Seizures bothersome
6 Seizure warning
7 postictal symptoms
8 Seizure related injuries
9 Seizure clusters

Category "Side effects"
10 Nr of medications
11 Anger / aggression
12 confusion / memory
13 Physical problems
14 Tiredness
15 Sleep
16 Headache€

Category "Comorbidities"
17 Depression
18 Anxiety
19 Thinking / memory
20 Work / school problems
21 Social limits
22 Transportation limits
23 Fear
24 Cost

25 Overall quality of life

- tool to quantify the impact of epilepsy longitudinally
- may help direct treatment decisions,
  especially in clinical settings with little time
- "the stroke scale for epilepsy"?

Fisher RS et al, Epilepsy & Behavior 2015

Predictors for pharmacoresistance

- Presence of multiple seizure types
- Etiology
- Positive family history
- Number of seizure before treatment
- Multifocal EEG abnormalities
- Inadequate response to initial therapy
- History of status epilepticus
- ALL UNMODIFIABLE

Predictors for pharmacoresistance

- Suboptimal AED choice
- Adherence
- Lifestyle factors
- MODIFIABLE

Psychiatric Comorbidities

TABLE 1. *Estimates of the prevalence of psychiatric disorders in patients with epilepsy*

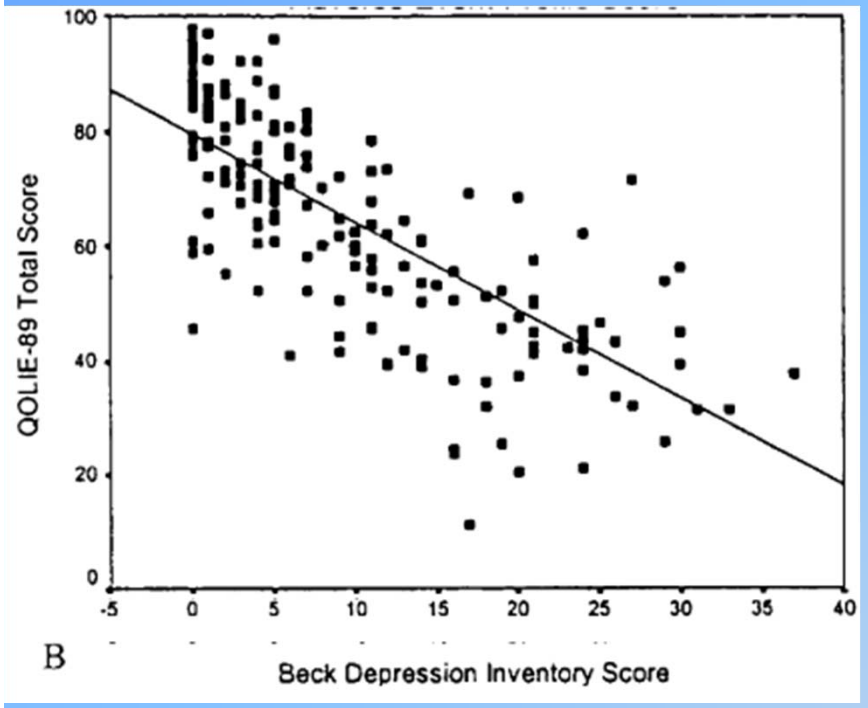
	Incidence		
	Patients with epilepsy	General population	Reference(s)
Depression	4% Seizure free	2–9% Women; 1–3% men	28
	9–22% Uncontrolled/partially controlled	2–9% Women; 1–3% men	28
	27–58% Medically intractable epilepsy	2–9% Women; 1–3% men	28
Depression	3–9% Controlled epilepsy		27
	20–55% Recurrent epilepsy		27
Major depressive disorder	~8–48%[a]	5–17%	29
Anxiety	3–50%		34
Neurotic disorders[b]	8%		30
Psychosis	6–10%	1.5–2%	30, 35
Bipolar disorder	1 or 8%	2%	28, 29
Mania	Rare		28
ADHD	14–40%	~5%	36

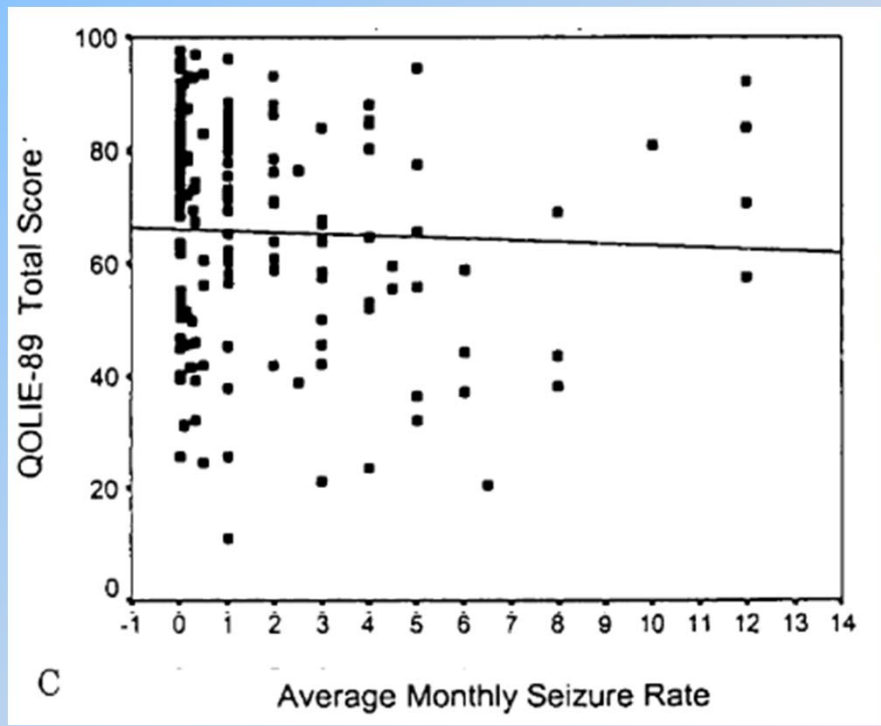
ADHD, attention-deficit-hyperactivity disorder.
[a] Lifetime-to-date prevalence.
[b] Includes dissociative disorder (2.5%), stress-related disorder (1.8%), anxiety-panic disorder (1.5%), and others (2.3%).

Likely combination of neurobiologic, psychosocial, and possibly iatrogenic effects

Bazil Epilepsia 2004
Gilliam Epilepsia 2002

Depression rather than seizure frequency is the major factor determining self-rated quality of life in people with pharmacoresistant epilepsy





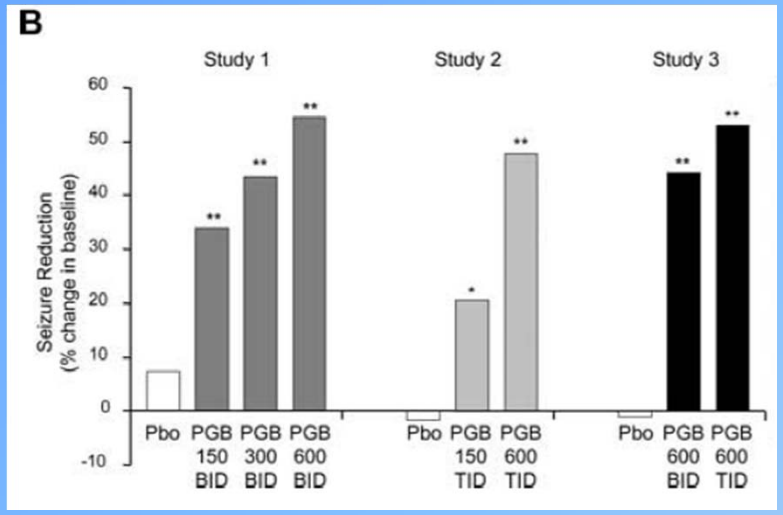
Gilliam Neurology 2002

Pharmacologic properties of Pregabalin

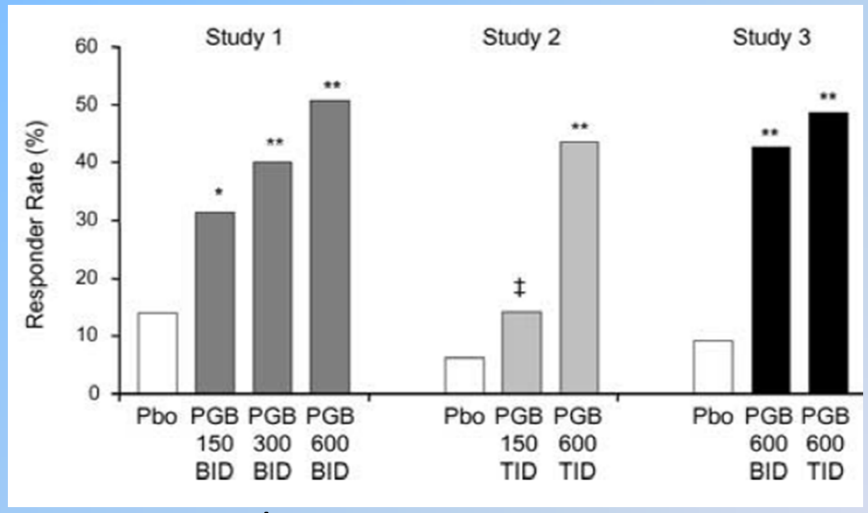
- Acts on voltage gated Calcium channels in the brain, modulating neurotransmitter release
- Note: although structurally related to GABA, Pregabalin does not act on GABA-ergic mechanisms
- Absorption unaffected by meals
- linear dose-uptake relationship in adults
- No hepatic metabolism, no induction, no inhibition
- >98% renaly excreted without being metabolised
- No protein binding
- No interactions with other drugs, including oral contraceptives
- No effect of PGB on CBZ, LTG, PHB, PHT, TPM and VPA

Ben Menachem, Epilepsia 2004
Bockbrader et al, Epilepsia 2011

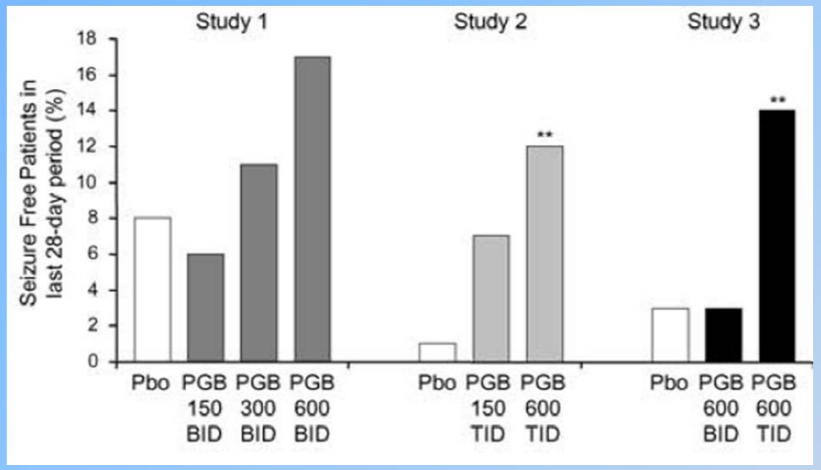
Pregabalin compared to placebo as add-on in licensing trials: robust and dose-dependent seizure reduction



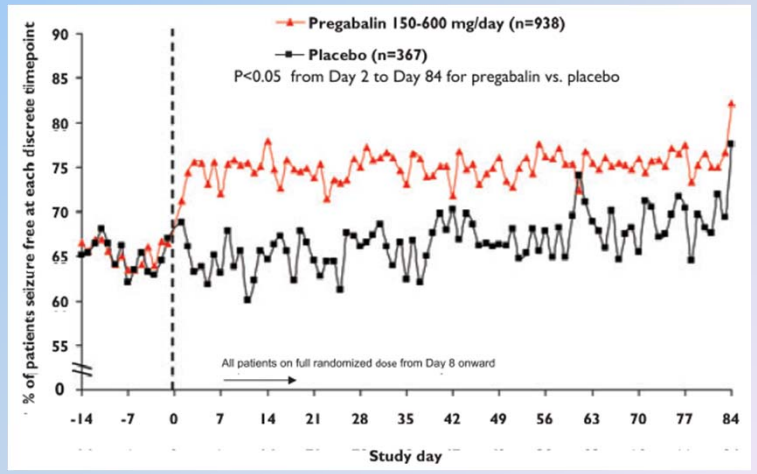
Seizure reduction



Responder rate



Rate of sz freedom



Daily rate of sz freedom

Brodie, Epilepsia 2004; Ramsay et al, Epilepsia 2009

Side effects in licensing trials

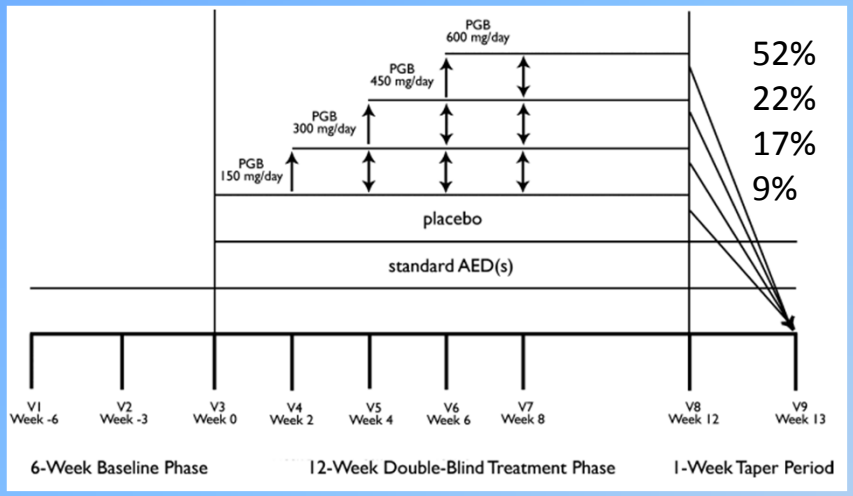
Adverse event	Frequency (%)		Withdrawals due to event (%)	
	Pregabalin (n = 758)	Placebo (n = 294)	Pregabalin (n = 758)	Placebo (n = 294)
Dizziness	28.9[a]	10.5	5.3	0.3
Somnolence	20.8[a]	10.9	3.3	0.0
Ataxia	13.2[a]	4.1	3.0	0.3
Asthenia	11.2	8.2	1.8	0.3
Weight gain	10.4[a]	1.4	0.4	0.0
Accidental injury	9.9[a]	5.4	0.9	0.0
Headache	9.1	11.6	1.2	0.0
Amblyopia (blurred vision)	9.0[a]	4.4	1.6	0.0
Diplopia	8.4[a]	3.7	1.6	0.7
Tremor	7.5[a]	3.7	1.5	0.0
Thinking abnormal (difficulty concentrating)	7.0[a]	2.0	1.3	0.0

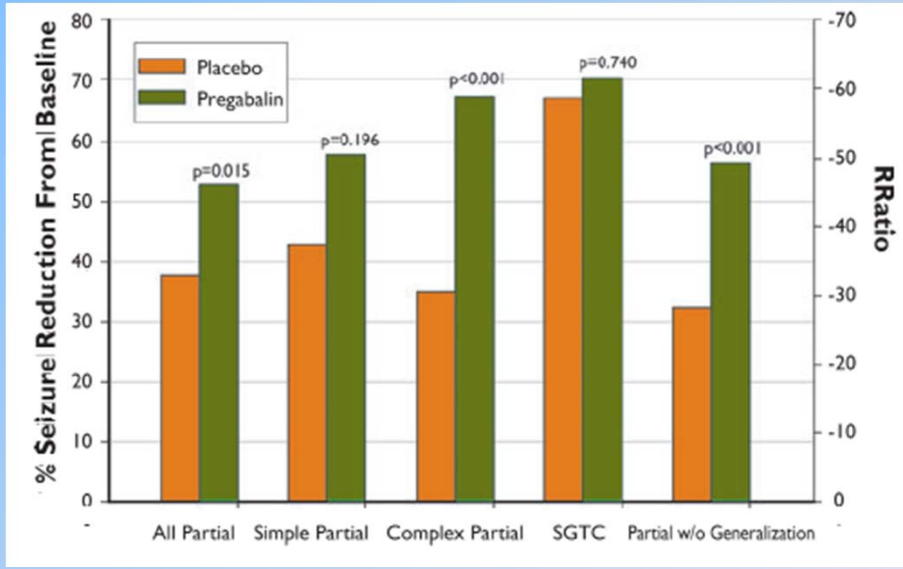
Some patients reported >1 adverse event.
[a]Significantly different from placebo.

French et al, Neurology 2003
Arroyo et al, 2004
Beydoun et al, 2005
Elger et al, 2003

Pregabalin effective in Asians with focal epilepsy (add-on, flexible dosing)

178 Korean adults, 75% on 3 AEDs





46% responder rate in PGB arm, 32% in placebo arm
7 patients discontinued PGB during study,
19 patients requested dose reduction due to side effects

Lee et al, Epilepsia 2009

Pregabalin well tolerated in Asians, too

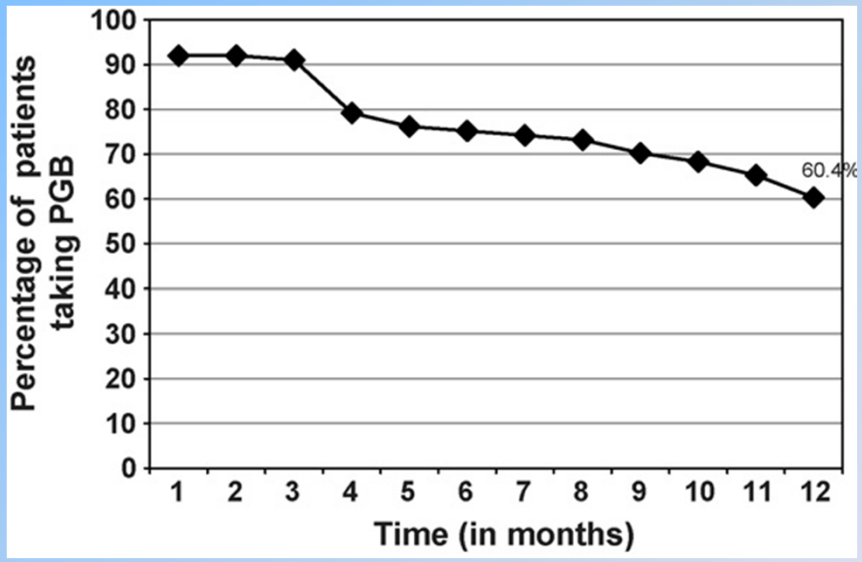
- No idiosyncratic side effects
- Main side effects: Dizziness, Somnolence, Weight gain

	Pregabalin (N = 119)		Placebo (N = 59)	
MedDRA preferred term	All causality	Treatment-related	All causality	Treatment-related
Dizziness	46 (38.7)	42 (35.3)	6 (10.2)	5 (8.5)
Somnolence	26 (21.8)	26 (21.8)	3 (5.1)	3 (5.1)
Weight increase	14 (11.8)	14 (11.8)	2 (3.4)	2 (3.4)
Fatigue	11 (9.2)	11 (9.2)	3 (5.1)	3 (5.1)
Headache	9 (7.6)	6 (5.0)	7 (11.9)	6 (10.2)
Increased appetite	6 (5.0)	5 (4.2)	1 (1.7)	1 (1.7)
Tremor	6 (5.0)	6 (5.0)	0	0
Constipation	5 (4.2)	5 (4.2)	0	0
Coordination abnormal	5 (4.2)	4 (3.4)	0	0
Vision blurred	3 (2.5)	3 (2.5)	1 (1.7)	1 (1.7)
Dyspepsia	4 (3.4)	3 (2.5)	5 (8.5)	2 (3.4)
Paraesthesia	4 (3.4)	3 (2.5)	0	0
Convulsion	3 (2.5)	3 (2.5)	1 (1.7)	1 (1.7)
Nasopharyngitis	4 (3.4)	0	4 (6.8)	0
Memory impairment	3 (2.5)	0	0	0
Insomnia	1 (0.8)	1 (0.8)	5 (8.5)	2 (3.4)
Sleep disorder	3 (2.5)	3 (2.5)	2 (3.4)	1 (1.7)

Lee et al, Epilepsia 2009

Audits in clinical practice I: Spain

- 101 adults, focal epilepsy
- 40% responders at 12 months
- 6% seizure free at 12 months
- Increase in seizure frequency in 4%



Main side effects:

- >10% weight gain seen in 26%
- Dizziness 20% (esp in combination with PHT, CBZ, OXC)
- leg edema 10%
- blurry vision 3%

No idiosyncratic side effects
Cognitive side effects rare

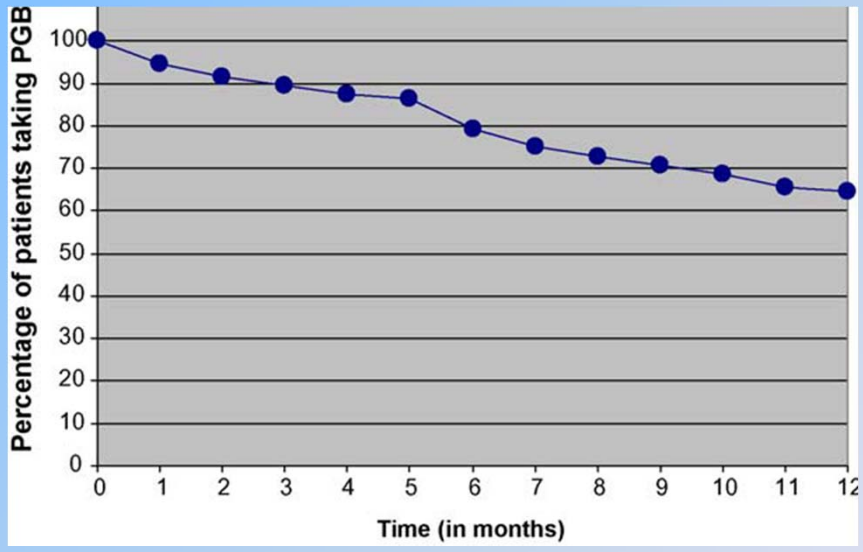
Reasons to discontinue at 12 months (total 40%):

- Inefficacy 16%
- Side effects 15%
- Worsening of seizures 9%
- 1 seizure-related death (drowning)

Carreno et al, Seizure 2007

Audits in clinical practice II: UK (Kings)

- 96 adults, 85 focal epilepsy
- 2 (0-4) concomittant AEDs
- 3 (1-9 previous AEDs)
- 30% ultimate responders (median 23 months)
- 10% incicental decrease in anxiety
- Increase in seizure frequency in 4%



Main side effects:

- >10% weight gain seen in 18%
- Dizziness 15% (esp in combination with PHT, CBZ, OXC)
- Drowsiness 17%

No idiosyncratic side effects
Cognitive side effects rare

Reasons to discontinue (total 45%):

- Inefficacy 30%
- Side effects 10%
- Inefficacy and side effects 9%

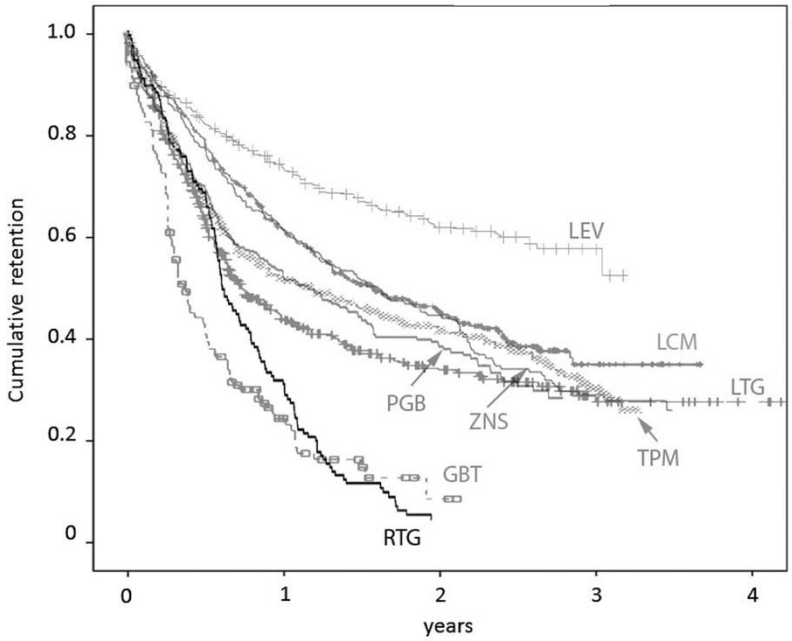
Valentin et al, Seizure 2007
Brandt et al, Seizure 2013

Audits in clinical practice III: UK (NHNN)

- 402 patients, 88% focal epilepsy
- 2 (0 - >4) concomittant AEDs
- Patients had failed median 8 AEDs

Retention higher in men than women:
at 1 year 60% vs 45%
at 2 years 46% vs 32%

Higher doses attained in men > women

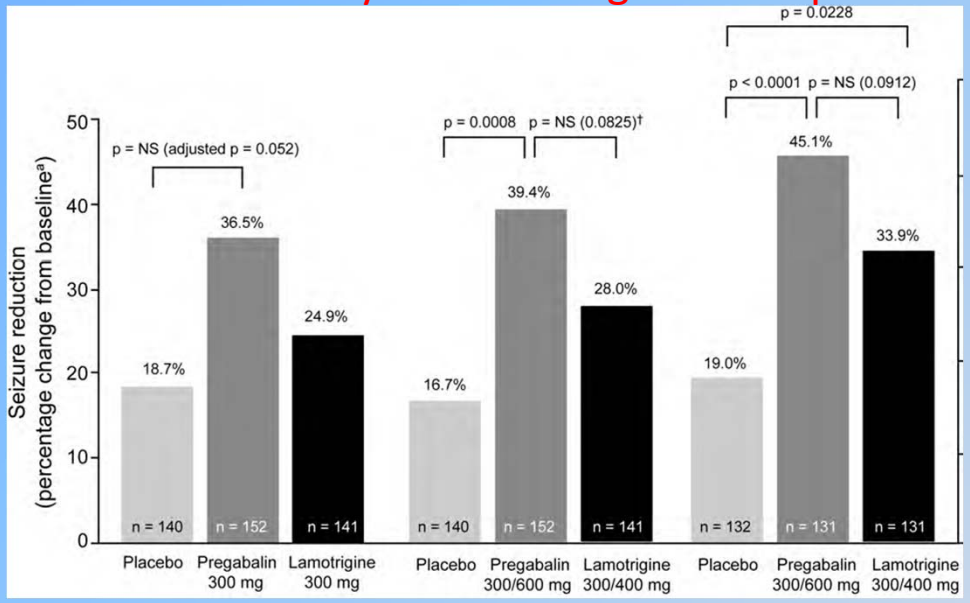


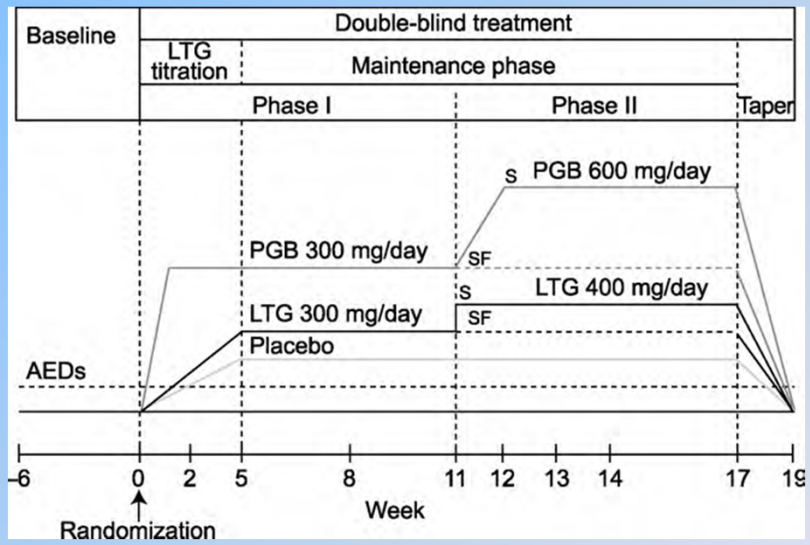
40% discontinued PGB due to side effects:
- CNS-related (35%) and weight gain (12%)
- Women more likely to report side effects and stop PGB due to side effects
- Decision to stop PGB not linked to number of concomitant AEDs

Yen et al, Epilepsy Research 2009; Wehner et al, Seizure 2014

PGB non-inferior to LTG and Placebo as add-on in focal epilepsy: Randomized controlled double blind trial

- 97 centres in Europe, Australia, Canada
- Adults with pharmacoresistant focal epilepsy, on 1 - 3 AEDs, including at least one inducer, randomized to PGB or LTG or Placebo
- PwE had failed 4 (1-7) AEDs
- Note 2 phase design
- Note unusually high placebo response (53%) in one country contributing ~20% of patients



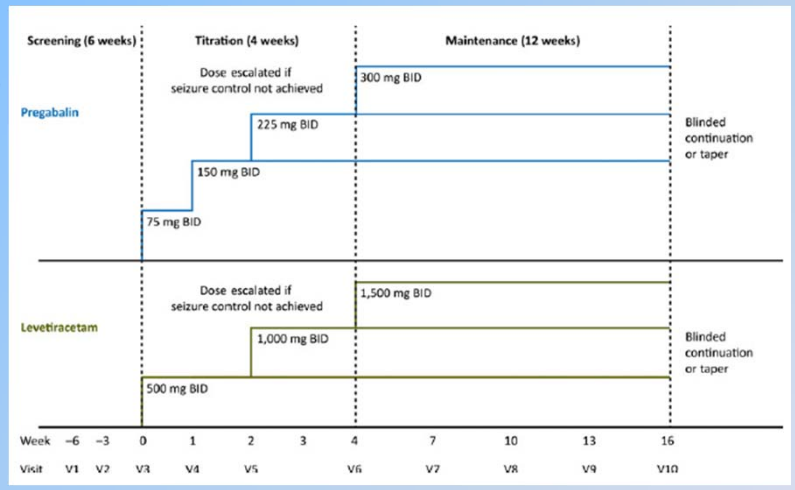


Most common side effects in PGB arm:
Dizziness (25%), somolence (20%), weight gain (9%),ataxia (9%).
No new adverse events

Baulac et al, Epilepsy Research 2010

PGB non-inferior to LEV as add-on in focal epilepsy: Randomized controlled double blind trial

- 71 centres in Europe, Asia, South America
- Adults with pharmacoresistant focal epilepsy, on 1 or 2 AEDs (largely CBZ, VPA, TPM, OXC), randomized to LEV or PGB
- Responder rates 59% for both LEV and PGB
- 8.4% on PGB vs 16% on LEV seizure free during maintenance phase
- Higher responder rates with lower(!) doses in both PGB and LEV group



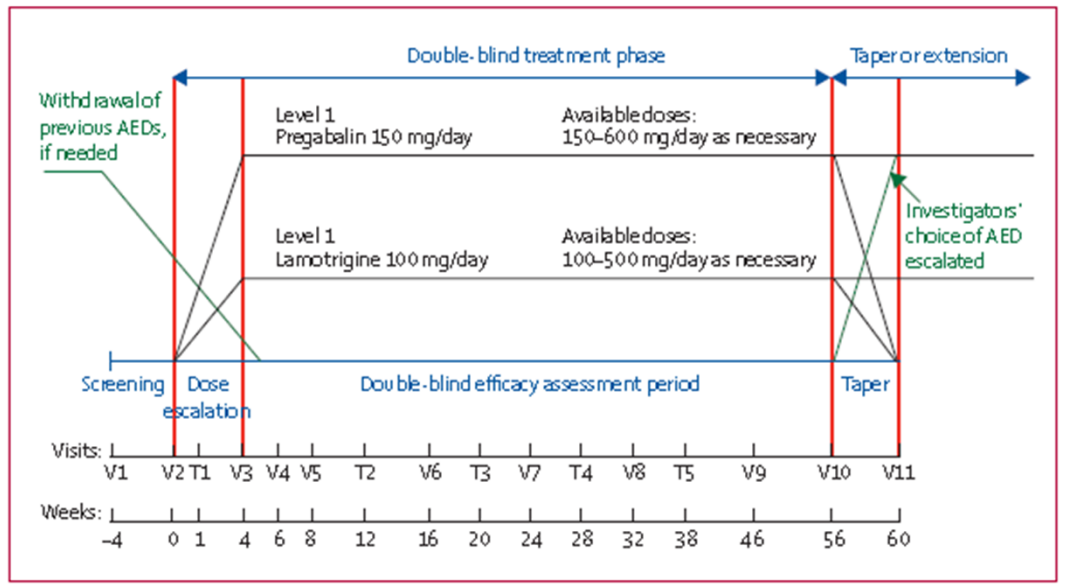
	Pregabalin (N = 254)	Levetiracetam (N = 255)
TEAEs, n	557	475
Patients with TEAEs, n (%)	188 (74.0)	164 (64.3)
Patients with SAEs, n (%)	11 (4.3)	9 (3.5)
Discontinuations due to TEAEs, n (%)	16 (6.3)	14 (5.5)
Common TEAEs,[a] n (%)		
Somnolence	79 (31.1)	73 (28.6)
Dizziness	56 (22.0)	39 (15.3)
Headache	30 (11.8)	24 (9.4)
Weight increased	24 (9.4)	5 (2.0)
Nasopharyngitis	13 (5.1)	16 (6.3)
Nausea	3 (1.2)	15 (5.9)

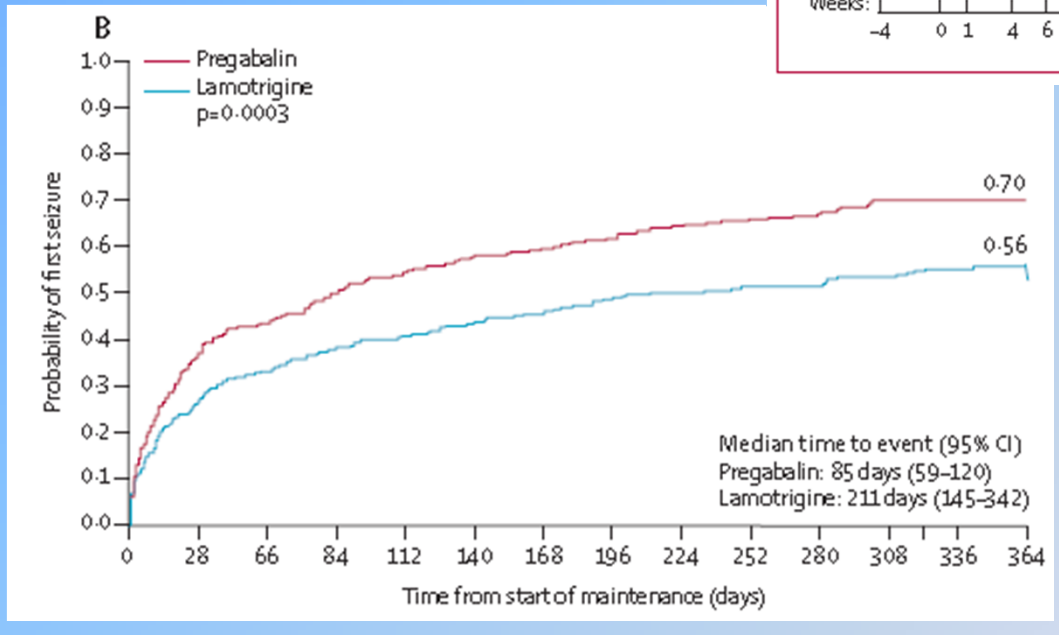
Discontinuation tended to occur
- in the titration phase with PGB
- in the maintenance phase with LEV

Zaccara et al, Epilepsia 2014

PGB vs LTG as monotherapy in newly diagnosed focal epilepsy

People with 2 focal seizures,
on treatment < 2 weeks
Pregabalin inferior to LTG in terms of efficacy: first seizure, first sGTCS occured earlier on PGB than LTG





- Side effects overall similar in PGB and LTG
- Weight gain, somnolence more common in PGB
- Oropharyngeal pain more common in LTG

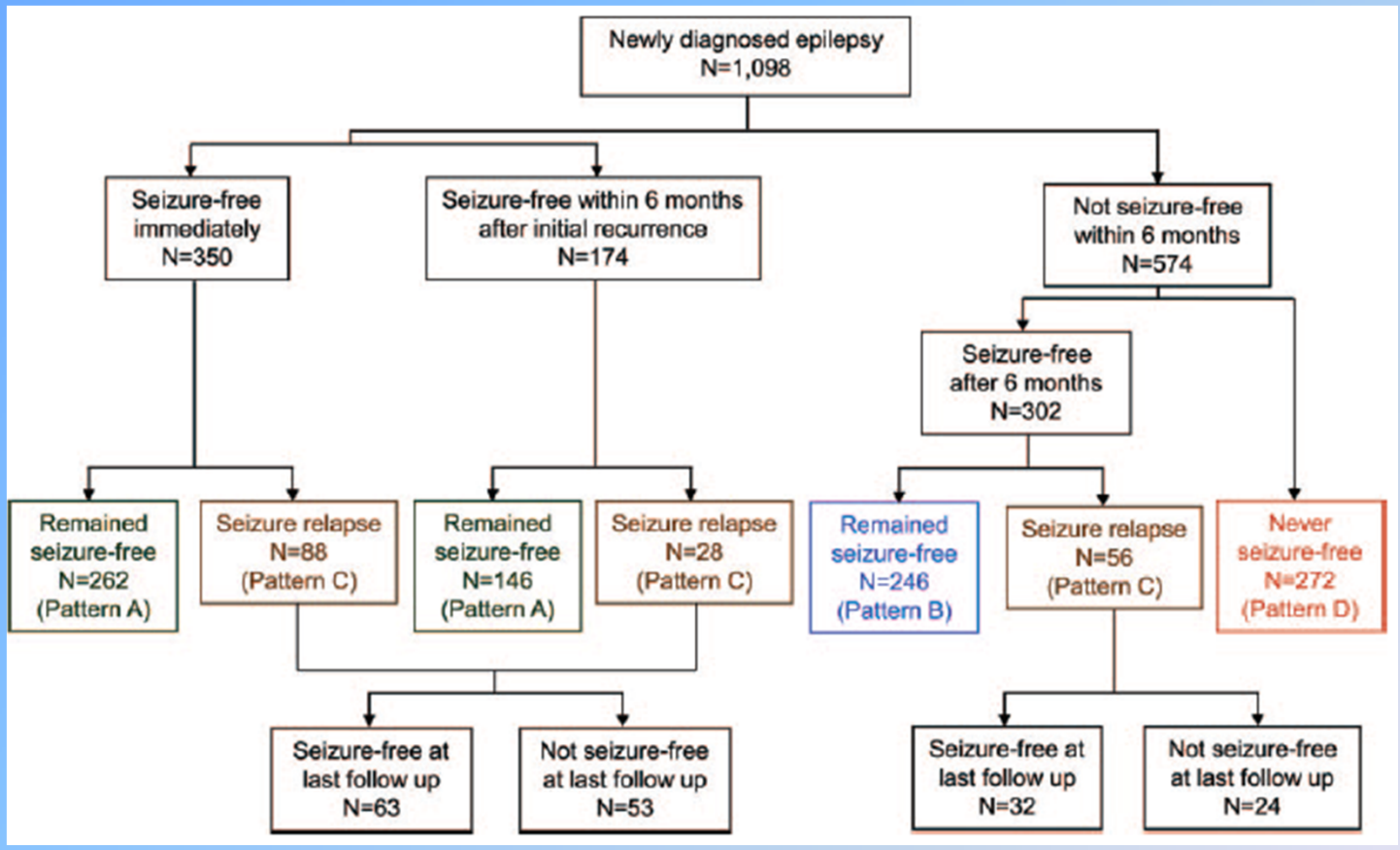
Kwan et al, Lancet Neurology 2011

However, mind the fine print: Methodological issues in monotherapy trials

- Remember prognosis in newly diagnosed epilepsy
- 37% will do well, with no seizure over 1 year
- 25% will be pharmacoresistant
- Primary outcome was seizure freedom for 6 months, comparing essentially the first target dose

French, Lancet Neurology 2011
Brodie et al, Neurology 2012

Prognosis in newly diagnosed epilepsy



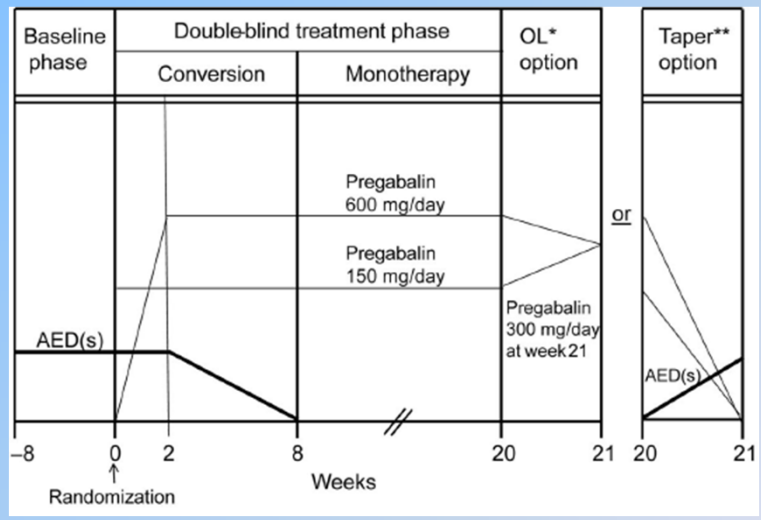
A: early and sustained sz freedom 37%
B: delayed but sustained sz freedom 22%
C: fluctuating 16%
D: never sz free 25%

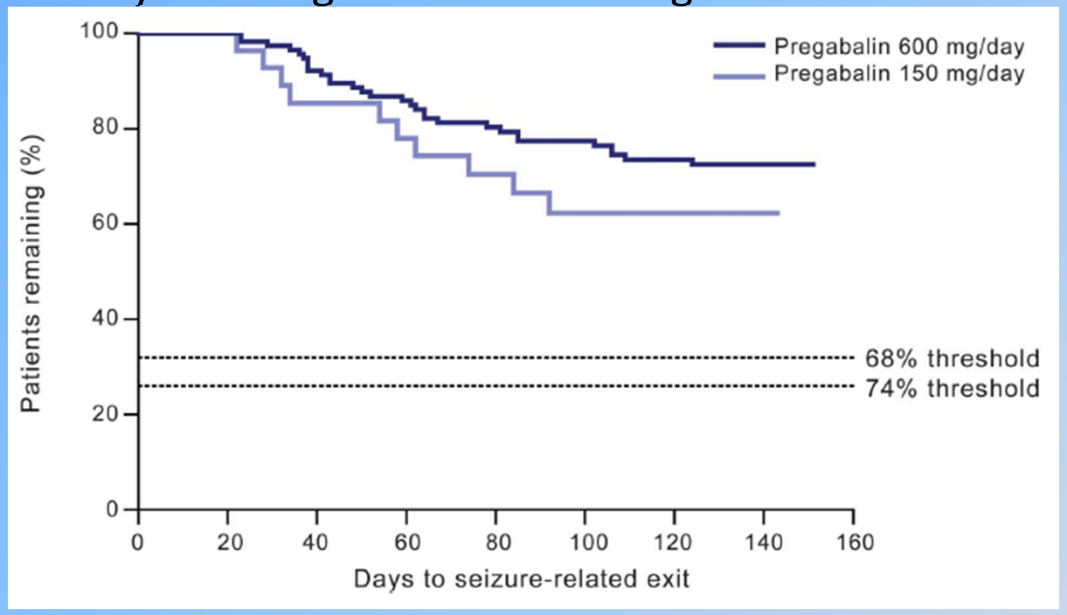
Brodie et al, Neurology 2012

Pregabalin as monotherapy vs historic control

-Trial design developed to mandate FDA-US criteria-

Adults with uncontrolled epilepsy on 1 or 2 AEDs
Patients randomized to 600mg/d or 150mg/d ("pseudoplacebo"), predefined exit criteria:
- doubling of seizure rate at 2 or 28 days
- occurence of status epilepticus
- re-occurence of generalised tonic clonic seizures
- any other significant worsening





Main side effects in PGB 600mg/d:
Dizziness, somnolence (17% each)
Weight gain 16% vs 6% in 150mg/d

Trial stopped early because PGB 600mg/d did better "than expected"
(based on historic control design)

French et al, Neurology 2013

Data on Pregabalin in children are extremely limited

- Pregabalin safe and tolerated over 7 days at doses of up to 15mg/kg/d in children age 1 month to 6 years; pharmakokinetics suggest that 15mg/kg/d may be needed in children <30kg to reach an equivalent dose to 600mg/day in adults
- Follow up data in these children with epilepsy on 1-3 further AED pending

- 1 fetal malformation in 30 pregancies exposed to Pregabalin monotherapy (Veiby G J Neurol 2014)

Mann et al, Epilepsia 2014

Pregabalin and cognitive side effects

Rates and predictors of patient-reported cognitive side effects of antiepileptic drugs: An extended follow-up

Asif Javed [a], Brian Cohen [a], Kamil Detyniecki [b], Lawrence J. Hirsch [b], Alexander Legge [a], Baibing Chen [b], Carl Bazil [a], Kenneth Kato [a], Richard Buchsbaum [c], Hyunmi Choi [a,*]

Rates of patient-reported intolerable cognitive side effects <5% with Pregabalin in polytherapy and monotherapy; comparable to most other AEDs

positive outlier: Lamotrigine (2.5%)

negative outlier: Topiramate (22.8%)

Javed et al, Seizure 2015

Sleep and Epilepsy

- PwE, especially those with uncontrolled seizures of any kind, report worse quality of sleep than healthy controls
- PwE have increased sleep latency, increased number of arousals, more shifting between sleep stages, less REM-sleep, and less slow wave sleep compared to controls
- Sleep apnea and periodic limb movement disorder of sleep more common in PwE
- Poor sleep may increase seizure frequency, increase depression, contribute to memory problems in PwE, and decrease performance during daytime

Jain & Glauser, Epilepsia 2015

Effect of AEDs on Sleep

CRITICAL REVIEW AND INVITED COMMENTARY

Effects of epilepsy treatments on sleep architecture and daytime sleepiness: An evidence-based review of objective sleep metrics

Sejal V. Jain and Tracy A. Glauser

Epilepsia, 55(1):26–37, 2014
doi: 10.1111/epi.12478

- "Virtually all AEDs affect sleep architecture"
- AEDs with positive effect on sleep latency / sleep efficiency:
  Carbamazepine, Clobazam, **Pregabalin**, Gabapentin, Tiagabine
- AEDs that increase daytime sleepiness:
  Phenobarbitone, Valproate, Levetiracetam in high doses
- AEDs without effect on daytime sleepiness:
  Topiramate, Zonisamide

Pregabalin and dependency

- Pregabalin over-proportionally prescribed in imprisoned patients
- 50% of apprehended drivers had serum levels outside the recommended range, often in combination with other drugs
- Risk factors for abuse appear to be current or history of polytoxic drug misuse
- Physicians need to be aware of abuse potential and “street value” of Pregabalin

Gahr et al, 2013

Conclusion

- Few predictors of pharmacoresistance are modifiable, including adherence and lifestyle factors
- Pregabalin is effective and comparable to LTG and LEV as add-on therapy in pharmacoresistant focal epilepsy, with very early effect
- Pregabalin has a favorable pharmakokinetic profile, and is generally well-tolerated
- Somnolence, dizziness, and weight gain are the most common reported side effects, more common in women
- Pregabalin reduces anxiety in some people with epilepsy
- Role as monotherapy and in children to be defined