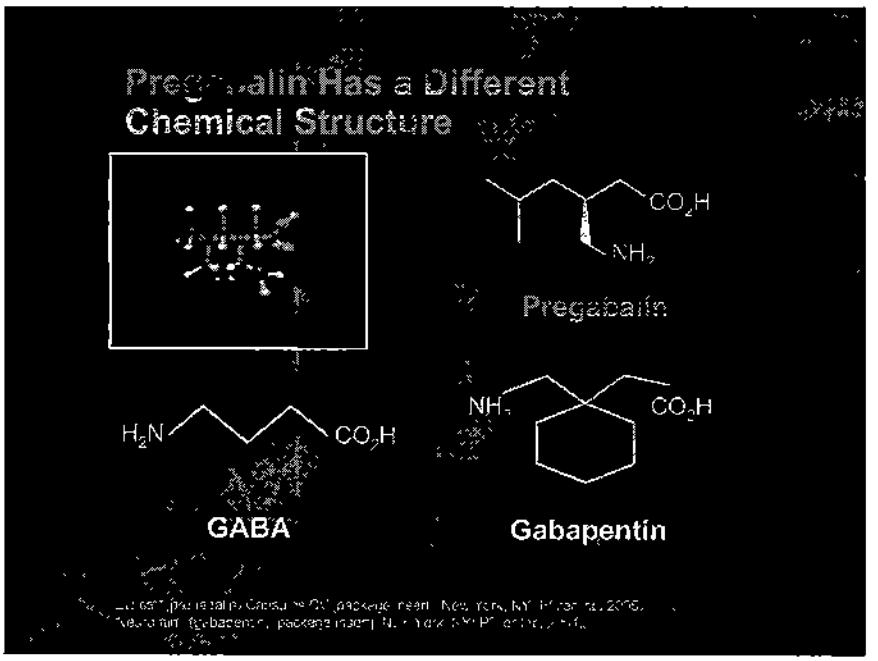
2008 LYRICA (pregabalin)

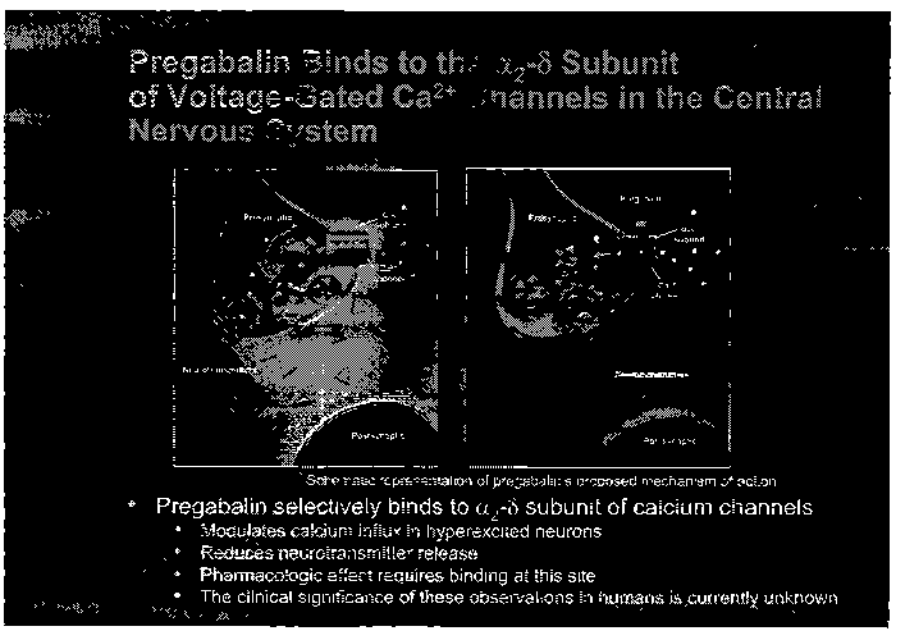


Chemical Structure

(S)-3-(aminomethyl)-5-methylhexanoic acid, an amino acid. It has two charged groups (a negatively charged carboxylic acid and positively charged amine) at neutral pH

Mechanism Of Action

reduction of neurotransmitter release occurs because pregabalin selectively binds to the alpha 2 delta subunit of calcium channels of neurons in the central nervous system thereby modulating calcium influx into presynaptic cells.



Physiological Effects

Reduces the release of several neurotransmitters in hyperexcited neurons including substance P, glutamate and noradrenalin
Is not active at the GABA receptor and has no GABA-like biological activity
It is not a vascular calcium channel blocker

PREGABALIN PHARMACOKINETIC PROFILE

Variable	Characteristic	Clinical Relevance
absorption	Tmax-<1.5h	rapid
bioavailability	>90%	no food effect; dose proportions
pic 150-600mg/d	linear	predictable levels
exposure	dose proportional (Cmax and AUC)	predictable levels
plasma half-life	6.3h	BID or TID dosing
steady state	24-48 hrs	first dose adjustment
protein binding	No	predictable levels
metabolized	No	predictable levels
renal excretion	90% unchanged	Removed by dialysis adjust if renal impairment

PREGABALIN AND GABAPENTIN PHARMACOLOGY FACTS

	Pregabalin	Gabapentin
FDA-approved pain indication	Neuropatic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia, fibromyalgia. Adjunctive therapy – adults with partial onset seizures	Postherpetic neuralgia
Mechanism of Action	ligand • Selectively binds to the Site in CNS tissues	ligand • Selectively binds to the Site in CNS tissue
PharmacokineticProfile	Linear • Plasma concentration is dose proportionate	Nonlinear • Plasma concentration increases disproportionately to dose
Oral bioavailability	>90% all doses	60% 900 mg 47% 1200 mg 34% 2400 mg 33% 3600 mg
Dose potency for PHN	Effective @ 150mg/d • Dose range from 150 mg/day to 450 mg/d	Effective @ 1800 mg/d
Dosing (PHN)	BID or TID	TID
Time to effective dose (PHN)	1 day • Effective starting dose of 150 mg/d	9 or more days • Titrate to effective dose of 1800 mg/d

Peak plasma concentration (C mx, 1hr) and total exposure (area under the plasma concentration- time curve (AUC) are similar in either a BID or TID regimen.

Does not inhibit CYP 450 enzymes and has no clinically significant PK interactions.

Pregabalin administered concomitantly with Oxycodone, Ethanol, or Lorazepam did not result in any clinical significant effect on respiration, but may exacerbate effects on both cognition and gross motor functioning.

ADVERSE EVENTS	> 10,000 pts. Initially exposed	
	> 6 mos	> 5,000
	> 1 yr	> 3,100
	> 2 yr	> 1,400

Most Common:	**(29%)**	dizziness
	(22%)	somnolence
	(9%)	dry mouth
(75% or 2 x rate observed in placebo)	**(6%)**	peripheral edema
	(6%)	blurred vision
	(6%)	weight gain
	(5%)	thinking abnormal

Most are dose related

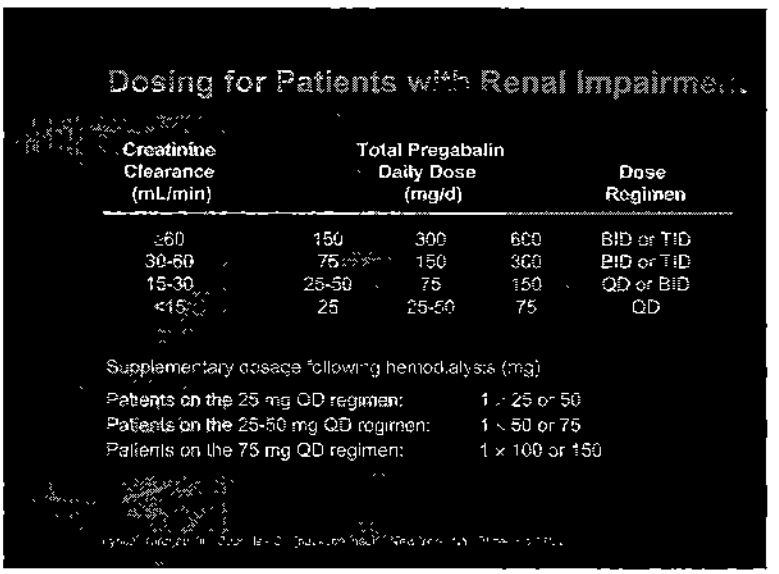
Warnings & Precautions:

- Angiodema during initial and chronic therapy, especially with prior history of angiodema or ACE inhibitors.
- Withdrawal should be gradual and occur over a minimum of 1 week in epileptics
- Abrupt or rapid discontinuation will cause insomnia, nausea, headache, and diarrhea in 2%
- An increased incidence of hemangiosarcoms was observed in B6C3F1 and CD-1 mice, but not in 2 rat strains when exposed to human equivalent dose of 600 mg/d. These tumors are rare in humans. In 6396 patient years of pregabalin exposure, 57 patients had new or worsening tumors (none were vascular in nature) and relationship to pregabalin is unknown.
- No overall difference in safety and efficacy were observed between older patients and younger patients.
- Peripheral edema was not associated with cardiovascular complications such as HTN or CHF.
- 2% incidence of ↑ CPK and 3 patients developed rhabdomyolysis (all had other risk factors).
- Higher incidence of decreased platlet count (20% below baseline values and <150,000/ul) but no serious concurrent bleeding complication.
- Mild PR interval prolongation (3-6 ms) at doses $\geq$ 300 mg/d, but no association with cardiac sequelae

- Schedule V designation:

    1. Incidence of euphoria 1% to 12%, median time to onset: 1 day; median duration: 7 days
    2. Subgroup populations:
        - Epilepsy 0.8% vs 0.3% placebo
          Painful DPN/PHN 1.4% vs 0% placebo
          Generalized anxiety disorder 4.5% vs 1.2% placebo
          Not active at opioid or benzodiazepane receptors
          No evidence of tolerence in 51 patients with euphoria and open label exposure >400 days
          No evidence of diversion, abuse, or addiction in pregabalin clinical program safety database – 53 studies N=8666
          Examples of scheduled products
          C-I heroin
          C-II morphine
          C-III Tylenol with codeine, vicodin
          C-IV Ambien, Xanax, Phenobarbital
          C-V Robitussin A-C, Lomotil

- Overdose: highest dose reported 8000 mg; no clinical consequences
  Dosages up to 2400 mg used in clinical trials

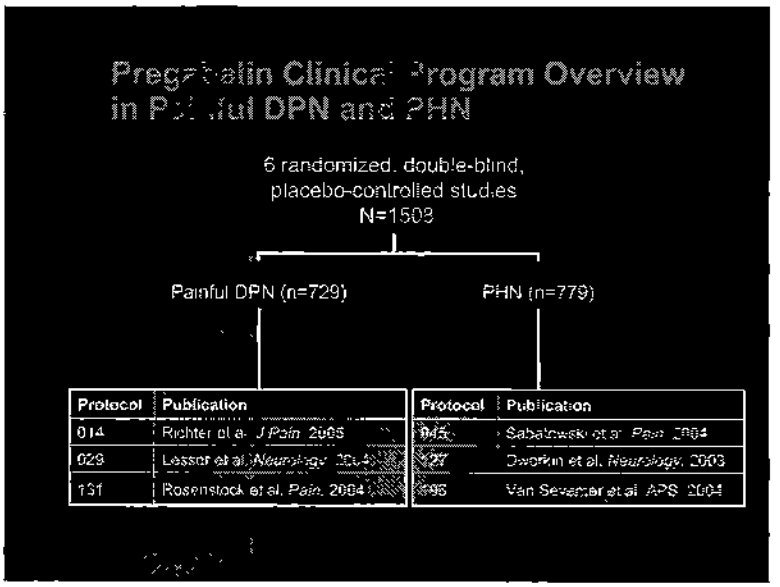


Pregabalin Dosing:

Available in capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg
Approved total daily dosage ranges:

- Partial onset seizures: 150 – 600 mg/d in 2 or 3 divided doses
- Painful DPN 150 – 300 mg/d in 3 divided doses
- PHN: 150 – 600 mg/d in 2 or 3 divided doses

Supportive Clinical Studies



DPN

Lesser

- Mean weekly pain scores were decreased by average 2 points (VAS 6.0 – 4.0) by week 1 and maintained for 5 weeks ($p \leq .001$)
- 50% responder rate obtained by 17% placebo group, 46% Pregabalin group ($p = .001$)
- Pregabalin 75 mg/d not effective
- No difference between Pregabalim 300 mg/d or 600 mg/d

Rosenstock

- VAS 6 – 4 with Pregabalin by week 1, and maintained through week 8 ($p \leq .01$)
- 50% responder rate:
  - Pregabalin: 40%
    $p = .001$
  - Placebo: 15%

PHN

Dworkin

- VAS 6-4 by week 1 and maintained through week 8 $p \leq .01$
- 50% responder rate in 50% Pregabalin vs 20% placebo ($p=.001$)

Van Seventer

- VAS 7- 5 by week 1 and maintained by week 13 ($p \leq .001$)
- 50% responder rate Pregabalin: 150 – 26%, 300 – 27%, 600 – 38%

p = .001 placebo: 8%

Fibromyalgia

- 53% responder rate vs. 33%placebo had a ≥ 30% pain reduction vas 6.7-4.4 sustained for six months

ALTERNATIVE TREATMENTS

PHN

Gabapentin: 33% 50% responder rate

Rise; Pain 2001; 94:215-224
Rowbotham; JAMA 1998; 280:1837-1842

Lidocaine patches:
Barbano; Arch Neuro 2004; 61:914-918
Low; Pain 1995; 62:163-168

Capsaicin:
Arch Internal Med 1991; 151; 2225-2229

CR morphine:
Rasa; Neurology 2002; 59:1015-1021

CR oxycodone:
Watson; Neurology 1998; 50: 1837-1841

DPN

1. Anti-depressants
   - Amitriptyline- Max; Neurology 1987:37:589-596
   - Desipramine- Max; NEJM 1992: 326: 1250-1256
   - Venlafaxine- Rowbotham; Pain 2004; 110: 697-706
   - Duloxetine- Goldstein; Pain 2005; 116:109-118
2. Anti-convulsants
   - Carbamazeppane- Wilton; S Afr Med Journal 1974
   - Gabapentin- Backonja; JAMA 1998:280; 1831-1836
   - Lamotrigine- Eisenberg; Neurology 2001; 57:505-509
3. Opiods
   - CR Oxycodone- Gimbel; Neurology 2003; 60: 927-934
   - Tramadol- Harati; Neurology 1998; 50: 1842-1846

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