

Pharmacotherapeutic Considerations in the Treatment of Neuropathic Pain

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www.NOVAPAIN.net

LEARNING OBJECTIVES:

Upon completion of this educational program, the participant should be able to:

Peripheral Neuropathy:


1. List the various drug classes used to treat peripheral neuropathy.
2. Understand the pathophysiology of peripheral neuropathy.
3. List the various toxicities associated with the different drug therapies used in peripheral neuropathy.
4. List advantages and disadvantages of the drug classes discussed.
5. Understand the importance of drug-drug interactions when prescribing or dispensing medications used in the treatment of neuropathy.

Pharmacotherapeutic Considerations in the Treatment of Neuropathic Pain



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NEUROPATHIC PAIN



Neuropathic pain arises as result of a primary lesion or dysfunction of the nervous system which leads to the loss of the capacity to conduct information. The nervous system is in a sense short-circuited and action potential generation becomes out of control.

1. Gallagher RM. Primary care and pain medicine. *Med Clin N Am.* 1999;83(3):555-583
2. Semenchuk M. Adjuvant analgesic for management of neuropathic pain. *Pharmacy Newswatch.* Biezer JL ed. Park-Davis. 1999;(6) no 1.

Nociceptive vs Neuropathic Pain States

<p style="text-align: center;">Nociceptive</p> <ul style="list-style-type: none"> Arises from stimulus outside of nervous system Proportionate to receptor stimulation When acute, serves protective function 	vs	<p style="text-align: center;">Neuropathic</p> <ul style="list-style-type: none"> Arises from primary lesion or dysfunction in nervous system No nociceptive stimulation required Disproportionate to receptor stimulation Other evidence of nerve damage
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Serra. *Acta Neurol Scand.* 1999;173(suppl):7-11.

DPN and PHN Produce Positive and Negative Symptoms

<p style="text-align: center;">Positive Sensory Symptoms</p> <ul style="list-style-type: none"> Spontaneous pain Dyesthesias Paresthesias Evoked pain 	<p style="text-align: center;">Negative Sensory Symptoms</p> <ul style="list-style-type: none"> Loss/impairment of sensory quality Numbness, reduced sensation
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Baron. *Clin J Pain.* 2000;16(2 suppl):S12-S20.

Examples of Nociceptive and Neuropathic Pain

<p><i>Nociceptive</i></p> <p>Caused by tissue damage</p>	<p><i>Mixed</i></p> <p>Caused by combination of primary injury and secondary effects</p>	<p><i>Neuropathic</i></p> <p>Caused by lesion or dysfunction in the nervous system</p>
<ul style="list-style-type: none"> Arthritis Mechanical low back pain Sports/exercise injuries Postoperative pain 	<ul style="list-style-type: none"> Low back pain Fibromyalgia Neck pain Cancer pain 	<ul style="list-style-type: none"> Painful DPN PHN Neuropathic low back pain Trigeminal neuralgia Central poststroke pain Complex regional pain syndrome Distal HIV polyneuropathy

Spontaneous Symptoms

Symptom	Description
Spontaneous pain	Persistent burning pain, shocklike pain
Dyesthesias	Abnormal, unpleasant sensations (eg, shooting, lancinating, burning)
Paresthesias	Abnormal, not unpleasant sensations (eg, tingling)

Baron. *Clin J Pain.* 2000;16(2 suppl):S12-S20; International Association for the Study of Pain Website. Available at: <http://www.iasp-pain.org/terms-p.html>. Accessed September 30, 2004.

Stimulus-Evoked Symptoms

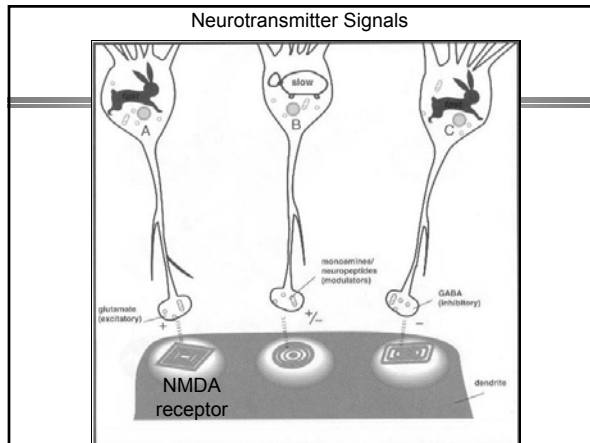
Symptom	Definition
Allodynia	Painful response to nonpainful stimulus
Hyperalgesia	Heightened response to normally painful stimulus
Hyperpathia	Explosive response to normally painful stimulus

International Association for the Study of Pain Web site. Available at: <http://www.iasp-pain.org/terms-p.html>. Accessed September 30, 2004.

Overview

- Etiology and Pathogenesis
- Tricyclic Antidepressants
- SSRIs, SNRIs, SARIs, MOAIs
- Drug Interactions (iso-enzyme metabolism)
- Anti-convulsants
- Anti-arrhythmic
- Topicals

Neurotransmitter Signals



Limiting Calcium Influx Can Temper Hyperexcitable Neurons

- Limit amount of Ca^{2+} entering presynaptic neuron upon excitation
- Allow enough Ca^{2+} for normal nerve function
- Two pharmacologic strategies
 - Block Ca^{2+} channels
 - Modulate channels without blocking (allosteric)

Mechanisms of Neuropathic Pain: Central Sensitization

- Peripheral nociceptor inputs trigger molecular changes in central neurons

Modification of GABA, glycine receptors \rightleftharpoons Reduce effect of inhibition

NMDA and AMPA receptor activation \rightleftharpoons Lower firing threshold

- Long-lasting changes may result from
 - Altered receptor expression
 - Inhibitory interneuron death

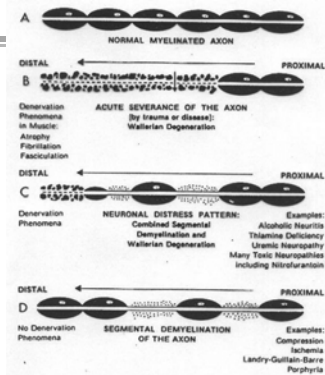
GABA = γ -aminobutyric acid; NMDA = *N*-methyl-D-aspartate; AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate.

Woolf, Salter. *Science*. 2000;288:1765-1768.

NEUROPATHIC PAIN AND PHARMACOLOGY

- Tricyclic Antidepressants-enhancement of inhibitory pathway
- Anticonvulsants-sodium channel blockade
- Antiarrhythmics/Anesthetics-sodium channel blockade
- Clonidine-decrease sympathetic tone
- Capsaicin-substance P depletion
- Ketamine/Amantadine-NMDA receptor blockade
- Baclofen-enhance inhibitory blockade

Effects on Nerve Axon



Pathogenesis related to DM

- Poorly controlled hyperglycemia.
- Accumulation of sorbitol in nerve cells.
- Decrease in nerve free myoinositol and decreased activity of nerve sodium-potassium adenosine triphosphate.
- Increased nonenzymatic peripheral nerve glycosylation.
- Nerve hypoxia.

Other Causes-1

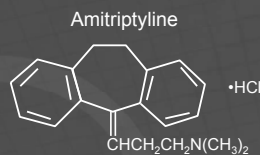
- Diseases
 - A.I.D.S.
 - Herpes Simplex Virus
 - Syphilis
 - Sclerotic/Connective Tissue Disorders
- Back/Tissue Injury
- Iatrogenic Causes

Differential Diagnosis

- Organic Peripheral Neuropathy
- B-12
- Porphyria
- Heavy Metal poisoning
- Collagen Disease
- Cancer
- Lymphoma
- Diabetes

Mechanism of Action Tricyclic Antidepressants

- Amitriptyline
- Imipramine
- Nortriptyline
- Desipramine
- Clomipramine
- Doxepin
- Trimipramine
- Amoxapine
- Protriptyline



Baldessarini, In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed. 2001.

Pharmacological tx PN w/ TCAs

	Dose [mg]	Amine Effects	Sedation	Anticholinergic
3^o Amine TCA				
Amitriptyline [Elavil]	25-300	NE > 5HT	3	3
Clomipramine [Anafranil]	25-300	5HT	2	3
Doxepin [Sinequan]	25-300	NE > 5HT	3	2
Imipramine [Tofranil]	25-300	NE > 5HT	2	2
Trimipramine [Surmontil]	25-300	NE > 5HT	3	3
2^o Amine TCA				
Amoxapine [Asendin]	50-600	NE	1	1
Desipramine [Norpramin]	25-300	NE	0.5	1
Maprotiline [Ludiomil]	25-225	NE	2	2
Protriptyline [Vivactil]	10-60	NE	0.5	2
Nortriptyline [Pamelor]	25-250	NE	1	1

Serotonin Reuptake Inhibitors				
Fluoxetine [Prozac]	5-80	5HT	0.5	0
Fluvoxamine [Luvox]	50-300	5HT	0.5	0
Paroxetine [Paxil]	10-50	5HT	0.5	0.5
Citalopram [Celexa]	10-60	5HT	0.5	0
Sertraline [Zoloft]	50-200	5HT	0.5	0
Escitalopram [Lexapro]	10-20	5HT	0.5	0
Atypical Antidepressants				
Venlafaxine [Effexor]	25-375	5HT > NE	0	0
Duloxetine [Cymbalta]	20-120	5HT > NE	0	0
Bupropion [Wellbutrin]	100-450	NE, DA	0	0
Nefazodone [Serzone]	100-600	5HT > NE	3	0
Trazodone [Desyrel]	50-600	5HT > NE	3	0
Mirtazapine [Remeron]	15-45	NE (?)	3	0
MAOIs				
Nardil (phenelzine)	45-90mg	NE, DA, 5-HT	1	0
Selegiline (Eldepryl)	5-20mg	NE, DA?, 5-HT	0	0
Parnate (Tranylcypromine)	30-60mg	NE, DA, 5-HT	1	0

Anti-depressants, continued

Tricyclic Antidepressants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
<i>Painful DPN</i>				
Max	Amitriptyline (25-150, PBO)	29	12	Pain relief
Max	Desipramine (12.5-150, PBO), Amitriptyline (12.5-150, PBO)	108	14	Pain relief
Sindrup	Desipramine (50 or 200, PBO), Clomipramine (50 or 75, PBO)	26	6	Neuropathy symptoms
Max	Desipramine (12.5-250, PBO)	20	12	Pain relief
<i>PHN</i>				
Watson	Amitriptyline (<=12.5, PBO)	24	8	Pain relief
Max	Amitriptyline (12.5-150, PBO)	58	12	Pain relief
Graff-Radford	Amitriptyline (12.5-200, PBO)	49	8	Pain intensity
Kishore-Kumar	Desipramine (12.5-250, PBO)	26	12	Pain relief
Raja	Nortriptyline (10-160, PBO)	76	24	Pain intensity, relief; cognitive function

Max et al. *Neurology*, 1987;37:589-596; Max et al. *N Engl J Med*, 1992;326:1250-1256; Sindrup et al. *Br J Clin Pharmacol*, 1990;30:683-691; Max et al. *Pain*, 1991;45:3-9; Watson et al. *Neurology*, 1982;32:671-673; Max et al. *Neurology*, 1988;38:1427-1432; Graff-Radford et al. *Clin J Pain*, 2000;16:188-192; Kishore-Kumar et al. *Clin Pharmacol Ther*, 1999;47:305-312; Raja et al. *Neurology*, 2002;59:1015-1021.

Tricyclic Antidepressants: Adverse Effects

- Most common adverse effects
 - Sedation
 - Anticholinergic effects
 - Dry mouth
 - Blurred vision
 - Increased intraocular pressure
 - Mydriasis (pupil dilation)
 - Constipation
 - Paralytic ileus
 - Urinary retention
 - Delayed micturition
 - Urinary tract dilation
 - Hyperpyrexia
 - Sinus tachycardia
- Often have unacceptable side effects in the elderly !

Drug Facts & Comparisons, 2004; AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*, 2002;50(suppl):S205-S224.

SE/Problems of TCAs

- adverse behavior effects
- anticholinergic
- seizures (highest w/ maprotiline)
- autonomic side effects
- cardiac side effects
- lag time = 3-5 days
- troublesome SEs (addressed by SSRIs)
- narrow therapeutic index

Pharmacokinetics & Drug Interactions

Important Considerations when Prescribing RXs for Neuropathy

What is Cytochrome P450?

- CP450 is a group of heme-containing proteins that differ slightly from each other with respect to:
 - MW
 - CO binding spectra
 - electrophoretic properties
 - immunological properties
 - catalytic activities toward different drugs

Why call it Cytochrome P450?

- All these enzymes have a spectral absorbance maximum produced at or near 450nm (actual variant is P448)
- At 448nm CO binds to the enzyme in question in it's reduced state

Slaughter and Edwards, 1995

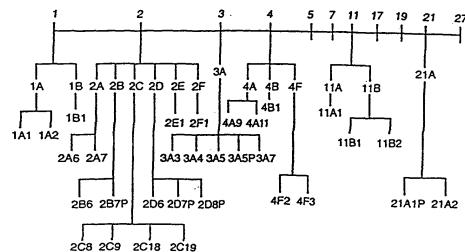
Individual P450 Isoenzymes

- Identified by:
 - spectral properties
 - molecular masses
 - substrate selectivities
 - immunoactivity-Monoclonal Ab specific for different epitopes
- Families:
 - >40% sequence identity are included in same family
 - >55% homology are included in same subfamily

P450 Nomenclature

- Cytochrome is designated CYP
- CYP (#) - # identifying the enzyme family
- CYP (#) (**A,C**) - Subfamily designation
- CYP (#) (**A,C**) (**#**) - Individual enzyme (this is based on when enzyme was discovered)
- EXAMPLES:
 - CYP3A4, CYP2D6, CYP1A2

Cytochrome P450 Enzyme Tree



Adapted from Riddick (1997)

Terminology

- Inducer
- Inhibitor
- Substrate
- What is Genetic Polymorphism?

Are SSRI's Effective for PN?

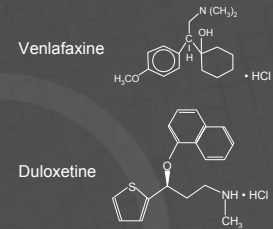
- Paroxetine: Sindrup SH, Gram LF, Broesen K, Aaes-Jorgensen T, Gram LF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990;42:135-44.
- Venlafaxine / Nafazodone?????
 - Galer BS, 1995.
 - Songer DA, Schultz H, 1992.
 - Lang E, Hord AH, Denson D
- Mirtazapine (Remeron)???

Mirtazapine (Remeron)

- Mirtazapine (Remeron)-Chemically unrelated to SSRIs, TCAs, MAOIs
- Analog of Mianserin
- M/A:
 - Blocks presynaptic alpha2 adrenergic receptors (net effect incr. NE release)
 - Blocks postsynaptic 5-HT2 and 5-HT3 receptors (net effect, enhances serotonin release)
- Metabolism: Hepatic P450
 - 1A2, 3A4, 2C9, 2D6/inhibits 1A2, 2D6,3A4
- May also have anxiolytic and sedative effect

Pharmacologic Options: SNRIs

- SNRIs
 - Venlafaxine
 - Duloxetine



Baldessarini. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed. 2001; Physicians' Desk Reference®, 59th ed. 2005.

SNRIs: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
<i>Painful DPN</i>				
Rowbotham	Venlafaxine (75 or 150-225, PBO)	244	6	Mean change in VAS-PI, VAS-PR
Duloxetine Study 1	Duloxetine (20, 60, or 120; PBO)	457	12	End point mean pain score
Duloxetine Study 2	Duloxetine (60 or 120, PBO)	334	12	End point mean pain score

PBO = placebo; VAS-PI = Visual Analog Scale of Pain Intensity; VAS-PR = Visual Analog Scale of Pain Relief; SNRI = serotonin-norepinephrine reuptake inhibitor.

Goldstein DL, et al. Pain. 2005;116:109-118; Rowbotham et al. Pain. 2004;110:697-706; Physicians' Desk Reference®, 59th ed. 2005.

Venlafaxine

- M/A: inhibition of NE and 5-HT as with ?
- active metabolites
- lacks antiACh, adrenergic and histaminergic activity, although may cause somnolence, dry mouth and sweating
- weak inhibitor of cytochrome P450
- dose: up to 375mg/day (split bid-tid)

Duloxetine

- Indication: Diabetic Neuropathy
- M/A: inhibition of NE and 5-HT
- Lacks antiACh, adrenergic and histaminergic activity, although may cause somnolence, dry mouth and sweating
- Substrate of cytochrome P450, 1A2, 2D6
- Dose: up to 120mg/day (qd to bid)

Duloxetine: Additional Safety Information

- Warnings
 - Suicide risk
 - Monoamine oxidase inhibitors (MAOIs)
- Precautions
 - Hepatotoxicity
 - Increased blood pressure (BP) (requires BP lowering and periodic monitoring)
 - Activation of mania/hypomania
 - Seizures
 - Controlled narrow-angle glaucoma
 - Increase in fasting blood glucose
- Drug-drug interactions
 - CYP1A2 inhibitors (eg, cimetidine)
 - CYP2D6 inhibitors (eg, paroxetine)
 - Drugs metabolized by CYP2D6 (eg, amitriptyline)
- Contraindications
 - Hypersensitivity to duloxetine
 - Patients taking MAOIs
 - Uncontrolled narrow-angle glaucoma

Physicians' Desk Reference®, 59th ed. 2005.

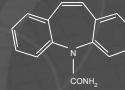
Duloxetine: Dosing

- Major depressive disorder
 - 40 to 60 mg/d given once or twice daily
- Painful DPN
 - 60 mg/d given once daily
 - 120 mg/d not shown to confer additional benefit and is less well tolerated

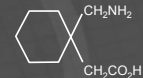
Physicians' Desk Reference®, 59th ed., 2005.

Anticonvulsants

- First generation
 - Phenytoin
 - Phenobarbital
 - Primidone
 - Ethosuximide
 - Carbamazepine
 - Valproic acid
- Second generation
 - Gabapentin
 - Lamotrigine
 - Topiramate
 - Tiagabine
 - Levetiracetam
 - Oxcarbazepine
 - Zonisamide
 - Felbamate



Carbamazepine



Gabapentin

McNamara, In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. 2001; Physicians' Desk Reference®, 59th ed. 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc.; 2004.

Anticonvulsants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
<i>Painful DPN</i>				
Wilton	Carbamazepine (600, PBO)	40	4	Pain relief
Rull	Carbamazepine (600, PBO)	30	6	Neuropathy symptoms
Backonja	Gabapentin (900-3600, PBO)	165	8	Daily pain severity
Eisenberg	Lamotrigine (25-400, PBO)	59	6	Pain intensity
<i>PHN</i>				
Rice	Gabapentin (1800 or 2400, PBO)	334	7	Mean daily pain
Rowbotham	Gabapentin (300-3600, PBO)	229	8	Mean daily pain

Wilton, *S Afr Med J*, 1974;48:869-872; Rull et al. *Diabetologia*, 1969;5:215-219; Backonja et al. *JAMA*, 1998;280:1831-1836; Eisenberg et al. *Neurology*, 2001;57:505-509; Rice, *Maton. Pain*, 2001;94:215-224; Rowbotham et al. *JAMA*, 1998;280:1837-1842.

Anticonvulsants: Safety and Adverse Events

	Carbamazepine*	Gabapentin ^{†‡}	Lamotrigine [§]
Neuropathic pain indication	Trigeminal neuralgia	PHN	Not currently indicated
Most common adverse events	Dizziness Drowsiness Nausea Unsteadiness Vomiting	Dizziness Somnolence Peripheral edema	Vomiting Dyspepsia Dizziness Ataxia Somnolence Incoordination Insomnia Rash Diplopia Blurred vision
Black box warnings	Aplastic anemia and agranulocytosis	None	Severe rash including Stevens-Johnson syndrome

*Frequency not specified; [†]adverse events occurring in >5% of patients and with at least twice the incidence of placebo group; [‡]postherpetic neuralgia; [§]adjunctive therapy in adults with epilepsy.

Physicians' Desk Reference®, 59th ed. 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc.; 2004.

Carbamazepine: Efficacy and Dosing

- Efficacy
 - Indicated for trigeminal neuralgia
 - Significant pain relief compared with placebo shown in DPN trials
- Dosing (trigeminal neuralgia)
 - Beginning dosage: 200 mg/d (2 divided doses)
 - Titration: 100-mg increments every 12 hours
 - Maximum dosage: 1200 mg/d

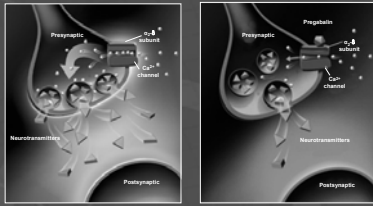
Physicians' Desk Reference®, 59th ed. 2005; Wilton, *S Afr Med J*, 1974;48:869-872; Rull et al. *Diabetologia*, 1969;5:215-218.

General Considerations

Autoinduction
carbamazepine
phenytoin

Plasma Protein Displacement
phenytoin
valproate
carbamazepine

Pharmacology: Gabapentin & Pregabalin Binds to the $\alpha_2\text{-}\delta$ Subunit of Voltage-Gated Ca^{2+} Channels in the Central Nervous System

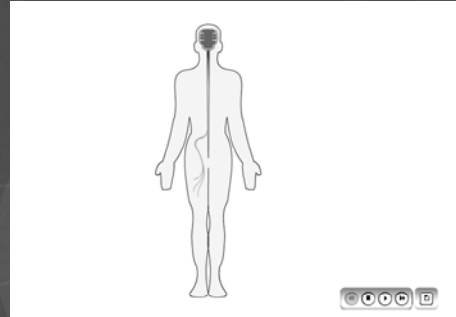


Schematic representation of pregabalin's proposed mechanism of action

- Pregabalin selectively binds to $\alpha_2\text{-}\delta$ subunit of calcium channels
 - Modulates calcium influx in hyperexcited neurons
 - Reduces neurotransmitter release
 - Pharmacologic effect requires binding at this site
 - The clinical significance of these observations in humans is currently unknown

Taylor. CNS Drug Rev. 2004;10:183-188.

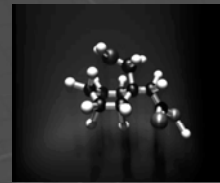
Gabapentin and Pregabalin Mechanism of Action are identical.



Gabapentin

- FDA Approved Indication:
 - post herpetic neuralgia, neuropathic pain, partial seizures
- dose: 900-1800mg (300-3600mg/d) TID
- No protein binding
- SE: generally well tolerated, somnolence, syncope, ataxia

Gabapentin: Chemical Structure



Gabapentin is indicated for the management of PHN in adults. Gabapentin is contraindicated in patients who have a demonstrated hypersensitivity to the drug or its ingredients.

Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

Gabapentin: Mechanism of Action

- Interacts with $\alpha_2\text{-}\delta$ subunit of voltage-gated Ca^{2+} channels
- In animal models
 - Prevents allodynia and hyperalgesia
 - Prevents pain-related responses in models of neuropathic pain
 - Decreases pain-related responses after peripheral inflammation
- Relevance of these models to human pain is not known

Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

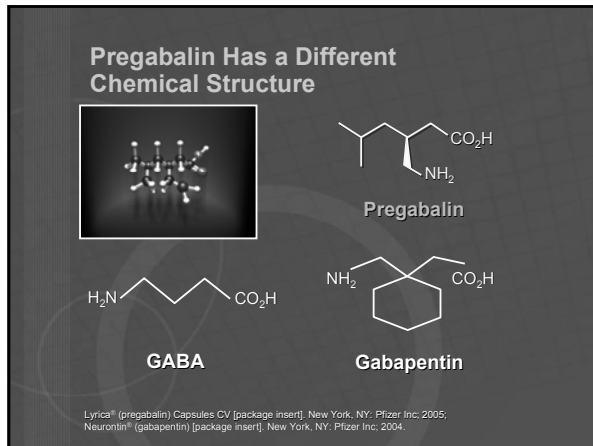
Pharmacokinetic Properties of Gabapentin

- Few drug-drug interactions
- Not protein bound or hepatically metabolized
- No blood level monitoring or liver function testing required

Half-life	Protein Binding	Bioavailability	Metabolism	Excretion
5-7 hours	<3% bound	Approximately 60% (300 mg TID)	Not appreciably metabolized	Renal

Dosage adjustment is recommended in patients with compromised renal function and those undergoing hemodialysis. See full prescribing information for instructions on proper adjustments. In general, dose selection for an elderly patient should be cautious, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

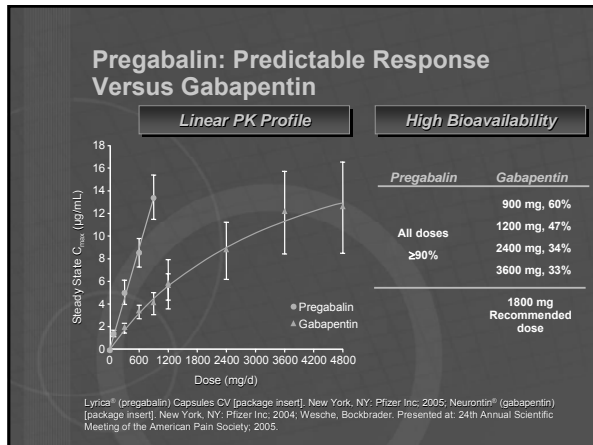
Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.



Pregabalin and Gabapentin Pharmacology Facts

	Pregabalin <chem>CC(C)C(C)CNC(=O)O</chem>	Gabapentin <chem>NC1CCC(CC1)C(=O)O</chem>
FDA-approved pain indication	Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia	Postherpetic neuralgia
Mechanism of action	$\alpha_2\text{-}\delta$ ligand • Selectively binds to the $\alpha_2\text{-}\delta$ site in CNS tissues	$\alpha_2\text{-}\delta$ ligand • Selectively binds to the $\alpha_2\text{-}\delta$ site in CNS tissues
Pharmacokinetic profile	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 at 150 mg/d • Dose range from 150 mg/d to 600 mg/d*	Effective at 1800 mg/d • No additional benefit at higher doses
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

*Some patients with PHN may benefit from up to 600 mg/d given after 2 to 4 weeks of treatment with 300 mg/d. Adverse events may increase with dose. CNS = central nervous system.
Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc; 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.



- ### Antiarrhythmic Agents
- Lidocaine
 - Mexiletine:
 - Kastrup et al. Pain 1987.
 - Dejgard et al. Lancet 1988.
 - Strack et al. Diabetes Care 1992.

- ### My Recommendations
1. TCA's (amitriptyline)- first line???
 2. Elderly (frail) patients TCA vs. SNRIs
 3. Tramadol (Ultram®)
 4. Gabapentin (Neurontin®)
 5. Other Anti-convulsants
 6. Anti-arrhythmics: Mexiletine (Mexitil®)- ECG

	Dose [mg]	Amine Effects	Sedation	Anticholinergic
3° Amine TCA				
Amitriptyline [Elavil]	25-300	NE > 5HT	3	3
Clomipramine [Anafranil]	25-300	5HT	2	3
Doxepin [Sinequan]	25-300	NE > 5HT	3	2
Imipramine [Tofranil]	25-300	NE > 5HT	2	2
Trimipramine [Surmontil]	25-300	NE > 5HT	3	3
2° Amine TCA				
Amoxapine [Asendin]	50-600	NE	1	1
Desipramine [Norpramin]	25-300	NE	0.5	1
Maprotiline [Ludiomil]	25-225	NE	2	2
Protriptyline [Vivactil]	10-60	NE	0.5	2
Nortriptyline [Pamelor]	25-250	NE	1	1
Serotonin Reuptake Inhibitors				
Fluoxetine [Prozac]	5-80	5HT	0.5	0
Fluvoxamine [Luvox]	50-300	5HT	0.5	0
Paroxetine [Paxil]	10-50	5HT	0.5	0.5
Citalopram [Celexa]	10-60	5HT	0.5	0
Sertraline [Zoloft]	50-200	5HT	0.5	0
Escitalopram [Lexapro]	10-20	5HT	0.5	0
Atypical Antidepressants				
Venlafaxine [Effexor]	25-375	5HT > NE	0	0
Duloxetine [Cymbalta]	20-120	5HT > NE	0	0
Bupropion [Wellbutrin]	100-450	NE, DA	0	0
Nefazodone [Serzone]	100-600	5HT > NE	3	0
Trazodone [Desyrel]	50-600	5HT > NE	3	0
Mirtazapine [Remeron]	15-45	NE [?]	3	0
MAOIs				
Nardil (phenelzine)	45-90mg	NE, DA, 5-HT	1	0
Selegiline (Eldepryl)	5-20mg	NE?, DA?, 5-HT	0	0
Parnate (Tranylcypromine)	30-60mg	NE, DA, 5-HT	1	0

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Neuropathy Pre/Post Test Questions

1. List two different THERAPEUTIC classes of drugs that are used to treat peripheral neuropathy.
(incorrect examples: antibiotics, antiretrovirals, calcium channel blockers, diuretics)
 - a.
 - b.

2. Which SSRI/SNRI would be suitable for treating neuropathic pain, based on it's mechanism of action?
 - a. venlafaxine
 - b. duloxetine
 - c. gabapentin
 - d. clomipramine
 - e. a and b above

3. Which of the following therapies for the treatment of peripheral neuropathy is/are enzyme inducers?
 - a. erythromycin
 - b. carbamazepine
 - c. theophylline
 - d. fluoxetine
 - e. fluvoxamine

4. True or False: Gabapentin is extensively metabolized in the liver by the Cytochrome P450 system.

Answer Key

1. Antipsycotics, antidepressants, anticonvulsants, antiarrhythmics
2. E
3. B
4. False