

# Neuropathic Pain and Paresthesias

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## Neuropathic Pain

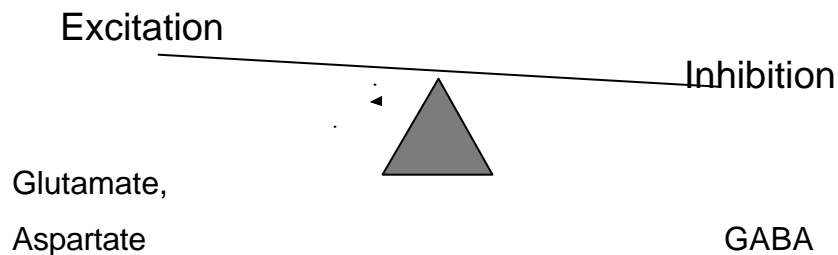
- Neuropathic pain affects 3.5 to 4 million Americans
- The Joint Commission on Accreditation of Healthcare Organizations has mandated pain as the “Fifth” Vital Sign  
BP, Resp , Pulse, Temp and Pain
- Implemented by Congress in Jan 2001
- Congressionally declared medical decade (1990s decade of the brain; 2000 Bone and Joint)



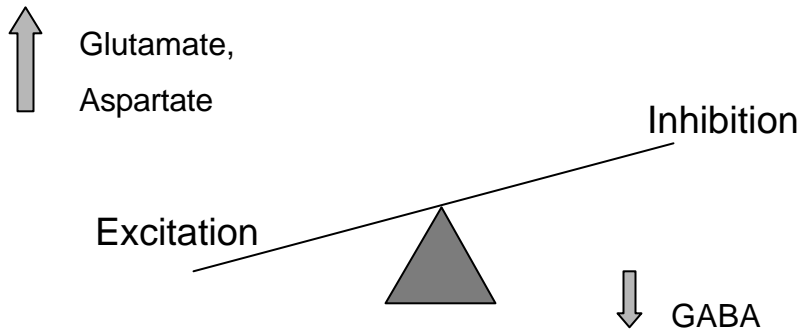
## Definition

- Neuropathic pain is defined by the International Association for the Study of Pain
- As pain initiated or caused by a primary lesion or dysfunction in the nervous system
- Nociceptive pain is evoked by noxious stimulus (damaging to normal tissues), thus represents a protective mechanism
- Neuropathic pain does not

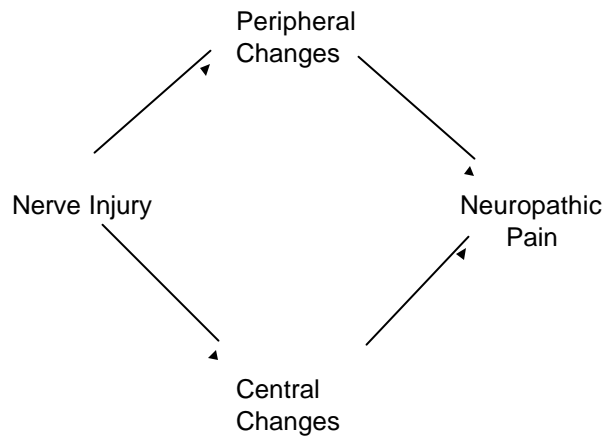
## Normal CNS Function



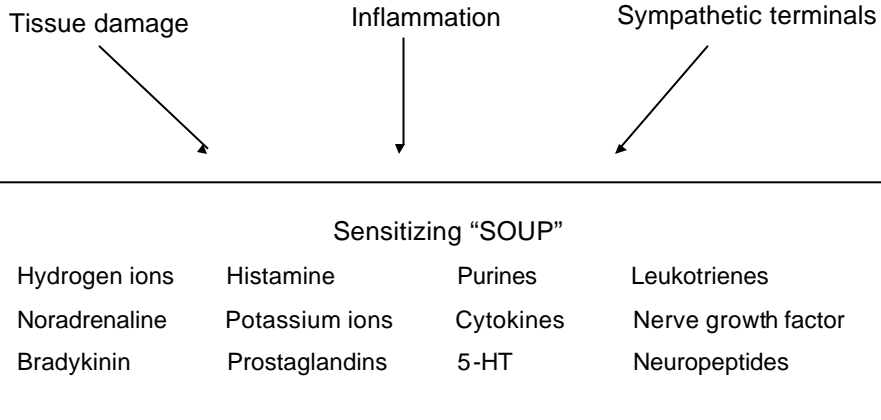
# Abnormal Excitation



# Nerve Injury Leads to Peripheral and Central Changes



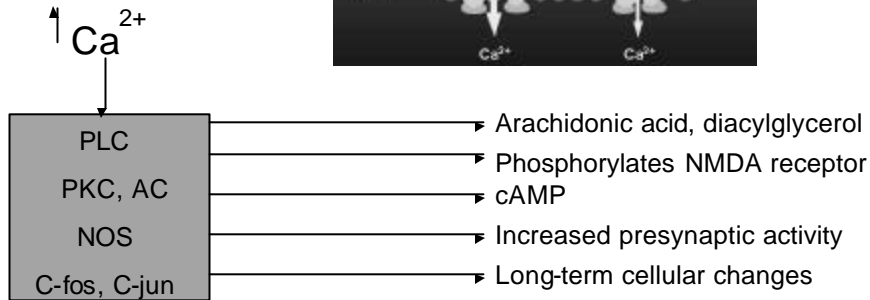
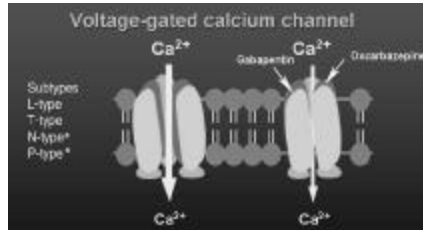
# Peripheral Sensitization



Woolf CJ et al. *Anesth Analg* 1993, 77: 1-18.

Erlanger and Gasser	Lloyd and Hunt (Sensory)	Diameter (nm)	Velocity (m/s)	Function M=motor S=sensory
Aa	Ia	10-20	50-120	M: $\alpha$ motor neuron S: spindle afferents
Aa	Ib	10-20	50-120	S: Golgi tendon organ, touch, pressure
Ab	II	4-12	25-70	M: motoneurons to intra/extrafusal muscle fibers S: secondary spindle afferents, touch, pressure, vibration, proprioception
Ag	·	2-8	10-50	M: g motor neurons to intrafusal muscle fibers
Ad	III	1-5	3-30	S: small touch, pain, temperature
B	·	1-3	3-15	M: small unmyelinated preganglionic autonomic
C	IV	<1	<2	M: all post ganglionic autonomic fibers S: pain, temperature

## Mechanisms of Neuropathic Pain



PLC=phospholipase C; PKC=protein Kinase; AC=adenyl cyclase; NOS=nitric oxide synthase; cAMP=cyclic adenosine monophosphate

## Na Channelopathies

- 9 different genes encode distinct voltage-gated  $Na^+$  channels
- Selective expression of these different genes provide for different ensembles of  $Na^+$  channel
- Different ensembles provide different functional properties for different neurons

Waxman SG. Neurology 56(12), 2001.

## Na Channelopathies

- Genetic channelopathies
  - Mutation of genes can produce abnormal channel proteins
    - Fail to function
    - Function abnormally
- Acquired channelopathies
  - Peripheral nerve injury

Waxman SG. Neurology 56(12), 2001.

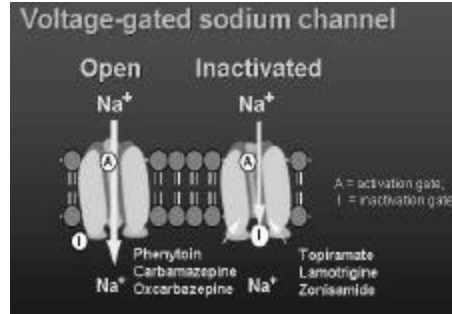
## Na Channelopathies

- Paresthesias and neuropathic pain arise, at least in part, from abnormal firing of injured axons/DRGs
- Electrophysiologic studies have shown that it is Na<sup>+</sup> channels that cause this neural hyperexcitability
  - “slow depolarization”
  - Seen also in “chronic constriction” nerve injury models associated with allodynia and hyperalgesia

Waxman SG. Neurology 56(12), 2001.

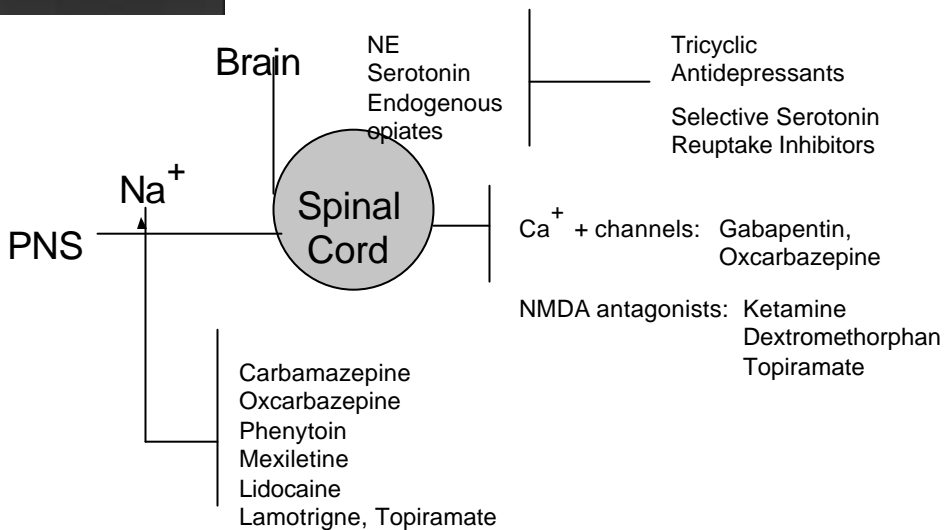
# Na Channelopathies

- Molecular identification and characterization of these Na<sup>+</sup> channels in nerve injury models
  - Turning off of previously active Na<sup>+</sup> channel genes in DRG
  - Turning on of other previously silent Na<sup>+</sup> channel genes in DRG



Waxman SG. Neurology 56(12), 2001.

# Peripheral and Central Mechanisms



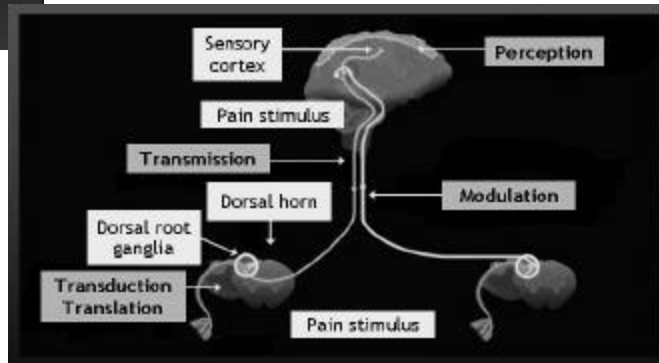
## Peripheral and Central Mechanisms

- Peripheral
  - Sensitization of peripheral neurons
  - Collateral sprouting of A fibers
  - Increased activity of damaged axons and their sprouts
- Central
  - Central sensitization
  - Reorganization of synaptic connectivity
  - Disinhibition

## Hyperalgesia

- Increased response to a painful stimulus
  - Pinprick pain
  - Heat
- Acute inflammatory type of pain
- C fiber mediated
- Normally seen in an area of scar that becomes hypersensitive

## Central Sensitization



- Increased nociceptor drive leads to central sensitization of dorsal horn neurons. A  $\beta$  fiber input is now sufficient to activate spinal cord pain pathways.

Woolf CJ, Mannion RJ. *Lancet* 1999; 353:1959-1964.

## Allodynia

- The interpretation of a non-painful stimulus as being painful
- The result of a qualitative change in the interpretation of a stimulus
  - Dynamic A  $\beta$  fiber mediated
  - Static C fiber mediated

## A b fiber sprouting and disinhibition

- After a nerve injury, C fiber terminals atrophy
- A  $\beta$  fiber terminals sprout into the superficial dorsal horn
- Further, nerve injury reduces inhibitory input and thus increases excitability in dorsal horn neurons
- Now primary afferent input evoke a much greater response
- Dorsal neurons may fire spontaneously

Woolf CJ, Mannion R.J. *Lancet* 1999; 353:1959-1964.

## Hyperpathia

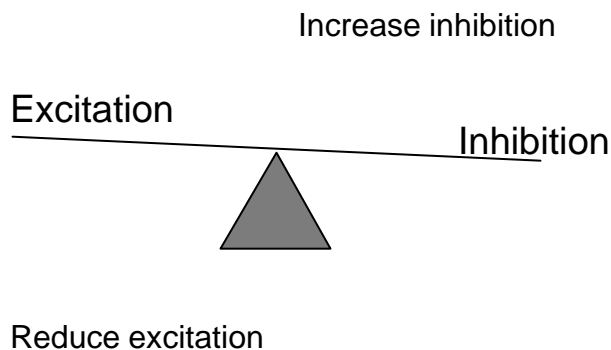
- An exaggerated and prolonged response to a painful stimulus (EMG/NCS – normally painful, but felt as intense pain)
- A quantitative change in the interpretation of a stimulus
  - Drop out of interneurons that normally inhibit and dampen the signal
  - Ungated flow due to DISINHIBITION

## Spontaneous Stimuli

- Peripheral/DRG sodium channel function
  - Sprouting of sympathetic nerve terminals
- Paresthesia- burning , tingling, numbness, skin crawling, buzzing, itching, "pins and needles" feeling
  - Arises spontaneously without apparent stimulus
  - Usually not painful
- Dysesthesia
  - Painful or unpleasant

DRG=dorsal root ganglia

## Restoring Balance



## Pain! Which Pain?

*Inflammatory pain* (e.g. rheumatoid arthritis)

- Nociceptor activation
- Severity of pain = severity of disease

Physiology of pain

*Chronic neuropathic pain* (e.g. pain multiple sclerosis)

- Nervous system is changed
- Severity of pain = degree of neuroplasticity

Pathophysiology of pain

## Neuropathic Pain Symptoms

- Spontaneous stabbing
- A  $\beta$  dependent mechano - allodynia
- Movement or vibration produces electric shock like pain
- Palpation evokes radiating pain

# Neuropathic Pain

## *Syndromes (common examples)*

- Painful diabetic neuropathy
- Postherpetic neuralgia
- Trigeminal neuralgia
- Traumatic neuralgia – complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD), post amputation
- Radiculopathies (cervical, thoracic, lumbosacral)
- Cancer-related neuropathic pain
- Central pain syndrome – spinal cord, brainstem, brain (thermonociceptive pathways and relays)

# Neuropathic Pain Patterns

- |                              |                              |
|------------------------------|------------------------------|
| • <u>Central examples</u>    | • <u>Peripheral examples</u> |
| Hemicord (B-S syndrome)      | Mononeuropathy               |
| Transverse myelitis          | Mononeuropathy multiplex     |
| Disseminated myelopathy (MS) | Brachial plexopathy          |
| Brainstem syndromes          | Lumbosacral plexopathy       |
| Thalamic lesions             | Monoradiculopathy            |
| Cortical lesions             | Polyradiculopathy            |
|                              | Polyradiculoneuropathy       |

# Neuropathic Pain

## *Etiologies*

- Injury
- Compression
- Inflammation
- Ischemia
- Infections
- Demyelination
- Axonopathies
- Metabolic / toxic
- Neoplasm

# Complexity of Neuropathic Pain

## *Sensory abnormalities*

- Positive sensory phenomena
  - Ongoing spontaneous pain
  - Spontaneous paroxysms
  - Hyperalgesia
- Negative sensory phenomena
  - Sensory deficits at varying degrees to any or all sensory modalities (light touch, pain...)

## *Can be seen in concert with motor abnormalities*

- Negative motor phenomena
  - Weakness
  - Clumsiness
  - Fatigue
- Positive motor phenomena
  - Tremor
  - Dyskinesias
  - Ataxia
  - Dystonia

## **How do we assess it? Neuropathic Pain Scales**

- The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale
- Galer and Jensen 1997
- Brief Pain Inventory

Modest changes in pain numeric rating scale scores (2 to 3 points) are associated with clinically meaningful changes in patient and physician impressions of overall improvements

Galer BS, Jensen MP. *Neurology* 1997; 48:332-338.

Bennett M. *Pain* 2001; 92: 147-157.

Breitbart W. et al *Pain* 1996

Farrar JT et al. *Pain* 2001; 94:149-158.



# Pain Assessment

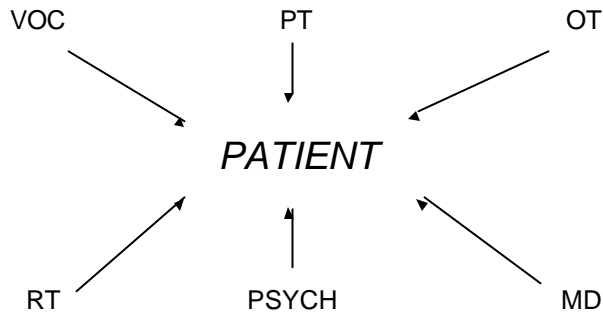
Items/Issues	Questions
Onset	When and how did the pain start?
Location (s) / site (s)	Where is (are) pain (s) located?
Temporal profile	What has happened since onset?
Characteristics / quality of pain (s)	Describe the pain.
Severity	How severe is the pain?
Unpleasantness / distress	How unpleasant is the pain?
Associated symptoms	Are there any other symptoms, such as numbness, weakness, bowel / bladder dysfunction, or insomnia?
Psychological factors	Does the patient suffer from depression? Anxiety?
Aggravating factors	What makes the pain(s) worse?
Alleviating factors	What makes the pain(s) better?
Impact of function and activities	How are work and daily activities affected? Is the patient active in recreational pursuits?



# Pain Assessment (cont'd)

Items / Issues	Question
Response to past treatments	What prior treatments has patient received?
Habits	Does the patient smoke? Drink? Use illegal drug? If yes, how much and how often?
Coping skills	How is the patient coping with pain?

## Bio-psycho-social Disease



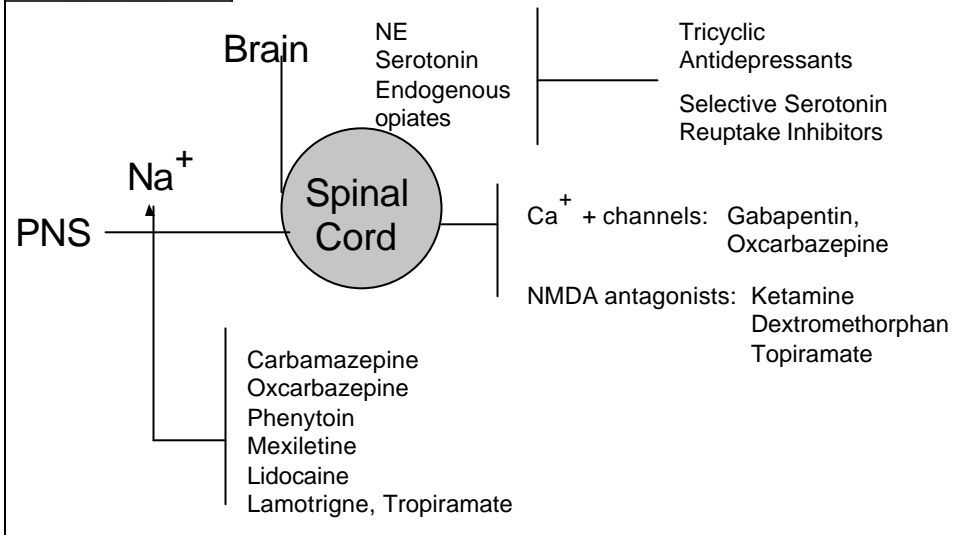
## Treatment of Neuropathic Pain

- Determination of mechanisms
  - neuropathic
  - bony, lig, referred
  - inflammatory
- Specific therapy

Targets underlying cause (ie spasticity)  
 Targets pain characteristics  
 Targets putative pathophysiological mechanisms

Thermal Biofeedback	Heat	Massage
Herbal Medicine	Progressive Muscle Relaxation (PMR)	
	Blood Flushing	
Acupuncture	Diaphragmatic Breathing	
Occlusal Adjustment	Placebo	
<b>TENS</b>		
<b><u>BIOFEEDBACK</u></b>		
YOGA	Physical Therapy	Meditation
	Galvanic Skin Response (GSR)	Relaxation
Electromyography (EMG) Biofeedback	Hypnosis	Autogenics
Chiropractic Adjustment	Ice	Occlusal Splint

## Neuropathic Pain Agents and Their Site of Action

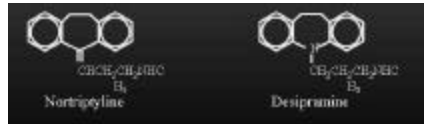
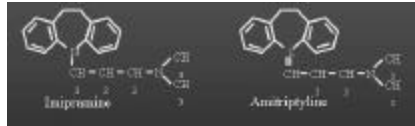


## Pharmacologic Management of Neuropathic Pain

Antidepressants	Amitriptyline, imipramine, desipramine, nortriptyline, SSRI
Anticonvulsants	Carbamazepine, oxcarbazepine, clonazepam, gabapentin, lamotrigine, phenytoin, valproic acid, topiramate
Antiarrhythmics	Lidocaine, mexiletine
Topical formulations	Capsaicin, lidocaine, aspirin
Others	Tramadol, NMDA antagonists, clonidine, opioids

## TCAs in Postherpetic Neuralgia

- Watson et al. (1982)  
Amitriptyline vs placebo
- Max et al. (1988) Amitriptyline vs placebo
- Kishore-Kumar et al (1980)  
Desipramine vs placebo
- Watson et al. (1992)  
Amitriptyline vs maprotiline
- Watson and Evans (1985)  
Amitriptyline vs zimeldine (SSRI)



SSRI=selective serotonin reuptake inhibitor  
Max MB. *Ann Neurol* 1994; 35(suppl):s50-s53.

## Common Side Effects Associated with TCAs

	Sedation	Anti Cholinergic effects	Hypo-tension	Cardiac effects	Seizures	Weight gain
Amitriptyline	+++	+++	+++	+++	++	++
Clomipramine	++	+++	++	+++	+++	+
Desipramine	o/+	+	+	++	+	+
Nortriptyline	+	+	+	++	+	+

American Geriatrics Society has recommended that TCAs be used cautiously in those over age 65 due to anticholinergic side effects

o/+ = minimal; + = mild; ++ = moderate; +++ = moderately severe.

Hardman JG, Limbird LE, Motinoff PB, Rudden RW, Gilman AG, eds.

Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 9<sup>th</sup> ed. New York: McGraw-Hill. 1996

AGS J Am Geriatrics Soc 50:205-244;2002

## **SSRIs in Painful Diabetic Neuropathy (PDN)**

- Serotonin
  - paroxetine [Paxil] (20 mg -40 mg / day)
  - citalopram [Celexa] (20 mg -40 mg / day)
- Serotonin and Norepinephrine
  - venlafaxine [Effexor] (150 mg to 225 mg)

## **NMDA Antagonists and PDN**

- Animal and pilot data suggest that NMDA receptor blockade may alleviate neuropathic pain
- Significant side effects from NMDA antagonists (MK 801, Ketamine, phencyclidine)
- High doses of low affinity, noncompetitive, NMDA-receptor antagonists (dextromethorphan, remacemide) may have a better therapeutic ratio

## Topical Medications

### Capsaicin

- Inconsistent trial results; potential burning upon application

### EMLA Cream

- May help some patients with allodynia

### Clonidine gel

- Pilot studies suggest efficacy; controlled trial in progress

### Unstudied custom compounds

- Doxepin, other TCAs, gabapentin, opioids, ketamine, guanethidine

### Lidocaine patch 5%

{intravenous lidocaine Nadine Attal Neurology 54:564-74:2000 }



## Anticonvulsant drugs and Neuropathic Pain

### — First-generation —

- Carbamazepine<sup>A</sup>
- Divalproex sodium<sup>B</sup>
- Phenytoin<sup>A</sup>
- Valproic acid<sup>B</sup>
- Clonazepam<sup>B</sup>
- Phenobarbital<sup>B</sup>

### — Second-generation —

- Gabapentin<sup>A</sup>
- Lamotrigine<sup>A</sup>
- Levetiracetam<sup>B</sup>
- Oxcarbazepine<sup>A</sup>
- Tiagabine<sup>B</sup>
- Topiramate<sup>B</sup>
- Zonisamide<sup>B</sup>

A Published randomized controlled trials

B Clinical anecdotal and/or published case series.

## Mechanisms of Action of Phenytoin

- Slows recovery rate of voltage-activated Na<sup>+</sup> channels, limiting repetitive firing
- May inhibit somatostatin release
- Conflicting studies on efficacy

Saudek CD et al. *Clin Pharmacol Ther* 1977;22:196-199.

Chadda VS, Mathur MS. *J Asso Physicians India* 1978; 26:403-406.

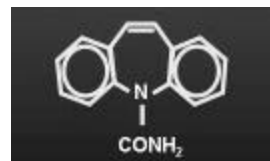
Hardman JG, Limbird LE, Molinoff PB, Rudden RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9<sup>th</sup> ed. New York: McGraw-Hill, 1996.

Reichin S, Mothon S. *Ann Neurol* 1991;29:413-417.

## Pharmacologic Properties of First Generation Anticonvulsants

- Slows recovery rate of voltage-activated Na<sup>+</sup> channels, limiting repetitive firing
- May inhibit release of somatostatin
- Some calcium antagonistic effect
- Tricyclic like compound, similar efficacy profile as the TCAs
- median dose 600 mg/day

### Carbamazepine



Trigeminal Neuralgia

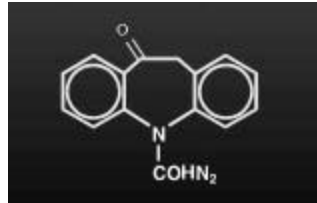
**Aplastic anemia**

Rull JA et al. *Diabetologia* 1969; 5: 215-218.

## Pharmacologic Properties of Second- Generation Anticonvulsants

- Slows recovery rate of voltage-activated Na<sup>+</sup> channels, limiting repetitive firing
- Modulates high-threshold N- and P-type calcium channels
- Reduces glutamatergic transmission

### Oxcarbazepine (OXC)



Trigeminal Neuralgia

Aplastic anemia

## Pharmacologic Properties of Second-generation Anticonvulsants

### Gabapentin

- Increases GABA in brain, possibly by enhancing rate of synthesis from glutamate
- Binds to voltage dependent Ca<sup>+</sup> channel
- Inhibits sodium currents by mechanism distinct from phenytoin and carbamazepine
- Inhibits branched-chain amino acid transferase, possibly reducing glutamate concentration
- No effect on GABA<sub>A</sub> or GABA<sub>B</sub> receptors

Upton N. *Trends Pharmacol Sci* 1994; 15:456-463.  
Chadwick D. *Lancet* 1994; 343: 89-91.  
Petroff O et al. *Ann Neurol* 1996; 39:95-99.  
Goldlust A et al. *Epilepsy Res* 1995; 22:1-11.

## Gabapentin in Neuropathic Pain Double-Blind, placebo-controlled studies

Study/ year	indication	N	Dose (mg/day)	Duration (weeks)	Results
Backonja 1998	DPN	165	900- 3600	8	positive
Rowbotham 1998	PHN	225	1200- 3600	8	positive
Rice 2001	PHN	334	1800 or 2400	7	positive
Serpell	Neuropathic pain	305	900- 2400	8	positive

## Gabapentin in PDN

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel design trial in 165 patients titrated up to 3600 mg/day
- Average daily pain score dropped from 6.4 to 3.9 on gabapentin compared with a drop from 6.5 to 5.1 for placebo ( $p < .001$ )
- Most common adverse events of GBP were dizziness, somnolence, ataxia

Backonja M, et al. *JAMA* 1998; 280:1831-1836.

## Mechanisms of Action of Topiramate (TPM)

- Blocks voltage-gated Na<sup>+</sup> channels
- Blocks kainate and AMPA subtypes of the glutamate (non-NMDA) receptor
- Enhances GABA<sub>A</sub> receptor actions by interaction with a nonbenzodiazepine receptor

Ben-Menachem E. In: *Antiepileptic drugs*. 4<sup>th</sup> ed. New York: Raven Press, 1995:1063-1070.

## Topiramate (TPM) in PDN

- Double-blind, placebo-controlled (2:1) trial of 13 weeks duration in 27 patients
- TPM titrated over 9 weeks up to 400 mg/day
- Average daily pain score dropped from 6.9 to 4.1 on TPM compared with an increase from 6.5 to 7.0 for placebo (p=.007)
- 5/18 patients (28%) on TPM exited because of intolerable adverse events - Concentration/language problems, psychomotor slowing

Edwards KR et al. Presented at the 18<sup>th</sup> Annual Scientific Meeting of the American Pain Society; October 21-24;1999; Fort Lauderdale, FL.

## Mechanisms of Action of Lamotrigine (LMG)

- blocks voltage-activated Na<sup>+</sup> channels presynaptically
- Inhibits neurotransmitter glutamate release
- 2 studies showing effectiveness in central pain (stroke and spinal cord) at doses of 200 -400 mg/day
  - Vestergaard 2001 Neurology : 56:184-190
  - Finnerup 2002 Pain 96:375-383
- 1 PDN Eisenberg 2001 Neurology 57: 505-509
- Significant concerns: necrolyzing rash, Stevens-Johnson

## Antihyperalgesics/ Anticonvulsants/ Neuromodulators?

Mechanisms of Action	Drugs
Na <sup>+</sup> channel blocker	*Carbamazepine *Phenytoin *Lamotrigine *Valproate *Oxcarbazepine *Zonisamide
Ca <sup>++</sup> channel blocker	*Ethosuximide *Gabapentin *Oxcarbazepine *Zonisamide
GABA receptors	*Barbiturates *Benzodiazepines
GABA metabolism	*Vigabatrin *Tiagabine *Valproate *Gabapentin
Glutamate receptors	*Carbamazepine *Lamotrigine *Felbamate *Topiramate
Glutamate metabolism	* Gabapentin

## Conclusions

- Neuropathic pain can be difficult to diagnose, is often misdiagnosed and likely underreported
- Treating only the inflammatory (nociceptive) component of chronic pain will be ineffective
- The triad of pain, mood disorders and functional impairment, including sleep disorders, must be addressed
- Modest improvements in pain scores reported by patient can mean improved quality of life – the ultimate goal of treatment
- No one agent is approved
- Medications should be prescribed with careful consideration of intended effect
- “Rational polypharmacy” may be necessary to target symptoms

## Other Options

Future: With the availability of intrathecal pump systems, move toward the delivery of these medications intrathecally

Surgical Options:

Nerve lesioning-transection of spinal nerves (DREZ, cordotomies)

Brain and Spinal Cord Stimulators

Neuropathic Pain: Insights Into the Spectrum and Innovative Approaches to Treatment  
Dannemiller Foundation and Embryon: San Antonio, Texas  
And Pfizer Unrestricted Educational Grant