

Pharmacologic Management of Neuropathic Pain

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Objectives

At the conclusion of this presentation, pharmacists will be able to:

1. Differentiate between nociceptive and neuropathic pain
2. Identify classes of drugs commonly used to treat neuropathic pain
3. Correlate pharmacologic actions of medications to sites of action within the nervous system (rational polypharmacy)

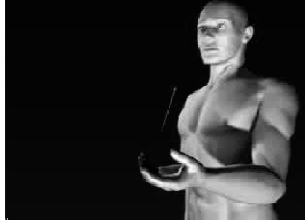
Types of Pain

- Nociceptive (somatic or visceral)
dull, aching, well localized or referred to distant sites
- Neuropathic
sharp, burning, shooting, stabbing, tingling, hot, cold, numb

Nociceptive Pain Examples

- Rheumatoid or osteoarthritis
- Myofascial pain
- Fibromyalgia
- Ischemic disorders
- Chronic back pain
- Ulcerative colitis, etc.

Pain Signaling



Neuropathic Pain

- Distinctly different from nociceptive pain
- Sustained by abnormal processing of sensory input by the peripheral or central nervous system
- Vast number of pain syndromes exist
- Often difficult to treat
- Relief may not be complete
- Drugs have "incomplete" efficacy and dose-limiting side effects

Neuropathic Pain Examples

- Trigeminal neuralgia
- Post-herpetic neuralgia
- Post-stroke pain
- Phantom pain
- Diabetic neuropathy pain

Peripherally Generated Neuropathic Pain

- painful polyneuropathies: pain felt along the distribution of diffuse peripheral nerves
- painful mononeuropathies: associated with peripheral nerve injury, pain felt along the distribution of the damaged nerve

Manifestations of Neuropathic Pain

Stimulus Independent

- persistent or paroxysmal
- shooting, lancinating, burning, tingling, aching, or cramp-like pain in deep tissue

■ Stimulus Evoked

- hyperalgesia
- allodynia

Neuropathic Pain: Stimulus Independent

- Constant, burning dysethetic* pain
 - often associated with aching or cramp-like pain in deep tissue
 - sometimes described as if the involved area were “on fire”
- May be severe pressure-like sensation, as if the involved limb were about to explode

*impairment of sensation, disagreeable sensation

Neuropathic Pain: Stimulus Independent

- Paroxysmal pain
 - usually fleeting and intense, shock-like or lancinating
 - can be spontaneous or evoked by movement or tactile stimulation

Neuropathic Pain: Stimulus Evoked

- Allodynia: perception of pain in response to what is normally an innocuous stimulus:
 - contact of clothing or gentle breeze across skin: unbearable pain
 - perception of ice as intense heat
- Hyperalgesia: exaggerated response to physical stimuli
 - intensely painful response to modest irritation such as pinprick

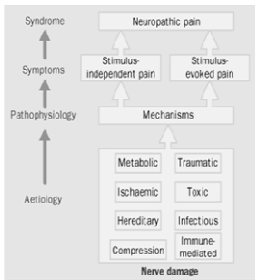
	Neuropathic Pain: Sympathetic Involvement
	<ul style="list-style-type: none">■ CRPS: evidence of autonomic instability<ul style="list-style-type: none">– involved limb swells, abnormal sweating– changes in skin, nails, bones

	Underlying Etiology: Peripherally Generated NP
	<ul style="list-style-type: none">■ Metabolic disorders: diabetes, renal failure, alcohol abuse, niacin deficiencies■ Infectious or postinfectious causes: HIV, Lyme disease, postherpetic neuralgia■ Toxin induced: heavy metals (arsenic), vincristine, cisplatin■ Immune mediated: vasculitis■ Inherited disorders

	Underlying Etiology : Centrally Generated NP
	<ul style="list-style-type: none">■ Caused by a lesion or dysfunction in the CNS<ul style="list-style-type: none">– One theory is that pain is the result of activity produced by an irritable focus created at the site of injury, an ectopic focus

	Centrally Generated NP Examples
	<ul style="list-style-type: none">■ Vascular lesions in brain and spinal cord■ Multiple sclerosis■ Traumatic spinal cord injury■ Tumors■ Abscesses■ Inflammatory diseases: myelitis caused by viruses, syphilis■ Epilepsy■ Parkinson's disease

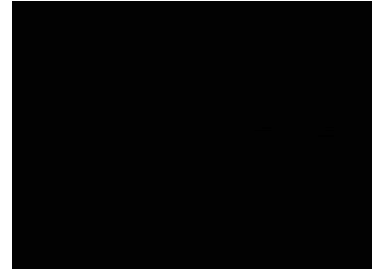
Manifestation & Physiology of Neuropathic Pains



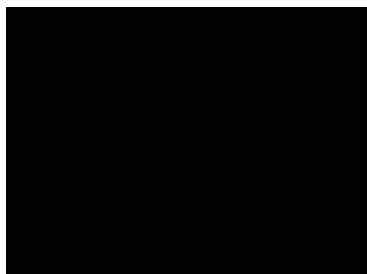
- **Possible Mechanisms of Neuropathic Pain:**
 - **Peripheral sensitization**
 - **Ectopic foci of hyperexcitability in neuron**
 - **Sympathetic maintained activity**
 - **Loss of inhibition of dorsal horn neuron**
 - **Central sensitization**
 - **Rewiring of synaptic connection in the dorsal horn**
 - **Phenotypic switch**

Woolf CJ, et al. Neuropathic Pain: Aetiology, Symptoms, Mechanisms and Management. *Lancet*. 1999;353:1959-64

Neuropathic Pain: ectopic activity



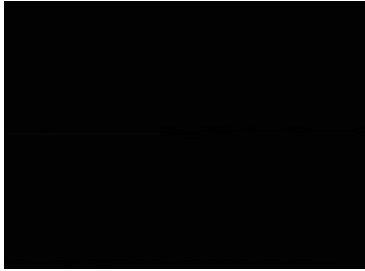
Neuropathic Pain: ephaptic activity



Central Sensitization

- Central neurons at the level of the spinal cord become hyperexcitable following a peripheral nerve injury
 - This is called central sensitization and contributes to the pain of peripheral neuropathies
- Transmitters released in the dorsal horn include glutamate and others
 - Glutamate binds to NMDA receptors
 - Wind-up phenomenon

Neuropathic Pain: wind-up



Summary: Manifestations, Etiology & Pathophysiology

- Diverse sets of diseases
- No single mechanism for a defined disease state
- Different pain symptoms from same mechanism
- Same pain symptoms from different mechanism
- Multiple overlapping mechanisms possible for pain symptoms
- Can not predict mechanism based on pain symptoms

Otto M, et al. Pain Phenomena and Possible Mechanisms in Patients with Painful Polyneuropathy. *Pain*.2003;101:187-192

Neuropathic Pain: Assessment

- Based on underlying pathophysiology
 - provide benefit in determining differential diagnosis
 - **provides no benefit in determining clinical management**
- Galer Neuropathic Pain Assessment
 - Provides information about the type and degree of sensations felt.
 - Evaluates 8 common qualities (sharp, dull, hot, cold, sensitive (like raw skin or sunburn), itchy and deep versus surface pain)
 - Each item is rated on a 0-10 scale

Galer BS, et al. Development and Preliminary Validation of a Pain Measure Specific to Neuropathic Pain: The Neuropathic Pain Scale. *Neurology*. 1997;48:332-338
HT Benzon. The Neuropathic Pain Scales. *Reg Anesth and Pain Med*. 2005;30:417-421

Management of NP

- Aggressively manage the underlying disease
- Similar pharmacologic management for neuropathic pains of diverse etiologies

Drugs for Neuropathic Pain

- Antidepressants
- Anticonvulsants
- Local Anesthetics
- Opioids
- Others

Antidepressants

- Analgesic effect does not depend on antidepressant activity
- Effective dose often lower than antidepressant dose, onset of analgesia sooner
- Block reuptake of norepinephrine and serotonin in spinal cord: affect modulation, enhance descending inhibitory pathways

Antidepressants

- Tricyclics
- Non-tricyclic dual reuptake inhibitors (SNRIs)
 - venlafaxine and duloxetine
- SSRIs
 - All are effective antidepressants
 - SSRIs not conclusively proven effective against NP

Tricyclic Antidepressants

- Amitriptyline, imipramine, clomipramine, nortriptyline, desipramine, maprotiline
- Most studied, particularly for diabetic neuropathy pain
- Generally least tolerated in elderly
- Risk of conduction abnormalities: get baseline EKG

Tricyclics

- Advantages
 - can get some relief with most chronic pain syndromes
 - no end organ damage
- Disadvantages
 - side effects persistent and troublesome
 - many pain syndromes don't respond well
 - therapeutic ceiling

Side Effects

- Sedation (often helpful)
- Orthostatic hypotension
- Anticholinergic effects
 - Dry mouth
 - Blurred vision
 - Urinary retention
 - Constipation
- Weight gain
- Cardiac arrhythmia (usually atrial tachycardias)

Tricyclics

Drug	Trade Name	Starting Dose (Range)	Sedation	Anticholinergic	Orthostatic Hypotension
Amitriptyline	Elavil	25-75	+++	+++	++++
Desipramine	Norpramin	50-100	+	+	++++
Doxepin	Sinequan	10-50	+++	+++	++
Imipramine	Tofranil	25-50	++	++	++++
Nortriptyline	Pamelor	10-50	+	+	++

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- duloxetine (Cymbalta®)
 - first drug released for both depression and NP
 - 60 mg/d
 - nausea : start with 30 mg/d
 - effect within a week?
- venlafaxine (Effexor®)
 - fewer side effects than TCAs
 - 75 mg/d, increase by 75 mg each week; max 225 mg/d of extended release; 375 mg/d standard drug
 - effect in 2-4 weeks
- desvenlafaxine (Pristiq®)
- milnacipran (Savella®)

SSRIs

- Evidence for modest analgesic effect with paroxetine and citalopram
- Others by relieving depression, may reduce pain
- Most prescribed antidepressants
- Drugs of choice for GAD
- SSRIs inhibit CYP 2D6

Traditional Anticonvulsants

- Carbamazepine (Tegretol)
- Phenytoin (Dilantin)
- Valproic acid (Depakote)
- Clonazepam (Klonopin)

2nd Generation Anticonvulsants

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Levetiracetam (Keppra)
- Oxcarbazepine (Trileptal)
- Zonisamide (Zonegran)

Gabapentin

- Blocks $\alpha_2\delta$ subunit of voltage-dependent calcium channel
- Reduce influx of Ca^{2+} , less glutamate released from nerve endings
- Not metabolized, few drug interactions
- Sedation common; ataxia, peripheral edema, dizziness, diplopia, nausea
- Start 100-300 mg tid
 - At least 1800 mg/d usually needed
 - 3600-4800 mg/d good trial

Gabapentin

- Gabapentin absorbed by an L-amino acid transporter in the proximal small bowel
- Capacity limited, becomes saturated at high doses

Pregabalin (Lyrica®)

- Also an $\alpha_2\delta$ ligand with analgesic, anxiolytic and anticonvulsant activity
- 6X stronger binding than gabapentin
- Linear pharmacokinetics, rapid onset, and few drug interactions
- 150-600mg/day-low subject variability
- Improved pain and sleep
- A controlled substance

Anticonvulsants: Side Effects

- Carbamazepine*: sedation, dizziness, nausea, unsteadiness, 2% leukopenia, thrombocytopenia
- Phenytoin*: sedation, mental clouding, unsteadiness
- Valproic acid*: sedation, nausea, tremor
- Clonazepam: drowsiness, ataxia
- Gabapentin: sedation, dizziness, nausea
- Lamotrigine: rash, Stevens-Johnson syndrome

*teratogenic



Local Anesthetics

- Block sodium channels – that blocks the action potential
- Suppress abnormal electrical activity or hypersensitivity in neural structures involved in causing the pain
- Can treat with IV lidocaine

Topical Lidocaine

- Maximum of 3 patches daily for a maximum of 12 hours
- No titration needed
- Two weeks provides an adequate therapeutic trial
- Can cut the patch to fit the painful area

Opioid Analgesics

- Degree of response may be less than seen with nociceptive pain
- Controlled release opioids and oxycodone have been studied
- Sedation, nausea, constipation, itching are common side effects

Eisenberg E, et al. Efficacy and Safety of Opioid Agonists in the Treatment of Neuropathic Pain of Nonmalignant Origin
JAMA 2005; 293: 3043-305

Opioid Analgesics

- Morphine: start with 10-30 mg every 4 hours; may increase by 20-30% per day
- If pain is persistent, switch to a long-acting or controlled release opioid once the daily dose requirements are known
- 4-6 weeks an adequate trial period

Opioid Analgesics

- Advantages: efficacy, no ceiling effect, no end organ damage
- Disadvantages: significant side effects
- Uncertain as to risks vs benefits of long-term therapy

Tramadol (Ultram)

- Some weak morphine-like activity
- Weak inhibitor of norepinephrine and serotonin reuptake
- Start with 50 once or twice daily
- Increase by 50-100 mg per day to maximum of 400 mg/day
- Many adverse effects reported: dizziness/vertigo, nausea, constipation, headache, sleepiness

Other drugs that may benefit persons with persistent pain

- Capsaicin
- Ketamine
- Baclofen
- Clonidine
- Tizanidine

Management of Neuropathic Pain

- Should be multidimensional
- Drug therapy
- Psychological intervention
- Treat underlying cause; maintain blood sugar in diabetics, hyperglycemia can result in peripheral nerve injury
- Vaccinate against herpes zoster

Osman MN, et al. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. *N Engl J Med* 2005; 352: 2271-2284

Pharmacologic Management

- First-line treatments have been identified
- Current practice: "Trial and Error"
- There may be advantages to combining two first-line drugs

Gilron I, et al. Morphine, Gabapentin, or Their Combination for Neuropathic Pain. *N Eng J Med.* 2005;352:1324-1334

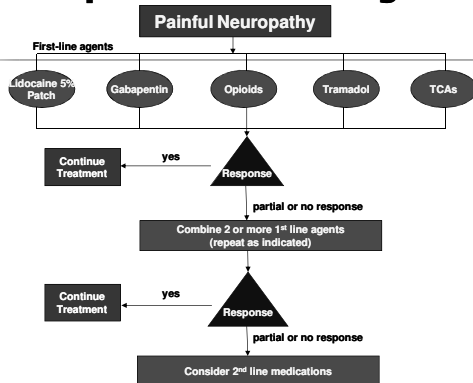
First-Line Drugs for NP

Not in order of preference

- Antidepressants
 - Tricyclic antidepressants
 - Venlafaxine and duloxetine
- Alpha 2-delta ligands (calcium channel subunits)
 - Gabapentin and pregabalin
- Topical analgesics: 5% lidocaine patch
- Systemic analgesics
 - Opioids and tramadol

Dworkin RH, et al. Advances in Neuropathic Pain: Diagnosis, Mechanisms, and Treatment Recommendations. *Arch Neurol* 2003; 60: 1524-1534

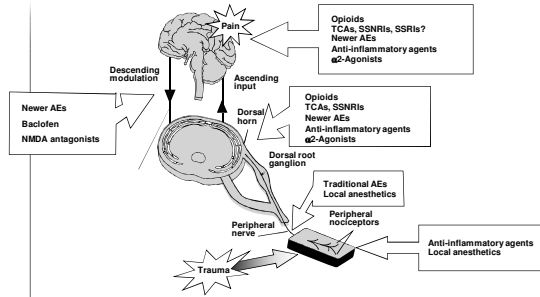
Example Treatment Algorithm



Pharmacological Targets

		SHT	NE	α	Na	Ca	GABA	Glu	NMDA
Antidepressants	TCA								
	Amitriptyline 3 rd amine	✓	✓						
	Nortriptyline 2 nd amine								
	SSNRI		✓						
	Venlafaxine Duloxetine	✓+	✓						
	SSRI	✓							
Anticonvulsants	Traditional								
	Carbamazepine				✓				
	Phenytoin				✓				
	Oxcarbazepine				✓	?			
Newer Agents	Gabapentin				✓	✓	?		
	Lamotrigine				✓	✓			
	Topiramate				✓	?		+/-	?
	Tiagabine				✓	✓	✓		
	Felbamate				✓	✓	+/-		✓
	Zonisamide				✓	✓			
	Levetiracetam	?			✓	✓			?
	Pregabalin				✓	✓	?	?	
Antiarrhythmics	Lidocaine, Mexiletine				✓				
Alpha Agonists	Clonidine, Tizanidine		✓						
	Dexmedetomidine		✓						
NMDA	Dextromethorphan, Methadone								✓
	Ketamine, Memantine								✓
GABA Agonist	Baclofen						✓		

Analgesics Affect Different Parts of the Pain Pathway



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