

# Neuropathic Pain & Adjuvant Drug Therapy

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## Disclosures

- Dr. Crossno discloses his employment as
  - VistaCare Regional Medical Director
- VistaCare has provided commercial support for this activity
- Palliative medicine frequently involves the use of medications for “off-label” purposes. Such use may be discussed during this presentation.

## Objectives

- ◆ Discuss the types of neuropathic pain
- ◆ Discuss medications from several drug classes used to treat neuropathic pain
- ◆ Identify common side effects and/or precautions in using these medications

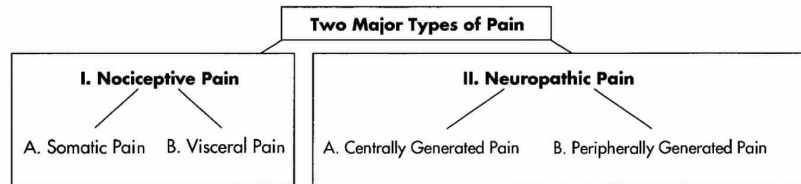
## Overview

- ◆ Nociception
  - ◆ The process by which one becomes conscious of pain, through the following processes:
    - ◆ Transduction
    - ◆ Transmission
    - ◆ Perception
    - ◆ Modulation
- ◆ Virtually this entire talk is “off-label”

# Neuropathic Pain

- ♦ Abnormal processing of sensory input by the peripheral or central nervous system; treatment usually includes adjuvant analgesics
- ♦ Reported pain is often disproportionate to physical findings
- ♦ Many different presentations and syndromes, complicating treatment

## CLASSIFICATION OF PAIN BY INFERRED PATHOLOGY



## Theories of Neuropathic Pain

- Injury to sensory neurons or axons (death or loss of myelin sheath) results in repetitive spontaneous depolarization and transmission of pain
- Central sensitization with *N*-methyl-*D*-aspartate (NMDA) receptors result in neuronal “wind-up”
  - Progressive increase in the discharge of dorsal horn neurons (hyperexcitability) from prolonged noxious stimuli
  - Innocuous stimuli produce pain (allodynia)

## Centrally-Generated Neuropathic Pain

- Deafferentation pain
  - Injury to either the peripheral or central nervous system
    - Examples: Phantom pain may reflect injury to the peripheral nervous system; burning pain below the level of a spinal cord lesion reflects injury to the central nervous system
- Sympathetically maintained pain
  - Associated with dysregulation of the autonomic nervous system
    - Examples: May include some of the pain associated with reflex sympathetic dystrophy/causalgia (complex regional pain syndrome type I / type II)

## Peripherally-Generated Neuropathic Pain

- ◆ Painful polyneuropathies
  - ◆ Pain is felt along the distribution of many peripheral nerves
    - ◆ Examples: diabetic neuropathy, alcohol-nutritional neuropathy, those associated with Guillain-Barre syndrome
- ◆ Painful mononeuropathies
  - ◆ Usually associated with a known peripheral nerve injury and pain is felt at least partly along the distribution of the damaged nerve
    - ◆ Examples: nerve root compression, nerve entrapment, trigeminal neuralgia

## Etiologies

- ◆ Cancer
- ◆ Liver disease
- ◆ Metabolic / diabetic
- ◆ Post-traumatic
- ◆ Drug-related
- ◆ Idiopathic

## Treatment of Neuropathic Pain

- Traditionally opioids & NSAIDs “thought” to be less effective
- Often require adjuvant medications to control
- Different syndromes may respond to different medications
- Growing body of EB studies
  - But generally compared to placebo
  - Few head-to-head

## Opioids for Neuropathic Pain

- Several recent, small trials comparing opioids with tricyclic antidepressants or gabapentin
- Findings – equally effective
- Fewer side effects with opioids

## Methadone

- Is a *mu*-agonist
  - Analgesia like other opioids
- Is an NMDA-antagonist
  - Blocks standard opioid tolerance
  - Blocks depolarization of spinal cord neurons
    - Prevents hyperalgesia
    - Prevents “wind-up”

## Adjuvant Analgesics

- Antidepressants
- Anticonvulsants
- Systemic anesthetics
- Alpha2-adrenergic agonists
- Corticosteroids
- Other agents

## Example 1

- 86-yo M with end-stage COPD
- Comorbid conditions
  - Type 2 diabetes
  - Peripheral diabetic neuropathy
- Unable to sleep due to causalgia
- Failed treatments included
  - HC/APAP; ibuprofen; tramadol
  - Could not tolerate gabapentin

## Example 1 (cont)

- Admitted to hospice
- Nortriptyline 10mg q hs begun
- First full night of sleep in over a year
- Pain returned after 10 days
- Resolved with dose titration to 20mg

## Antidepressants

- TCA's
- SSRI's
- SNRI's

## Tricyclic Antidepressants for Neuropathic Pain

- Best for peripherally-arising continuous pain
  - Burning pain (causalgia)
  - Allodynia
- Helpful as adjuvant with other analgesics
- Analgesic effect is independent of antidepressant activity
- Best studied

## Mechanism of Action

- Block reuptake of serotonin and/or norepinephrine increasing the activity on endogenous pain-modulating pathways
- Block sodium channels
- When combined with opioids, have a pharmacokinetic interaction potentiating the opioid analgesic effect (without necessarily increasing side effects)

## Tricyclic Antidepressants (1)

- ◆ Amitriptyline
  - most extensively studied
  - 10(elderly) – 25(younger) mg po q hs, titrate (escalate q 4–7 d) up to antidepressant doses if needed
  - analgesia in days to weeks

## Tricyclic Antidepressants (2)

- ◆ Amitriptyline
  - monitor plasma drug levels  
> 100 mg / 24 h for risk of toxicity
  - anticholinergic adverse effects prominent, cardiac toxicity
  - Sedating, limited usefulness in frail, elderly

## Tricyclic Antidepressants (3)

- ◆ Desipramine
  - minimal anticholinergic or sedating adverse effects
  - 10–25 mg po q hs, titrate
  - tricyclic of choice in seriously ill
- ◆ Nortriptyline is an alternative
  - Less well studied

## TCA (4)

- Amitriptyline effective topically and with local infiltration
- Doxepin (Zonalon®) effective topically

## SSRI's

- Selective Serotonin Reuptake Inhibitors
- Limited usefulness with most SSRI's (selectively affect serotonin)
- May be useful if depression is an amplifier of pain
- Better tolerability than TCA's

## SNRI's

- ◆ Duloxetine (Cymbalta®)
  - Approved for Diabetic Peripheral Neuropathy
  - Little info for other neuropathic pain
  - Effective only at higher doses
    - ◆ 60mg daily or bid
  - Caution with renal failure
  - Contraindicated with hepatic failure

## SNRI's (2)

- ◆ Venlafaxine (Effexor®)
  - At higher doses effects both serotonin and norepinephrine
  - Some reports demonstrate utility
  - Inconsistent effects

## Tramadol

- ◆ Has both opioid and SSRI activity
- ◆ Cochrane systemic review confirms effectiveness in neuropathic pain
- ◆ NNT = 3.5 for 50% pain improvement
- ◆ NNH = 7.7 for withdrawal from trials
- ◆ Requires intact cytochrome P450 2D6 pathway for activation
  - ◆ Absent in 7-10% of U.S. population

## Example 2

- ◆ 56-yo M entered my practice one year after thalamic stroke
- ◆ Minimal motor deficit
- ◆ Continuous, difficult-to-describe “cold-heat, tingling-numbness” in entire L body
- ◆ Had been taking HC/APAP “as many as I can get” a day with incomplete relief

## Example 2 (cont)

- ◆ Started valproic acid 250mg po bid
- ◆ Titrated to therapeutic blood level
- ◆ Reported the affected side
  - “Still doesn’t feel right” but
  - “It doesn’t hurt any more”
- ◆ Sustained relief for over 18 months until patient lost to follow-up

## Anticonvulsants for Neuropathic Pain

- ◆ More useful for centrally-generated pain
  - Lancing (“shooting, stabbing, knifelike”) pain
  - Paroxysmal pain
- ◆ Minimal information comparing one anticonvulsant against another
- ◆ May be useful for peripherally-arising pain
- ◆ May be useful for chronic, ongoing pain

## Anticonvulsants

- ◆ Mechanism of action
  - Specific mechanisms unknown
  - May be related to their membrane stabilizing action to prevent paroxysmal, aberrant action potentials
  - May be related to reduction of central neuronal excitability

## Carbamazepine (Tegretol®)

- ◆ Most studied
- ◆ Evidence of efficacy for
  - Trigeminal neuralgia
  - Postherpetic neuralgia
  - Diabetic neuropathy
  - Other paroxysmal neuralgias
  - Phantom limb pain
- ◆ Dosage
  - 100mg bid and titrate by blood level
- ◆ Adverse effects
  - Sedation, dizziness, nausea, unsteadiness
  - Leukopenia/thrombocytopenia in 2% of patients

## Oxcarbazepine (Trileptal®)

- ◆ Chemically related to carbamazepine
- ◆ Markedly better adverse effect profile
- ◆ Studied for trigeminal neuralgia
- ◆ Dosage
  - 300 – 600mg bid

## Phenytoin (Dilantin®)

- ◆ Evidence of efficacy for
  - Diabetic neuropathy
  - Trigeminal (and similar) neuralgias
  - Postherpetic neuralgia
  - Postsympathectomy pain
- ◆ Dosage
  - 100mg bid-tid, titrate by blood level
- ◆ Adverse effects
  - Related to blood levels
  - Sedation, dizziness, mental clouding
  - Drug interactions

## Gabapentin (Neurontin®)

- ◆ Evidence of efficacy for
  - Reflex sympathetic dystrophy
  - Deafferentation neuropathy
  - HIV-related neuropathy
  - Postherpetic neuralgia
  - Mixed neuropathies
- ◆ Dosage
  - 100-300mg qhs & titrate

## Gabapentin (2)

- ◆ Reputation of lower side effects
- ◆ Adverse effects
  - Sedation, dysphoria, mood changes, cognitive impairment, urinary incontinence, rare movement disorders
- ◆ Head to head with amitriptyline
  - Equally effective
  - More side effects with gabapentin

## Lamotrigine (Lamictal®)

- ◆ Evidence for efficacy in
  - Phantom limb pain
  - HIV induced neuropathy
  - Trigeminal neuralgia
  - Central post-stroke pain
  - Diabetic neuropathy
- ◆ Dosage
  - Initial 50mg/d, titrated weekly to 600mg/d max
- ◆ Adverse effects
  - Ataxia, incoordination, blurred vision, diplopia

## Clonazepam (Klonopin®)

- ◆ Evidence of efficacy for
  - Trigeminal neuralgia
  - Paroxysmal postlaminectomy pain
  - Posttraumatic neuralgia
  - Lancing phantom limb pain
- ◆ Dosage
  - 0.5 mg bid and titrate
- ◆ Adverse effects
  - Drowsiness, rare idiosyncratic reactions

## Valproic Acid (Depakote®)

- ◆ Evidence of efficacy for
  - ◆ Trigeminal neuralgia
  - ◆ Postherpetic neuralgia
- ◆ Dosage
  - ◆ 250 mg po q hs, titrate by blood levels
- ◆ Adverse effects
  - ◆ Sedation, nausea, tremor, weight gain, hepatotoxicity, dermatitis and rare idiosyncratic reactions
  - ◆ Fewer drug-drug interactions
  - ◆ May be used rectally

## Bupropriion (Wellbutrin®)

- ◆ Some evidence for central neuropathy
- ◆ Dosage as for depression

## Pregabalin (Lyrica®)

- ◆ GABA / gabapentin congener
- ◆ More potent than gabapentin
  - ◆ Better efficacy with lowered side effects
- ◆ Approved in Europe & US for
  - ◆ Diabetic peripheral neuropathy
  - ◆ Postherpetic neuralgia
- ◆ Marketing expected soon
- ◆ Dosage:
  - ◆ 300 – 600mg daily

## Example 3

- ◆ 82-yo ENT physician with mesothelioma
- ◆ L lung, pleural, rib involvement
- ◆ Comorbid condition
  - ◆ Paroxysmal atrial fibrillation
  - ◆ Osteoarthritis
- ◆ Complained of arthritic pain in hips/knees

## Example 3

- ◆ Never had pain in chest until decided to stop “non-essential” oral meds
- ◆ Immediately developed significant burning L chest wall pain
- ◆ Pain resolved with resumption of flecainide
  - ◆ Had been taking for heart rhythm

## Systemic Anesthetics

- ◆ Mechanism of action
  - ◆ Block sodium channels imposing a nondepolarizing conduction block of the action potential
- ◆ Adverse effects
  - ◆ CNS
    - ◆ Dizziness, numbness, paresthesias, tremors & seizures
  - ◆ Cardiovascular
    - ◆ Proarrhythmic effects, negative inotropic effects, hypotension

## Specific Anesthetic Agents

- ♦ Parenteral
  - Lidocaine, procainamide
- ♦ Oral
  - Flecainide, tocainide, mexilitine
- ♦ Dosage
  - Same as for their cardiac indications
- ♦ Generally are second-line (or lower) medications

## Alpha2-Adrenergic Agonists

- ♦ Clonidine
  - Best studied
  - Useful for
    - Sympathetically maintained reflex sympathetic dystrophy
    - Chronic low back pain
    - Deafferentation pain after spinal injury
- ♦ Mechanism of action – several proposed
  - Increases GABA

## Alpha2-Adrenergic Agonists (2)

- ◆ Dosage
  - ◆ Epidural
  - ◆ Transdermal patch
  - ◆ Oral (0.1mg and titrate)
- ◆ Adverse effects
  - ◆ Sedation, hypotension, dry mouth
- ◆ Tizanidine
  - ◆ Approved for spasticity, but may be useful

## Other Agents

- ◆ Neuroleptics
  - ◆ Prochlorperazine, haloperidol, olanzepine
- ◆ NMDA receptor antagonists
  - ◆ Dextromethorphan, ketamine
- ◆ GABA agonists
  - ◆ Baclofen
- ◆ Levadopa

## Corticosteroids

- ◆ Mechanism of action
  - Reduces inflammatory neuronal irritation
- ◆ Used for short-term treatment of refractory neuropathic pain
- ◆ Dexamethasone
  - 2 - 4 mg qd - qid
- ◆ Prednisone
  - 10 – 60mg qd

## Topical Agents

- ◆ TCA's
  - See above
- ◆ Capsaicin
  - Well studied & found effective
  - Adverse effects
    - ◆ Burning
    - ◆ Need for frequent application
- ◆ NSAIDs
  - Effective w/ adverse effects lower than oral

## Other treatments

- ◆ Percutaneous electrical nerve stimulation (PENS)
  - Invasive
  - More effective than acupuncture
    - ◆ Used as control
- ◆ Sympathectomy
  - Cochrane systemic review: poor quality evidence – unable to judge

## Guideline for Continuous Neuropathic Pain

- ◆ Try First
  - Antidepressants
  - Gabapentin
  - Systemic local anesthetics
- ◆ For Refractory Cases
  - Alpha2-adrenergic agonists
  - Anticonvulsants
  - NMDA receptor antagonist
  - Baclofen

## Guideline for Lancing or Paroxysmal Pain

- ◆ Try First
  - Anticonvulsants
  - Baclofen
- ◆ For Refractory Cases
  - Systemic local anesthetics
  - Tricyclic antidepressants
  - Newer antidepressants
  - Alpha2-adrenergic agonists
  - NMDA receptor agonists

## Summary

- ◆ Discussed
  - Neuropathic pain types
  - Classes of medications to treat
  - Specific drugs & side effects

