Myofascial and Neuropathic Pain
The Role of Long Acting Opioids

Physical Medicine Rehabilitation Update
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We are appalled by the needless pain that plagues the people of the world - in rich and poor nations alike. By any reasonable code, freedom from pain should be a basic human right limited only by our ability to achieve it.

Liebeskind J, Melzack R. Pain 1987;30:1
Chronic Pain

- Chronic pain can be a disease in itself
- Chronic pain has distinct pathology, causing changes throughout the nervous system that often worsen over time
- It has significant psychological and cognitive correlates and can constitute a separate and serious disease entity.

Institute of Medicine. Relieving Pain in America, 2011
The most prevalent, disabling, and expensive public health condition affecting over 100 million persons in the United States, with annual costs to society estimated at $635 billion.

Rational Pharmacotherapy

- Optimal therapy is mechanism-based

- Determine the mechanism of the pain and select pharmacotherapy accordingly

- Use evidence-based care when evidence exists
General Chronic Nonmalignant Pain Syndromes

- Myofascial Pain
  - following muscle injury or inactivity
  - following soft tissue surgery or trauma
  - fibromyalgia
- Nerve Injury Pain
  - neuropathic (deafferentation) pain
    - central (post-stroke, thalamic) pain
    - peripheral (PHN, diabetic neuropathy, etc.)
  - complex regional pain syndrome (CRPS); also called sympathetically maintained pain (SMP)
    - reflex sympathetic dystrophy
    - causalgia
Specific Chronic Nonmalignant Pain Syndromes

- headaches
  - tension-type
  - vascular
- arthritides
  - rheumatoid arthritis
  - degenerative joint disease (osteoarthritis)
Nociceptive Pain Pathway

adapted from Roberts WJ. Pain; 1986:24:297
Myofascial Pain Syndromes

- Chronic pain due to muscle injury/inactivity
  - decreased use causes muscle tightness, weakness, and tension (resulting in guarding)
- Local tender spots - trigger points
  - most common in large muscles
  - reproducible, radiating pain upon palpation
- Sleep and mood disturbance result
- Problem becomes self-perpetuating
Myofascial Pain Management

• Rehabilitation - mobilize affected muscles
  – stretching and strengthening
• Relieve pain to facilitate rehabilitation
  – analgesics
    • NSAIDs
    • opioids
• Release trigger points
  – noninvasive - massage, cooling sprays, ice
  – invasive - trigger point injections (TPIs)
Nerve Injury Pain

- Neuropathic Pain
  - peripheral
  - central post stroke, thalamic

- Complex Regional Pain Syndromes (CRPS)
  Sympathetically Maintained Pain (SMP)
  - reflex sympathetic dystrophy (RSD)
  - causalgia
Central Neuropathic Pain

- Thalamic injury
  - post stroke
  - post head injury

- Drug therapy same as for peripheral neuropathic pain
  - worse prognosis

- CNS stimulation may be useful
  - percutaneous nerve stimulators
  - dorsal column stimulators
Peripheral Neuropathic Pain

- Chronic pain due to damaged peripheral nociceptive (afferent) neurons
- Onset usually weeks to months after acute nerve injury
Allodynia from Neuropathic Pain

adapted from Roberts WJ. Pain 1986;24:297
Presentation of Postherpetic Neuralgia

1. area of allodynia
2. site of former herpetic plaques
3. hypoalgesia
Analgesics for Neuropathic Pain

- **tricyclic antidepressants**
  - amitriptyline, desipramine
- **anticonvulsants**
  - gabapentin, carbamazepine
- **Local anesthetics**
  - lidocaine dermal (not transdermal) patches
  - Intravenous lidocaine
- **topical capsaicin**
- **NMDA antagonists**
- **autonomic drugs**
- **opioids for selected patients**
Antidepressant Mechanisms in Neuropathic Pain

- depression and pain frequently occur concurrently
  - analgesic dose & onset 1/3-1/2 of antidepressant action
- mixed norepinephrine serotonin reuptake inhibition
  - tricyclic agents clearly effective
- SSRIs not effective in well controlled studies
  - Effect on central serotonin levels needed AND
  - effect on peripheral norepinephrine levels needed
  - animal work and poorly controlled clinical trials have suggested efficacy - not borne out in larger studies
### Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Tertiary Amines</th>
<th>Secondary Amines</th>
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<tbody>
<tr>
<td>amitriptyline</td>
<td>desipramine</td>
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<tr>
<td>imipramine</td>
<td>nortriptyline</td>
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<tr>
<td>doxepin</td>
<td>protriptyline</td>
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<tr>
<td>- more sedating</td>
<td>- less sedating</td>
</tr>
<tr>
<td>- more</td>
<td>- less</td>
</tr>
<tr>
<td>anticholinergic</td>
<td>anticholinergic</td>
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<tr>
<td>- more</td>
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<td>orthostasis</td>
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## Tricyclic Antidepressants Characteristics

### Tertiary Amines

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Relative Anticholinergic Effects</th>
<th>Relative Sedative Effects</th>
<th>Relative Norepinephrine Reuptake Inhibition</th>
<th>Relative Serotonin Reuptake Inhibition</th>
<th>Relative Orthostatic Effects</th>
<th>Half-life in hours</th>
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<tr>
<td>amitriptyline</td>
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<td></td>
<td>++++</td>
<td>++</td>
<td></td>
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<tr>
<td>imipramine</td>
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<td></td>
<td>++++</td>
<td>+++</td>
<td></td>
<td>10- 25</td>
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<tr>
<td>doxepin</td>
<td>++  +++  +</td>
<td></td>
<td>++++</td>
<td>++</td>
<td></td>
<td>8-  25</td>
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<tr>
<td>clomipramine</td>
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<td></td>
<td>++++</td>
<td>++</td>
<td></td>
<td>80-100</td>
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<tr>
<td>trimipramine</td>
<td>++  +++  +</td>
<td></td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>7-30</td>
</tr>
</tbody>
</table>

# Tricyclic Antidepressants Characteristics

## Secondary Amines

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<th>Relative Orthostatic Effects</th>
<th>Half-life in hours</th>
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<tbody>
<tr>
<td>desipramine</td>
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<td>+</td>
<td>++++</td>
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<td>+</td>
<td>12-25</td>
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<td>++</td>
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<td>+</td>
<td>18-45</td>
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<tr>
<td>amoxapine</td>
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<td>+ +</td>
<td>++++</td>
<td>++</td>
<td>+</td>
<td>8-30</td>
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<tr>
<td>protriptyline</td>
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<td>+</td>
<td>++++</td>
<td>++</td>
<td>+</td>
<td>65-90</td>
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</table>

Anticonvulsants as Analgesics

- Indicated in neuropathic pain
- Probably indicated in sympathetically maintained pain (complex regional pain syndrome)
  - reflex sympathetic dystrophy
  - causalgia
- No indication in myofascial pain
Mechanism of Anticonvulsants as Analgesics

- Reduce or prevent pathologically altered neurons from excessive discharge
- Reduce spread of excitation from abnormal foci to normal neurons
Other Newer Anticonvulsants that are Used as Analgesics in Neuropathic Pain

- lamotrigine
- levetiracetam
- oxcarbazepine
- pregabalin
- tiagabine
- topiramate
- zonisamide
- Lamictal
- Keppra
- Trileptal
- Lyrica
- Gabatril
- Topamax
- Zonegran
Systemic Local Anesthetics in Neuropathic Pain Management

- IV lidocaine effective
  - inconvenient
- oral lidocaine congeners
  - tocainide too toxic
  - mexiletine clinically disappointing
- topical (dermal) lidocaine effective
  - postherpetic neuralgia
  - other neuropathic pain
  - Possibly other types of pain?
Lidocaine Patch 5% Mechanism of Action

Epidermis

Dermis (Neuronal Level)

Subcutaneous Tissue (Systemic Level)

Lidocaine from patch penetrates the dermis to deliver direct analgesia to affected nerves
Topical Analgesics in Neuropathic Pain

- capsaicin
  - depletes Substance P
  - found in all hot peppers
- aspirin in diethyl ether
- other NSAIDs in volatile solvents
  - mechanism unclear
N-methyl-D-aspartate (NMDA) Antagonists

- ketamine
  IV anesthetic with profound psychotomimetic side effects

- dextrorphan
  metabolite of dextromethorphan (DM) with major side effects at effective doses

- investigational drugs side effects often intolerable
e.g. MK 801
Antivirals and Postherpetic Neuralgia

Goal: reduce incidence and severity of PHN

Acyclovir
- meta-analysis demonstrated efficacy

Famciclovir
- large, controlled trial showed efficacy at 500 mg tid for 7 days within 72 hours of shingles onset.

Drug Therapy for Neuropathic Pain

- Tricyclic antidepressants normally drugs of choice
  - SSRIs not effective
- Add anticonvulsant if necessary after ~2 weeks
  - May be drug of choice in lancinating pain
- Lidocaine patches may be 1st line for localized pain
- Topical capsaicin may be useful adjunctively
- Autonomic drugs provide variable results
- NMDA antagonists produce excessive side effects
- Opioids are effective, but have inherent risks
- Interdisciplinary care important; psychology, PT
Opioid Efficacy in CNP

- 100 patients with CNP for 2 weeks-14 years
  - 23 had pain for > 1 year
- good results from opioids in 51% of patients
- partial effectiveness in another 28%
- physical function declined in 21 patients
- 10 patients were non-compliant
- 20 patients could change to other therapies

Patient Characteristics for Opioid Use in Chronic Nonmalignant Pain

- Failure of other therapies
  - reasonable trials - types and durations
- Psychological approval
  - personality, behavioral factors, motivation, goals
- Stable life style
- Willingness to enter therapeutic contract
  - single prescriber
- No recent history of substance abuse
- No medical or other opioid contraindication
Tapering Opioid Medications

- drugs used irregularly can be stopped abruptly
- “pill” tapers OK for compliant, motivated patients
- “blind tapers preferred for most patients
  - ascertain highest daily use and increase by ~20%
  - dose taper medication tid on regular schedule
  - schedule taper over 5-10 days; end on weekday
    - use constant volume (10 mL) of flavored vehicle
    - include a few doses of placebo at end if indicated

Hare BD, Lipman AG. Problems in Anesthesia 1990;4 577-94
Warning Signs for Substance Abuse

- **Drug preoccupation/drug seeking behavior**
  - refusal to taper dose
  - insistence on short acting or bolus opioids
  - multiple prescribers; multiple pharmacies
  - use of street drugs
  - noncompliance with other therapies

- **Continued use with adverse effects**
  - decreased function with increased side effects

- **Loss of control**
  - not taking medications as prescribed
  - repeatedly running out or losing medications
  - violation of contract with prescriber
Before Using Opioids in CNMP

- define mechanism of pain
  - NSAIDs are first line in myofascial pain
  - TCAs, AEDs, lidocaine in neuropathic pain
- if opioids are needed, use as in any other patient
- use concurrent therapies for dose sparing effect
- enact a formal contract if indicated
  - require unannounced urine screens
  - use long acting opioids and only on a set schedule
  - only one prescriber and one pharmacy
  - do not accept claims of lost or destroyed drugs
The Use of Opioids for the Treatment of Chronic Pain

AAPM-APS Joint Consensus Statement

- Evidence supports the use of opioids in CNMP
- Pain management is often inadequate
- Many common assumptions need modification
- Policy is evolving
- Principles of practice for opioids are needed
- Good medical practice should guide the prescribing of opioids

October 1997
Physiological Responses to Repetitive Nociceptive Input

- **Windup**
  
  highly augmented response to repetitive afferent (C-fiber) input

- **Neuronal plasticity**
  
  changes in the CNS in response to repetitive afferent nociceptive input
Chronic Pain Symptom Complex

Pain Perception

sleep disturbance
(inomnia or hypersomnia)

anxiety → depression

anger → hostility → loneliness

A Cancer Pain Management Principle

- medication should be administered on an “around the clock” basis
- additional “prn” doses should be available for breakthrough pain
  - an immediate-release dosage form
  - make 1/2 of the q4h dose available q2h prn
  - this equals 1/6 of the q12h s.a.. (12 h) dose
- if > 2-3 prn doses are needed for > 2-3 days, add that amount into the scheduled 24 hour dose
# Oral Long Acting Opioid Dosage Forms

<table>
<thead>
<tr>
<th>Pharmacologically Long Acting</th>
<th>Pharmaceutically Long Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ methadone</td>
<td>◆ morphine</td>
</tr>
<tr>
<td>◆ levorphanol</td>
<td>- MS Contin, others, generics</td>
</tr>
<tr>
<td>- No longer routinely available</td>
<td>- OxyContin</td>
</tr>
<tr>
<td>- pharmacokinetics not well described</td>
<td>- Exalgo</td>
</tr>
<tr>
<td>◆ oxycodone</td>
<td>◆ hydromorphone</td>
</tr>
<tr>
<td>◆ oxymorphone</td>
<td>- Opana ER</td>
</tr>
<tr>
<td>◆ hydrocodone</td>
<td>- Zohydro</td>
</tr>
</tbody>
</table>
Controlled Release Morphine

- Often not the long acting opioid of choice
  - Active metabolites accumulate in renal impairment
  - Short acting forms available for breakthrough pain
- Pharmacokinetics vary with formulation
  - Several commercially available brands in U.S.
  - Common extemporaneously compounded form provides uneven release of morphine
- Some patients fear addiction and adverse effects
- Some patients associate morphine with poor outcomes due to its being used poorly
Methadone

Totally synthetic opioid
no risk of allergic reaction to plant protein
Racemic mixture
  L-methadone is 8-50 times more potent than D isomer
  D-methadone is antitusive
  NMDA activity of D (not L) isomer
    clinical utility not proven
Onset:  30-60 minutes after oral administration
Duration:  initially 4-6 hours
  extends over time
Methadone Pharmacokinetics

- Biphasic elimination
  - Alpha elimination half-life 2-3 hours
  - Beta elimination half-life
    • 8-97 hours in postoperative patients
    • 8.5-75 hours in opioid-dependent patients
    • Up to 120 hours in cancer pain outpatients
Methadone Biphasic Elimination

Analgesic onset ~ 1 h
Analgesic offset ~ 8 h

Lipman AG. Oncology. 1999;13:(9):1275-82
Plot of Methadone Accumulation (dosed q 8 h over 6 days)

Lipman AG. Oncology. 1999;13:(9):1275-82
Controlled Release Oxycodone

- short acting forms also available for breakthrough pain

- Relatively high lipid solubility
  - better activity in opioid-responsive neuropathy?
  - mu-kappa activity an advantage in visceral pain?
Relative Oxycodone-Morphine Potencies

- traditionally accepted as 1:1 in U.S.
- OxyContin labeling 1:2
- European studies 3:4
Time-effect Curves for Intramuscular Morphine According to Age of Patient

- Pain Relief
- Time (hr)

Years:
- 70-89
- 50-69
- 30-49
- 18-29

Kaiko RF: Clin Pharmacol Ther 1980;28:825
Effect of Age on Oxycodone Efficacy

Opioid Dose Conversion

- Change opioid when patient does not respond as expected after to multiple dose adjustments
  - no place for preemptive opioid rotation

- Dose equivalency tables are based on population averages
  - great interpatient variability to response
  - genetic polymorphism

- Reduce dose of new opioid by 25-50% to reduce risk of dose-related ADR
  - then titrate to response
Model Policy for the Use of Controlled Substances for the Treatment of Pain

Federation of State Medical Boards of the United States

- Quality medical practice dictates pain relief
- Inadequate care results from lack of knowledge
- Boards should define boundaries of practice
  - evaluate the patient
  - informed consent
  - consultation
  - compliance with laws and regulations
  - define treatment plan
  - periodic review
  - medical records

www.fsmb.org
All this needless pain and suffering impoverishes the quality of life of those afflicted and their families; it may even shorten life by impairing recovery from surgery or disease. People suffering severe or unrelenting pain become depressed. They may lose their will to live and fail to take normal health preserving measures; some commit suicide.

Liebeskind J, Melzack R. Pain 1987;30:1