Improving Strategies for the Management and Treatment of Chronic Pain

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Definition of Pain, Allodynia, & Hyperalgesia

• Pain: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”
  (Merskey and Bogduk. Classification of Chronic Pain. 1994. IASP)

• Allodynia: painful response to a non-painful stimulus
• Hyperalgesia: heightened response to painful stimulus
Chronic Pain, Sleep Disturbances, and Depression/Anxiety

Chronic pain

Optimal functionality

Sleep disturbances

Depression/anxiety


Common Pain Syndromes

Nociceptive Pain

Mixed Type (eg, Trauma, postoperative pain, cancer pain, chronic back pain & sciatica)

Neuropathic Pain

Visceral
- Abdominal
- Obstetrical

Musculoskeletal
- Osteoarthritis
- Rheumatoid Arthritis
- Low Back Pain

Mixed Type
- Head
- Headache
- Orofacial

Mixed Type
- Postoperative
- Cancer Pain

CRPS

Postherpetic Neuralgia

Distal Polyneuropathy (eg, diabetic, HIV)

CRPS = complex regional pain syndrome.
Principle & Practice of Chronic Pain Management

- Assess pain **systemically** and identify **comorbidities**
- Measure improvement in **pain** and **function capacity**
- **Universal precaution** in prescribing pain medicine
- Reinforce **patient** participation and **family** involvement
- Update any progress and modify pain management plan
- **Comprehensive** and multidisciplinary treatment plan

Comprehensive Approach in Chronic Pain Management

**Pharmacologic therapy**
- 1. Risk and benefits of non-opioid, adjuvant and co-analgesics, and opioids
- 2. Consider age-associated changes in physiology, pharmacokinetics & dynamics

**Non-Pharmacologic therapy**
- **1). Physical and Occupational therapy**
  - 1. Instruct exercise program especially in musculoskeletal pain
  - 2. Consider topical application of electrical stimulation, heat or cold, and massage etc.
- **2). Interventional procedure**: nerve block, epidural steroid injection, facet block etc.
- **3). Psychological management**
  - 1. Cognitive-behavioral therapy
  - 2. Hypnosis, relaxation, biofeedback and neurofeedback training
- **4). Complementary & Alternative Medicine (CAM)**
Interventions for Chronic Pain Management
Diagnostic & Therapeutic Approach

- Peripheral, neuraxial nerve and sympathetic blockade
- Epidural Steroid Injection
  1. Herniated disk, nerve root irritation
  2. Discogenic pain e.g. annulus tear
  3. Spinal stenosis or foraminal stenosis
- Facet Injection, Medial Branch Block and Radiofrequency Ablation
  1. Facet joint arthropathy
  2. Medial branch and posterior musculoskeletal structures
- Joint & bursa injection: facet, sacroiliac joint, knee, hip or other joints
- Neuromodulation: Spinal Cord Stimulation (SCS) or Spinal Infusion Therapy

Classification of NSAIDs
Chemical/Pharmacokinetic Subclasses

- Low potency/fast elimination
  - Salicylates: aspirin, salicylic acid
  - Propionic acid: ibuprofen
  - Anthranilic acid: mefenamic acid
- High potency/fast elimination
  - Propionic acid: ketoprofen
  - Pyrrolizine carboxylate: ketorolac
  - Phenylacetic acid: diclofenac
  - Indoleacetic acid: indomethacin
- Intermediate potency/elimination
  - Salicylates: diflunisal
  - Propionic acids: naproxen
  - Naphthylalkanone: nabumetone
- High potency/slow elimination
  - Oxicams: meloxicam, Piroxicam
**NSAIDs & COX-2 Selective Inhibitor in Chronic Pain Medicine**

**Key Clinical Pearls**

- Clinical data have shown **COX-2 selective inhibitors offer the similar pain relief as Non-specific NSAIDs**
  - COX-2 inhibitors have a better GI safety profile vs Non-specific NSAIDs up to 6 months
  - Overall safety is similar among all NSAIDs
  - Avoid COX-2 inhibitors & NSAIDs in patients with CV risk & those requiring aspirin
  - Use lowest dose and shortest duration for all NSAIDs

- All NSAIDs including COX-2 inhibitors possess potential risk for Cardiovascular or cerebrovascular thromboembolic events

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**Parenteral NSAID: Ketorolac (Toradol) in Pain Management**

- A potent analgesic but only a moderately effective anti-inflammatory drug (mainly a COX-1 inhibitor & minimal COX-2 inhibitor)
- No tolerance, withdrawal, or respiratory depression (vs. opioids)
- Achieving peak plasma concentration in 30-50 minute
- Elimination half life of 4-6 hours
- The rate of elimination is reduced in elderly & in renal failure
- Inhibit platelet aggregation & promote gastric ulceration, renal, cardiovascular & other systemic side effects

- **Recommend to start with loading dose of 30 mg, then use 15 mg q 6 hours around the clock up to 2 days**
- **or 15 mg q 6 hours as needed up to 4 days**
Intravenous Ibuprofen (Caldolor)

- **Caldolor** is indicated in adults for the
  1. management of mild to moderate pain,
  2. management of moderate to severe pain as an adjunct to opioid analgesics,
  3. reduction of fever

**Dosage and administration**
- Pain: 400 mg to 800 mg intravenously over 30 minutes every 6 hours as necessary
- Fever: 400 mg intravenously over 30 minutes, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary

- 1. Significant reduction in pain intensity scores above and beyond PCA-delivered opioids
- 2. Significant opioid-sparing effect
- 3. IV temperature reduction within 30 minutes

References:

Intravenous Injection of Acetaminophen (OFIRMEV)

- 1. management of mild to moderate pain
- 2. management of moderate to severe pain with adjunctive opioid analgesics
- 3. for the reduction of fever

**OFIRMEV** should be administered only as a **15-minute infusion**
- Do not exceed the maximum recommended daily dose of acetaminophen

References:
PHN & DPN: Pharmacologic Treatment
FDA Approved Label Use for Neuropathic Pain

- Agents with consistent efficacy demonstrated in multiple, randomized, controlled trials for **PHN (Postherpetic Neuralgia):**
  - **Topical agent:** 5% Lidocaine patch
  - **Gabapentin (Neurontin), Pregabalin (Lyrica)**

- Consider safety and tolerability when initiating treatment with off label agents e.g. TCA, other anti-epileptics, and opioids

- Agents with consistent efficacy demonstrated in **Painful DPN (Diabetic Polyneuropathy):**
  - **Duloxetine (Cymbalta) & Pregabalin (Lyrica), Tapentadol (Nucynta)**
Cymbalta (Duloxetine) & Savella (Milnacipran)
SNRI in Pain Management

- **Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules**
  - Diabetic Peripheral Neuropathic Pain & Fibromyalgia
  - Recommended dose for Cymbalta is 60 mg once daily.
  - There is no evidence that doses > 60 mg confer additional significant benefit and the higher dose is clearly less well tolerated
  - **Start with a lower dose and titrate**
    - Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment

- **Savella (Milnacipran) Tablets** indicated for the management of fibromyalgia. Initial U.S. Approval: 2009
  - Recommended dose is **100 mg/day**
  - May be increased to **200 mg/day** based on individual patient response
  - Dose should be adjusted in patients with severe renal impairment

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**Tri-cyclic Antidepressants in Pain Management**

**Common Adverse Events**

- Commonly reported AEs (generally anticholinergic):
  - Blurred vision
  - Cognitive changes
  - Constipation
  - Dry mouth
  - Orthostatic hypotension
  - Sedation
  - Sexual dysfunction
  - Tachycardia
  - Urinary retention

- Fewest AEs:
  - Desipramine
  - Nortriptyline
  - Imipramine
  - Doxepin
  - Amitriptyline

AEs = adverse events
**Structure & Classification of Opioids**

- **Alkaloid**
  - Derived from the poppy
  - 1. morphine
  - 2. codeine

- **Semisynthetic**
  - Modification of morphine functional groups
  - 1. diacetylmorphine
  - 2. hydrocodone
  - 3. hydromorphone
  - 4. oxycodone
  - 5. oxymorphone

**Classification of Opioids & Non-opioid Analgesics**

- **Synthetic opioids**: progressive reduction in the numbers of fused rings in phenanthrene moiety of morphine
  - 1. **Morphinan**: levorphanol, butorphanol
  - 2. **Phenylpiperidine**: meperidine, fentanyl, sufentanil, alfentanil
  - 3. **Propionicanilide**: methadone
  - 4. **Benzomorphinan**: pentazocine

- **Tramadol** is a synthetic codeine analog; nonscheduled with IR & ER. (Mechanism: Mu-opioid receptor agonist and inhibition on re-uptake of norepinephrine & serotonin)

- **Tapentadol** has a dual central mechanism (mu-opioid agonist activity and inhibition of norepinephrine reuptake) in analgesia based on animal model

  - **Tapentadol IR** for Moderate to severe acute pain in adults
  - **Tapentadol ER** for 1) Chronic pain for around the clock daily use in adults
  - 2) Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults
Cancer Pain Management
Comprehensive Evaluation and Treatment

♫ Cancer pain-related history, reports and physical exams
♫ Working diagnosis and cancer pain management
♫ Progressive diagnosis and evaluation
♫ Problem list development and treatment plans

♫ Time contingent & efficient approach in cancer pain
♫ We need patient's & family's feedback regarding ongoing treatment

WHO Three Step Analgesic Ladder
Guideline for Cancer Pain Management

➢ 1. Non-opioid analgesics & adjuvant meds
➢ 2. Weak opioid analgesics plus 1st step
➢ 3. Strong opioid analgesics plus 1st & 2nd

• Addendum: transdermal delivery, subcutaneous or IV PCA
• Neuraxial drug delivery system, Neuromodulation, Nerve block, Neurolysis (chemical or radiofrequency ablation)
Cancer Breakthrough Pain Management

• The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program is an FDA-required program
• It’s designed to ensure informed risk-benefit decisions before initiating treatment, and while patients are treated to ensure appropriate use of TIRF medicines.
• TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older who are already receiving and tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

• A list of TIRF medicines
  • Oral transmucosal lozenge
  • Buccal tablet, soluble film
  • Sublingual tablet, spray
  • Nasal spray

Pain Medication Treatment Agreement

Universal Precaution

• Pain Medication is responsibility of the patient
• No illicit substances are allowed
• Only one healthcare provider prescribes pain medications
• Unannounced drug screens can be enforced in follow up visit

• Periodically assess the 4A’s:
  • Analgesia
  • Activities of daily living
  • Adverse effects
  • Aberrant drug-related behavior
Methadone in Chronic Pain Management

- **Low cost** compared to other sustained release opioids
- Analgesic duration is short than the long elimination half life
- Need to titrate cautiously q 8-12 h for chronic pain management

Potential serious side effects: may cause **prolong QT interval** and "**torsades de pointe**"

**Risk factors of prolongation of QT**: Intravenous route, methadone dosage >200 mg/day, hypokalemia, hepatic failure, concomitant administration of P450 CY3A4 inhibitors, concurrent QT prolongation drugs and pre-existing heart disease

Treatment of Opioid-Induced Constipation

- **Methylnatrexolone (RELISTOR)** is the first selective peripherally acting mu-opioid receptor antagonist displacing opioid binding in the gastrointestinal tract
- **Methylnatrexolone** is indicated for the treatment of opioid-induced constipation (OIC) in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied. Initial U.S. Approval: 2008
- **Colace Stool Softener Products**
  The active ingredient in Colace Stool Softener – **docusate sodium** – is not a stimulant but a stool softener that allows water and fats to enter the stool, which helps soften fecal material, making natural defecation easier.
- **Peri-Colace Tablets**: contain docusate sodium and standardized **senna concentrate** – a stool softener plus a stimulant laxative – for use in the treatment of occasional constipation when more than just a stool softener is required.
- **SENOKOT Tablets**: Natural Vegetable Laxative Ingredient
  **SENOKOT-S Tablets**: Natural Vegetable Laxative Ingredient Plus **Docusate Sodium**.
Treatment of Opioid-Induced Constipation

- US Food and Drug Administration (FDA) (9-16-2014) approved Naloxegol (MOVANTIK) tablets as the first once-daily oral peripherally-acting mu-opioid receptor antagonist (PAMORA) medication for the treatment of opioid-induced constipation (OIC), in adult patients with chronic, non-cancer pain. Naloxegol is expected to be available to patients in the first half of 2015.

- Lubiprostone (AMITIZA) 24 mcg capsules twice daily is FDA approved to treat Chronic Idiopathic Constipation (CIC) in adults. "Idiopathic" means the cause of the constipation is unknown and not due to an underlying illness or medication.

- Lubiprostone 24 mcg twice daily is also approved to treat constipation caused by opioids, a type of prescription pain medicine, in adults with chronic, non-cancer pain.

- Lubiprostone 8 mcg capsules twice daily is approved to treat Irritable Bowel Syndrome with Constipation (IBS-C) in women 18 years of age and older.

- Lubiprostone is a chloride channel activator. Initial US approved in 2006.

Diagnosis & Treatment of Low Back Pain (LBP)

- A Joint Clinical Guideline from American College of Physicians & American Pain Society provide evidence-based information on LBP

- First-line medication for LBP: Acetaminophen, NSAIDs

- **Nonpharmacological therapy** with proven benefits for LBP

- **1. Acute LBP**: spinal manipulation

- **2. Sub-Acute LBP or Chronic LBP**: intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy (CBT), relaxation and biofeedback

National Institutes of Health (NIH) Consensus Statement on Acupuncture in 1997

- NIH organized a conference of panel of experts to evaluate the available literature on acupuncture in 1997
- While designing studies to evaluate efficacy remain a challenge, Acupuncture (AP) was widely practiced in the USA for treatment of Postoperative, chemotherapy nausea and vomiting; and postoperative dental pain
- Other promising results of AP have been seen in headache, low back pain, asthma, menstrual cramps, fibromyalgia, and myofascial pain.


Comprehensive Pain Management: Summary

- Gender & cultural differences
- Address co-morbid conditions
- Improve daily activity & function
- Universal precaution for analgesics
- Consider interventional approach
- Complementary & Alternative Treatment