Therapeutic Strategies for Pain and Disability

- Pharmacotherapy
- Rehabilitative approaches
- Psychologic approaches
- Neurostimulatory approaches

- Interventional approaches
  - Injection therapies
  - Neural blockade
  - Neuraxial analgesia

- Complementary and alternative approaches
- Lifestyle changes
Pharmacotherapy for Pain

Categories of analgesic drugs

- Opioid analgesics
- Nonopioid analgesics
- Adjuvant analgesics
- Drugs for headache
Evolutiong Role of Opioid Therapy

• From the 1980s to the present
  - More pharmacologic interventions for acute and chronic pain
  - Changing perspectives on the use of opioid drugs for chronic pain
Historically, opioids have been emphasized in medical illness and de-emphasized in nonmalignant pain.
Opioid Therapy in Pain Related to Medical Illness

Opioid therapy is the mainstay approach for

- Acute pain
- Cancer pain
- AIDS pain
- Pain in advanced illnesses

But undertreatment is a major problem
Barriers to Opioid Therapy

- **Patient-related factors**
  - Stoicism, fear of addiction

- **System factors**
  - Fragmented care, lack of reimbursement

- **Clinician-related factors**
  - Poor knowledge of pain management, opioid pharmacology, and chemical dependency
  - Fear of regulatory oversight
Opioid Therapy in Chronic Nonmalignant Pain

Undertreatment is likely because of

• Barriers (patient, clinician, and system)
• Published experience of multidisciplinary pain programs
  ■ Opioids associated with poor function
  ■ Opioids associated with substance use disorders and other psychiatric disorders
  ■ Opioids associated with poor outcome
Use of long-term opioid therapy for diverse pain syndromes is increasing

- Slowly growing evidence base
- Acceptance by pain specialists
- Reassurance from the regulatory and law enforcement communities
Opioid Therapy in Chronic Nonmalignant Pain

- Supporting evidence
  - >1000 patients reported in case series and surveys
- Small number of RCTs
Positioning Opioid Therapy

- Consider as first-line for patients with moderate-to-severe pain related to cancer, AIDS, or another life-threatening illness.

- Consider for all patients with moderate-to-severe noncancer pain, but weigh the influences:
  - What is conventional practice?
  - Are opioids likely to work well?
  - Are there reasonable alternatives?
  - Are drug-related behaviors likely to be responsible, or problematic so as to require intensive monitoring?
Opioid Therapy: Needs and Obligations

- Learn how to assess patients with pain and make reasoned decisions about a trial of opioid therapy
- Learn prescribing principles
- Learn principles of addiction medicine sufficient to monitor drug-related behavior and address aberrant behaviors
Opioid Therapy: Prescribing Principles

- Prescribing principles
  - Drug selection
  - Dosing to optimize effects
  - Treating side effects
  - Managing the poorly responsive patient
Opioid Therapy: Drug Selection

- Immediate-release preparations
  - Used mainly
    - For acute pain
    - For dose finding during initial treatment of chronic pain
    - For “rescue” dosing
  - Can be used for long-term management in select patients
Opioid Therapy: Drug Selection

- Immediate-release preparations
  - Combination products
    - Acetaminophen, aspirin, or ibuprofen combined with codeine, hydrocodone, dihydrocodeine
  - Single-entity drugs, eg, morphine, oxycodone, oxymorphone, others
  - Tramadol
Opioid Therapy: Drug Selection

- Extended-release preparations
  - Preferred because of improved treatment adherence and the likelihood of reduced risk in those with addictive disease
  - Morphine, oxycodone, oxymorphone, fentanyl, hydromorphone, codeine, tramadol, buprenorphine
  - Adjust dose q 2–3 d
Opioid Therapy: Drug Selection

- **Role of methadone**
  - Another useful long-acting drug
  - Unique pharmacology when commercially available as the racemic mixture
  - Potency greater than expected based on single-dose studies
  - When used for pain: multiple daily doses, steady-state in 1 to several weeks
  - Close monitoring needed until steady-state approached to reduce risk of side effects
Opioid Selection: Poor Choices for Chronic Pain

- Meperidine (Pethidine)
  - Poor absorption and toxic metabolite
- Propoxyphene
  - Poor efficacy and toxic metabolite
- Mixed agonist-antagonists (pentazocine, butorphanol, nalbuphine, dezocine)
  - Compete with agonists $\rightarrow$ withdrawal
  - Analgesic ceiling effect
Opioid Therapy: Routes of Administration

- Oral and transdermal—preferred
- Oral transmucosal—available for fentanyl and used for breakthrough pain
- Rectal route—limited use
- Parenteral—SQ and IV preferred and feasible for long-term therapy
- Intraspinal—intrathecal generally preferred for long-term use
Opioid Therapy: Guidelines

- Consider use of a long-acting drug and a “rescue” drug—usually 5%–15% of the total daily dose
- Baseline dose increases: 25%–100% or equal to “rescue” dose use
- Increase “rescue” dose as baseline dose increases
- Treat side effects
Opioid Therapy: Side Effects

- **Common**
  - Constipation
  - Somnolence, mental clouding

- **Less common**
  - Nausea
  - Sweating
  - Myoclonus
  - Amenorrhea
  - Itch
  - Sexual dysfunction
  - Urinary retention
  - Headache
Opioid Responsiveness

- Opioid dose titration over time is critical to successful opioid therapy
- **Goal**: Increase dose until pain relief is adequate or intolerable and unmanageable side effects occur
- No maximal or “correct” dose
- Responsiveness of an *individual* patient to a *specific* drug cannot be determined unless dose was increased to treatment-limiting toxicity
Poor Opioid Responsiveness

- If dose escalation → adverse effects
  - Better side-effect management
  - Pharmacologic strategy to lower opioid requirement
    - Spinal route of administration
    - Add nonopioid or adjuvant analgesic
  - “Opioid rotation”
  - Nonpharmacologic strategy to lower opioid requirement
Opioid Rotation

- Based on large intraindividual variation in response to different opioids
- Reduce equianalgesic dose by 25%–50% with provisos:
  - Reduce less if pain severe
  - Reduce more if medically frail
  - Reduce less if same drug by different route
  - Reduce fentanyl less
  - Reduce methadone more: 75%–90%
<table>
<thead>
<tr>
<th>PO/PR (mg)</th>
<th>Analgesic</th>
<th>SC/IV/IM (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>4–8</td>
<td>Hydromorphone</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>Methadone</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>Oxymorphone</td>
<td>1</td>
</tr>
</tbody>
</table>
Opioid Therapy and Chemical Dependency

- Physical dependence
- Tolerance
- Addiction
- Pseudoaddiction
Opioid Therapy and Chemical Dependency

- Physical dependence
  - Abstinence syndrome induced by administration of an antagonist or by dose reduction
  - Assumed to exist after dosing for a few days but actually highly variable
  - Usually unimportant if abstinence avoided
  - Does not independently cause addiction
Opioid Therapy and Chemical Dependency

- **Tolerance**
  - Diminished drug effect from drug exposure
  - Varied types: associative vs pharmacologic
  - Tolerance to side effects is desirable
  - Tolerance to analgesia is seldom a problem in the clinical setting
    - Tolerance rarely “drives” dose escalation
    - Tolerance does not cause addiction
Opioid Therapy and Chemical Dependency

- Addiction
  - Disease with pharmacologic, genetic, and psychosocial elements
  - Fundamental features
    - Loss of control
    - Compulsive use
    - Use despite harm
  - Diagnosed by observation of aberrant drug-related behavior
Pseudoaddiction

- Aberrant drug-related behaviors driven by desperation over uncontrolled pain
- Reduced by improved pain control

Complexities

- How aberrant can behavior be before it is inconsistent with pseudoaddiction?
- Can addiction and pseudoaddiction coexist?
Opioid Therapy and Chemical Dependency

- **Risk of addiction: Evolving view**
  - Acute pain: Very unlikely
  - Cancer pain: Very unlikely
  - Chronic noncancer pain:
    - Surveys of patients without abuse or psychopathology show rare addiction
    - Surveys that include patients with abuse or psychopathology show mixed results
Chronic Opioid Therapy in Substance Abusers

**Good outcome** \((N = 11)\)
- Primarily alcohol
- Good family support
- Membership in AA or similar groups

**Bad outcome** \((N = 9)\)
- Polysubstance
- Poor family support
- No membership in support groups

Opioid Therapy: Monitoring Outcomes

- Critical outcomes
  - Pain relief
  - Side effects
  - Function—physical and psychosocial
  - Drug-related behaviors
## Monitoring Drug-Related Behaviors

<table>
<thead>
<tr>
<th>Probably more predictive of addiction</th>
<th>Probably less predictive of addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Selling prescription drugs</td>
<td>□ Aggressive complaining</td>
</tr>
<tr>
<td>□ Forging prescriptions</td>
<td>□ Drug hoarding when symptoms are milder</td>
</tr>
<tr>
<td>□ Stealing or “borrowing” drugs from another person</td>
<td>□ Requesting specific drugs</td>
</tr>
<tr>
<td>□ Injecting oral formulation</td>
<td>□ Acquiring drugs from other medical sources</td>
</tr>
<tr>
<td>□ Obtaining prescription drugs from nonmedical source</td>
<td>□ Unsanctioned dose escalation once or twice</td>
</tr>
<tr>
<td>□ “Losing” prescriptions repeatedly</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring Drug-Related Behaviors (cont.)

Probably more predictive of addiction

- Concurrent abuse of related illicit drugs
- Multiple dose escalations despite warnings
- Repeated episodes of gross impairment or dishevelment

Probably less predictive of addiction

- Unapproved use of the drug to treat another symptom
- Reporting of psychic effects not intended by the clinician
- Occasional impairment
Monitoring Aberrant Drug-Related Behaviors: 2-Step Approach

Step 1: Are there aberrant drug-related behaviors?

Step 2: If yes, are these behaviors best explained by the existence of an addiction disorder?
Opioid Therapy and Chemical Dependency

- Differential diagnoses of aberrant drug-related behavior
  - Addiction
  - Pseudoaddiction
  - Other psychiatric disorders (e.g., borderline personality disorder)
  - Mild encephalopathy
  - Family disturbances
  - Criminal intent
Opioid Therapy and Chemical Dependency

- **Addressing aberrant drug-related behavior**
  - Proactive and reactive strategies
  - **Management principles**
    - Know laws and regulations
    - Communicate
    - Structure therapy to match perceived risk
    - Assess behaviors comprehensively
    - Relate to addiction-medicine community
    - Possess a range of strategies to respond to aberrant behaviors
Opioid Therapy and Chemical Dependency

- Addressing aberrant drug-related behavior

  - Strategies to respond to aberrant behaviors
    - Frequent visits and small quantities
    - Long-acting drugs with no rescue doses
    - Use of one pharmacy, pill bottles, no replacements or early scripts
    - Use of urine toxicologies
    - Coordination with sponsor, program, addiction medicine specialist, psychotherapist, others
Opioid Therapy: Conclusions

- An approach with extraordinary promise and substantial risks
- An approach with clear obligations on the part of prescribers
  - Assessment and reassessment
  - Skillful drug administration
  - Knowledge of addiction-medicine principles
  - Documentation and communication
Nonopioid Analgesics

- Acetaminophen (paracetamol)
- Dipyrone
- Nonsteroidal anti-inflammatory drugs
Nonopioid Analgesics

- Acetaminophen (paracetamol)
  - Minimal anti-inflammatory effects
  - Fewer adverse effects than other nonopioid analgesics
  - Adverse effects
    - Renal toxicity
    - Risk for hepatotoxicity at high doses
      - Increased risk with liver disease or chronic alcoholism
  - No effect on platelet function
Mechanism

- Inhibit both peripheral and central cyclo-oxygenase, reducing prostaglandin formation
- 3 isoforms of COX
  - COX-1: Constitutive, physiologic
  - COX-2: Inducible, inflammatory
  - COX-3: Central, blocked by acetaminophen
NSAIDs

- Properties
  - Nonspecific analgesics, but greater effectiveness likely in inflammatory pains
  - Dose-dependent effects, with ceiling dose
  - Marked individual variation in response to different drugs
  - Drug-to-drug variation in toxicities partly determined by COX-1/COX-2 selectivity
NSAIDs

- **Properties**
  - **Adverse effects:** GI toxicity, renal toxicity, cardiovascular toxicity, bleeding diathesis, prothrombotic effects
    - GI toxicity reduced by PPIs, misoprostol, and possibly high-dose histamine-2 blockers
    - COX-2 selective inhibitors have better GI safety profile
  - Use with caution in patients with renal insufficiency
  - Use with caution in patients with atherosclerotic disease, congestive heart failure, or hypertension
<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonacidic</td>
<td>nabumetone</td>
</tr>
<tr>
<td><strong>Acidic: Salicylates</strong></td>
<td>aspirin, diflunisal, choline magnesium trisalicylate, salsalate</td>
</tr>
<tr>
<td><strong>Acidic: Proprionic acids</strong></td>
<td>ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin</td>
</tr>
</tbody>
</table>
### NSAIDs

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acidic: Acetic acids</strong></td>
<td>indomethacin, tolmetin, sulindac, diclofenac, ketorolac</td>
</tr>
<tr>
<td><strong>Acidic: Oxicams</strong></td>
<td>piroxicam</td>
</tr>
<tr>
<td><strong>Acidic: Fenamates</strong></td>
<td>mefenamic acid, meclofenamic acid</td>
</tr>
<tr>
<td><strong>Selective COX-2 inhibitors</strong></td>
<td>celecoxib</td>
</tr>
</tbody>
</table>
NSAIDs

- Drug selection should be influenced by drug-selective toxicities, prior experience, convenience, cost.
- Relative cost-benefit of COX-2 selective drugs and nonselective drugs combined with gastroprotective therapy is not known.
Adjuvant Analgesics

- Defined as drugs with other indications that may be analgesic in specific circumstances
- Numerous drugs in diverse classes
- Sequential trials are often needed
Adjuvant Analgesics

- Multipurpose analgesics
- Drugs used for neuropathic pain
- Drugs used for musculoskeletal pain
- Drugs used for cancer pain
- Drugs used for headache
## Multipurpose Adjuvant Analgesics

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>amitriptyline, desipramine, nortriptyline, duloxetine, venlafaxine, paroxetine, others</td>
</tr>
<tr>
<td>Alpha-2 adrenergic agonists</td>
<td>tizanidine, clonidine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>prednisone, dexamethasone</td>
</tr>
</tbody>
</table>
Antidepressants

- Best evidence: $3^0$ amine TCAs (e.g., amitriptyline)
- $2^0$ amine TCAs (desipramine, nortriptyline) better tolerated and also analgesic
- Evidence for the SSNRI, e.g., duloxetine, and little evidence in favor of SSRIs/atypical antidepressants (e.g., paroxetine, bupropion, others); these are better tolerated yet
Alpha-2 adrenergic agonists

- Clonidine and tizanidine used for chronic pain of any type
- Tizanidine usually better tolerated
- Tizanidine starting dose 1–2 mg/d; usual maximum dose up to 40 mg/d
## Adjuvant Analgesics for Neuropathic Pain

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>gabapentin, pregabalin, valproate, lamotrigine, phenytoin, carbamazepine, clonazepam, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>mexiletine, tocainide</td>
</tr>
</tbody>
</table>
## Adjuvant Analgesics for Neuropathic Pain

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA receptor</td>
<td>dextromethorphan, ketamine, amantadine</td>
</tr>
<tr>
<td>Antagonists</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>baclofen, calcitonin</td>
</tr>
<tr>
<td>Topical</td>
<td>lidocaine, lidocaine/prilocaine, capsaicin, NSAIDs</td>
</tr>
</tbody>
</table>
Adjuvant Analgesics for Neuropathic Pain

Anticonvulsants

- Gabapentin or pregabalin commonly used
  - Favorable safety profile and positive RCTs in PHN/diabetic neuropathy
- Analgesic effects supported for phenytoin, carbamazepine, valproate, clonazepam, and lamotrigine
- Limited experience with other drugs
Adjuvant Analgesics for Neuropathic Pain

- Local anesthetics
- Oral therapy with mexiletine, tocainide, flecainide
- IV/SQ lidocaine also useful
- Useful for any type of neuropathic pain
Adjuvant Analgesics for Neuropathic Pain

Miscellaneous drugs

- **Calcitonin**
  - RCTs in CRPS and phantom pain
  - Limited experience

- **Baclofen**
  - RCT in trigeminal neuralgia
  - 30–200 mg/d or higher
  - Taper before discontinuation
Adjuvant Analgesics for Neuropathic Pain

NMDA-receptor antagonists

- N-methyl-D-aspartate receptor involved in neuropathic pain
- Commercially-available drugs are analgesic: ketamine, dextromethorphan, amantadine
Topical Adjuvant Analgesics

- Used for neuropathic pain
  - Local anesthetics
    - Lidocaine patch
    - Cream, eg, lidocaine 5%, EMLA
    - Capsaicin

- Used for musculoskeletal pains
  - NSAIDs
“Muscle relaxants”

- Refers to numerous drugs, eg, cyclobenzaprine, carisoprodol, orphenadrine, methocarbamol, chlorzoxazone, metaxalone
- Centrally-acting analgesics
- Do not relax skeletal muscle
Adjuvant Analgesics for Cancer Pain

- For bone pain
  - Bisphosphonates (eg, pamidronate, clodronate), calcitonin, radiopharmaceuticals (eg, Sr$^{89}$, Sm$^{153}$)

- For bowel obstruction pain
  - Anticholinergics, octreotide
Adjuvant Analgesics for Chronic Headache

- Beta blockers
- Anticonvulsants
- Calcium channel blockers
- Alpha-2 adrenergic agonists
- Antidepressants
- Vasoactive drugs
- ACE inhibitors
Novel Drug Therapies for Pain
Central Nociception: Emerging Analgesic Targets

- Excitatory amino acid and NK receptors
- N-type Ca^{++} receptors
- N-acetylcholine receptors
- Adenosine (A_{1}) receptors
- Cannabinoid (CB1) receptors
Peripheral Nociception: Emerging Analgesic Targets

- Sensory neuron specific Na\(^+\) channels (eg, PN3, NAN)
- Opioid receptors
- Vanilloid receptors
- Serotonin receptors
Peripheral Nociception: Emerging Analgesic Targets

- Alpha-adrenergic receptors
- Proton-sensitive channels (pH-sensitive)
- Nerve–growth-factor receptors (TrKA, p75)
- N- or T-type Ca^{++} channels
- Purine receptors
Nonopioid Analgesics and Adjuvants for Inflammatory Neuropathic Pain States

- Anticytokines (eg, anti–TNF-alpha antibodies, thalidomide, IV bisphosphonates)
Adjuvant Analgesics With Opioid Interactions

- NMDA antagonists (eg, dextromethorphan, ketamine, amantadine)
- Cholecystokinin-B antagonists (eg, proglumide)
- Ultra-low doses of opioid antagonists