Conflicts of Interest
None
Goals

Review basic physiology of the pain system & describe a taxonomy that distinguishes physiological and pathological pain states

Present a stepwise assessment and treatment strategy for neuropathic pain

Discuss use of opioid analgesics including risk mitigation strategies
I. Physiology and Taxonomy of Pain
Perception of pain occurs in the brain

René Descartes (1596 - 1650)
Physiology of nociception and pain

- Transduction
- Transmission
- Modulation
- Perception
- Behavior

Peripheral Nerve

Dorsal Root Ganglion

Dorsal Horn

C-Fiber
(A-beta Fiber)
A-delta Fiber

Noxious stimulus

Descending Pathways

Descending Pathways

Ascending Pathways

Ascending Pathways

Dorsal Horn of Spinal Cord
Taxonomy of Pain

- Nociceptive
- Inflammatory
- Neuropathic
Nociceptive Pain

No pathology
Requires an ongoing noxious stimulus
A high threshold (Aδ, C) protective alarm system
Nociceptive pain

No nervous system lesion or inflammation
Stimulus-dependent pain
Evoked by high-intensity (noxious) stimuli

Adaptive
Protects by signaling potential tissue damage

Physiological stimuli:
- mechanical (pinprick)
- thermal (noxious heat or cold)
- chemical injury

Clinically relevant stimuli:
- abnormal mechanical forces (osteoarthritis)
- organ injury (angina, ischemic claudication)
Inflammatory Pain

Tissue injury with inflammation
Allodynia, hyperalgesia, spontaneous pain
A low threshold protective system that promotes healing/repair
**Inflammatory Pain**

Spontaneous and stimulus-dependent pain
Sensory amplification
Evoked by low- and high-intensity stimuli

Adaptive and reversible
Protects by producing pain hypersensitivity during healing

Central amplification
Peripheral amplification

Clinically relevant stimuli:
tissue trauma, surgery, joint inflammation as in rheumatoid arthritis

**Diagram elements:**
- Pain
- Time (response duration)
- Central amplification
- Peripheral amplification
- Mast cell
- Macrophage
- Neutrophil granulocyte
Peripheral diabetic neuropathy

Neuropathic Pain

PNS or CNS lesions

Allodynia, hyperalgesia, spontaneous pain, negative symptoms

Low threshold – pathological/maladaptive
Neuropathic Pain

- Nervous system lesion or disease
- Marked neuroimmune response
- Spontaneous and stimulus-dependent pain
- Sensory amplification
- Evoked by low- and high-intensity stimuli

- Central amplification
- Neuroimmune interactions in the periphery and the CNS

- Peripheral amplification
- PNS lesion or disease: nerve trauma, toxic and metabolic neuropathies, Herpes zoster, AIDS

- Maladaptive and commonly persistent
- Abnormal amplification maintained independent of the lesion or disease

- Time (response duration)
II. Assessment and Treatment of Neuropathic Pain

Learning objective: present an evidenced-based approach to treating neuropathic pain
Neuropathic Pain - Definition

Pain caused by a lesion or disease of the somatosensory nervous system (IASP).
Common Etiologies of Neuropathic Pain (PNS and/or CNS injury/dysfunction)

- Stroke
- Spinal Cord Injury
- Metabolic abnormalities
  - diabetes
- Chemotherapy/irradiation
- Neurotoxins
- Inherited neurodegeneration
- Nerve root compression
- Tumor infiltration
- Inflammation & infection
- Herpes Zoster
- Trigeminal neuralgia
- Mechanical irritation
- Nutritional deficiencies
- Trauma/surgery
- Multiple sclerosis
- Amputation
- HIV
### Estimated Prevalence of Neuropathic Pain in the United States

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Painful diabetic neuropathy</strong></td>
<td>600,000</td>
</tr>
<tr>
<td><strong>Postherpetic neuralgia</strong></td>
<td>500,000</td>
</tr>
<tr>
<td>Cancer-associated</td>
<td>200,000</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>120,000</td>
</tr>
<tr>
<td>CRPS types I and II</td>
<td>100,000</td>
</tr>
<tr>
<td>HIV-associated</td>
<td>100,000&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>50,000</td>
</tr>
<tr>
<td>Phantom pain</td>
<td>50,000</td>
</tr>
<tr>
<td>Post-stroke</td>
<td>30,000</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>15,000</td>
</tr>
<tr>
<td><strong>Low back pain</strong></td>
<td>2,100,000</td>
</tr>
<tr>
<td>Total (excluding back pain)</td>
<td>1,765,000</td>
</tr>
<tr>
<td><strong>Total (including back pain)</strong></td>
<td><strong>3,865,000</strong></td>
</tr>
</tbody>
</table>

Symptoms of Neuropathic Pain

Evoked pain (stimulus-dependent)
- Allodynia
- Hyperalgesia

Spontaneous pain (stimulus-independent)
- Loss of function (sensory, motor, autonomic)
A Stepwise Approach to Treating Neuropathic Pain
Review and recommendations

Pharmacologic management of neuropathic pain:
Evidence-based recommendations

Robert H. Dworkin a,*, Alec B. O’Connor a, Miroslav Backonja b,
John T. Farrar c, Nanna B. Finnerup d, Troels S. Jensen d, Eija A. Kalso e,
John D. Loeser f, Christine Miaskowski g, Turo J. Nurmikko h,
Russell K. Portenoy i, Andrew S.C. Rice j,
Brett R. Stacey k, Rolf-Detlef Treede l, Dennis C. Turk f, Mark S. Wallace m
Pharmacologic management of neuropathic pain

Step 1: Initial evaluation

- Assess – is NP present?
- If possible, treat the underlying cause of NP; refer specialist(s) as appropriate.
- Identify relevant co-morbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might require dosage adjustment, additional monitoring of therapy, etc.
- Explain the diagnosis and treatment plan to the patient, and establish realistic expectations.
Establish the diagnosis, search for underlying etiology, and discuss…

Manage Expectations – Patient’s and Your Own
Pharmacologic management of neuropathic pain

Step 2: Symptom management

Initiate pain treatment with one or more of the following first-line agents:

1. A secondary amine TCA (e.g., nortriptyline) or an SNRI (duloxetine, milnacipran, venlafaxine)

2. A calcium channel α2-δ ligand: gabapentin or pregabalin
Pharmacologic management of neuropathic pain

(Step 2: Symptom mgt cont.)

• For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the first-line therapies.

• For patients with acute NP or episodic exacerbations of severe NP, and when prompt pain relief is required during titration of a first-line medication, opioid analgesics or tramadol/tapentadol may be used alone or in combination with one of the first-line therapies.

• Consider non-pharmacologic treatments, and initiate as appropriate.
Pharmacologic management of neuropathic pain

**Step 3: Reassessment**

- Reassess pain, functional status and quality of life regularly.
- If substantial pain relief and tolerable side effects, continue treatment.
- If partial pain relief after an adequate trial, add another first-line NP medication.
- If no or inadequate pain relief (e.g., < 30% reduction) at target dosage, switch to an alternative first-line medication or add a second agent.
Polypharmacy is often beneficial and necessary.

Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial

Ian Gilron, Joan M Bailey, Dongsheng Tu, Ronald R Holden, Alan C Jackson, Robyn L Houlden

Summary

Background Drugs for neuropathic pain have incomplete efficacy and dose-limiting side-effects when given as monotherapy. We assessed the efficacy and tolerability of combined nortriptyline and gabapentin compared with each drug given alone.

Methods In this double-blind, double-dummy, crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia, and who had a daily pain score of at least 4 (scale 0–10), were enrolled and treated at one study site in Canada between Nov 5, 2004, and Dec 13, 2007. 56 patients were randomised in a 1:1:1 ratio with a balanced Latin
Pharmacologic management of neuropathic pain

*Step 4: Referral as appropriate*

If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist, ideally at a multidisciplinary pain center, and/or other appropriate specialists.
FDA Approved Medications for Neuropathic & Chronic Pain

1. Carbamazepine (Tegretol) - trigeminal neuralgia
2. Triptans (5HT1 agonists) - migraine headache
3. Gabapentin (Neurontin) - postherpetic neuralgia
4. Duloxetine (Cymbalta) - diabetic peripheral neuralgia, fibromyalgia, chronic musculoskeletal pain
5. Pregabalin (Lyrica) - postherpetic neuralgia, diabetic peripheral neuralgia, fibromyalgia
6. Transdermal lidocaine 5% (Lidoderm) - postherpetic neuralgia
7. Transdermal capsaicin 8% (Qutenza) - postherpetic neuralgia
8. Milnacipran (Savella) - fibromyalgia
9. Prialt (ziconotide) - severe chronic pain in patients who are refractory to other therapies. Intrathecal delivery only.
First line Rx: TCAs/SNRIs

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Therapeutic index</th>
<th>Major side effects</th>
<th>Precautions</th>
<th>Other benefits</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary amine TCAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nortriptyline, desipramine (use a tertiary amine TCA only if a secondary amine is not available)</td>
<td>+</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
<td>Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol</td>
<td>Improvement of depression, improvement of insomnia</td>
<td>$</td>
</tr>
<tr>
<td><strong>SSNRIs</strong></td>
<td></td>
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</tr>
<tr>
<td>Duloxetine*</td>
<td>++</td>
<td>Nausea</td>
<td>Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol</td>
<td>Improvement of depression</td>
<td>$$</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+</td>
<td>Nausea</td>
<td>Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation</td>
<td>Improvement of depression</td>
<td>$/$$</td>
</tr>
</tbody>
</table>
First line Rx:
calcium channel α2-δ ligands

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Therapeutic index</th>
<th>Major side effects</th>
<th>Precautions</th>
<th>Other benefits</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel α2-δ ligands</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Gabapentin                | ++                | Sedation, dizziness, peripheral edema  | Renal insufficiency | Improvement of sleep disturbance, no clinically significant drug interactions | $/$$
| Pregabalin\(^\text{e}\)  | ++                | Sedation, dizziness, peripheral edema  | Renal insufficiency | Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions | $$      |
### Opioids as a second line Rx (?)

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Therapeutic index</th>
<th>Major side effects</th>
<th>Precautions</th>
<th>Other benefits</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone,</td>
<td>+</td>
<td>Nausea/vomiting, constipation, drowsiness, dizziness</td>
<td>History of substance abuse, suicide risk, driving impairment during treatment initiation</td>
<td>Rapid onset of analgesic benefit</td>
<td>$/$$</td>
</tr>
<tr>
<td>methadone, levorphanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>+</td>
<td>Nausea/vomiting, constipation, drowsiness, dizziness seizures</td>
<td>History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SSNRI, TCA</td>
<td>Rapid onset of analgesic benefit</td>
<td>$/$$</td>
</tr>
</tbody>
</table>
Third-line NP Agents

• Other antiepileptic and antidepressant medications – e.g., topiramate, lamotrigine, etc.
• Na-channel blockers – e.g., mexiletine
• Topical capsaicin 8% (PHN)
• NMDA receptor antagonists
Special Populations with Neuropathic Pain

Central neuropathic pain

Post-stroke pain → TCAs

Spinal-cord injury pain → α2-δ ligands

Multiple sclerosis → cannabinoids? (limited data, risk of psychosis)

Chronic radicular pain

Little long-term outcome data, but 1st line NP agents are likely effective
Summary

• A substantial body of evidence guides the pharmacologic treatment of patients with neuropathic pain (LEVEL I).
• Polypharmacy often required.
• The utility of chronic opioid management for NP is controversial.
IV. Opioid Therapy for Chronic, non-Terminal Pain: Utility and Risk Mitigation
“There is a Reason They Call it Dope”

by James E. Brick MD, EB Flink Professor and Chair of Medicine, West Virginia University, Morgantown and John F. Brick MD, Professor and Chair, Neurology, West Virginia University, Morgantown

Among the lists ranking various states and their attributes our beloved West Virginia is usually at the extremes of the rankings, either very good (e.g. murders) (e.g. obesity and its consequent complications) or very bad (e.g. guns). We should probably give us a break from the “bad end” of the science of prescription narcotic drugs and overdoses. These problems have now reached proportions all over West Virginia, perhaps particularly south of Route 60 where US 119 is referred to with gallows humor as the “Hillbilly Heroin Highway”. This relatively small area has frequently an outpouring of news down there and hardly a day goes by without us hearing of a home invasion or a S. O. B. seeking home invasion or personal violence in a small town that dreamed of such 20 years ago. We have not been kind to our professional parents’ knees. These drugs have serious implications. Patients taking them on a chronic basis are in danger of “losing their soul” to them. Don’t get your patients started on chronic narcotics for nonmalignant pain. It’s as simple as that. Don’t go there to begin with. Just say no. Barring that, think long and hard about it and other options and make sure your patient knows what they may be getting in for.

Opioid Misuse & Abuse: A National Scourge


B. Deaths from Unintentional Drug Overdoses in the United States According to Major Type of Drug, 1999–2007

U.S. Rates of Death from Unintentional Drug Overdoses and Numbers of Deaths, According to Major Type of Drug.

Shown are nationwide rates of death from unintentional drug overdoses from 1970 through 2007 (Panel A) and the numbers of such deaths from opioid analgesics, cocaine, and heroin from 1999 through 2007 (Panel B). Data are from the National Vital Statistics System, Centers for Disease Control and Prevention.

OBJECTIVE:
To assess the efficacy and safety of once-daily hydromorphone extended-release tablets (OROS [Alza Corporation, Mountain View, CA] hydromorphone ER) in patients with chronic neuropathic pain.

DESIGN:
Single-center, open-label, 12-week study.

PATIENTS:
Opioid-tolerant patients with chronic neuropathic pain for $6 months (N = 30). Interventions: Patients were converted from previous opioid therapy to OROS hydromorphone ER using a 5:1 morphine:hydromorphone equianalgesic dosing ratio, with an initial 50 percent reduction of the calculated equianalgesic dose, titrated every 3-4 days to adequate analgesia over 2 weeks.

OUTCOME MEASURES:
The primary efficacy measure was change from baseline to week 12 (end of study) on question #5 ("average pain") of the Brief Pain Inventory (BPI). Secondary measures included least pain, worst pain, current pain, and sleep interference on the BPI, as well as the Pain Quality Assessment Scale (PQAS) and patient global assessment of treatment satisfaction. Results: Thirty patients were enrolled and received $1 dose of OROS hydromorphone ER, titrated to a final mean dose of 26.4 mg/d. Mean (SE) BPI change from baseline to end of study was -1.3 (0.59) for current pain (p < 0.05) and -1.8 (0.61) for worst pain (p < 0.01). Mean (SE) change from baseline was also significant for BPI scores for sleep interference (-1.7 [0.61]; p < 0.01) and PQAS scores (-24.8 [7.9], p < 0.01). The majority (81 percent) of patients were satisfied or very satisfied with treatment. The most common treatment-related adverse events were dizziness, headache, and nausea (two patients each).

CONCLUSIONS:
Patients with chronic neuropathic pain were safely and effectively converted to and maintained on OROS hydromorphone ER.
Prescriber Guide to Interpreting Prescription Monitoring Program Data

This guide is designed to assist prescribers in understanding the scope and limitations of the patient prescription history reports and electronic alerts of the Massachusetts Online Prescription Monitoring Program (MA Online PMP). Developed in consultation with pain and addiction specialists, it provides guidance in treating all patients including those for whom prescribers may have concern. It is important to note that, whether in the context of an electronic alert or a routine patient prescription history lookup, this guide does not mandate any particular action on the part of the prescriber.

About the MA Online PMP

The MA Online PMP is a secure website that can be utilized by authorized providers to retrieve the most recent twelve months’ of Schedule II - V dispensed prescription histories on their patients. It is a tool that supports safe prescribing and dispenses and assists in addressing...
Chronic Opioid Therapy is Almost Never a Monotherapy

The Effects of Interdisciplinary Team Assessment and a Rehabilitation Program for Patients with Chronic Pain

ABSTRACT


Objective: The aim of this study was to evaluate the effects of interdisciplinary team assessment and a 4-wk rehabilitation program in chronic pain patients.

Design: This was a longitudinal cohort study evaluating interdisciplinary pain rehabilitation measures in a specialist care setting. A total of 93 women (42.2 ± 9.5 yrs) with chronic musculoskeletal pain (median pain duration, 8 yrs) were...
- Don’t rush to initiate opioid therapy, particularly if you have not cared for the patient longitudinally. Employ a step-wise approach to pain treatment.
- Prior to initiating opioids:
  - Goals of therapy with indicators of success and ‘failure’
  - Opioid agreement (communication tool)
  - Toxicology at time of initial request
  - Psychological assessment/opioid risk stratification
- Start low, go slow, and don’t titrate to heroic doses
- Regular, meaningful reassessment
- Trust but verify
  - Call other providers (communication is key)
  - Call pharmacies
  - Check prescription monitoring program, if available
  - Random toxicology (urine/saliva) – provide a little rope when appropriate
  - Utilize a multidisciplinary approach
Opioid Therapy – other thoughts…

- Remain open minded. There is much more that we don’t know than we do know.

- Don’t be an extremist.
  - I never prescribe (OIH), or
  - I don’t believe in a dose ceiling.

- Chronic pain in the elderly is very common and there are frequently few meaningful treatment options. Low dose opioid therapy may be the best analgesic choice.
Case Study:

82 y/o formerly high-functioning male presents with low back and lower extremity pain secondary to severe non-operable spinal stenosis and painful peripheral neuropathy.