Moving from Mechanisms to Treatment in Chronic Pain Patients

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Learning Objective

Summarize the various pain states in chronic pain and evaluate the effectiveness of the current treatment modalities.

Pharmacological Treatment of Chronic Pain

- Nociceptive (peripheral) pain
- Central (non-nociceptive) pain
- Neuropathic:
  - Random-controlled trials (RCTs) performed to date suggest that neuropathic pain patients respond to both peripherally- (e.g., NSAIDs and opioids) and centrally focused pharmacological therapies (e.g., tricyclics and gabapentinoid).
  - At present, neuropathic distinction is important in identifying who will be more likely to respond to interventions than who will respond to drugs.

NSAIDs = non-steroidal anti-inflammatory drugs


Drugs for Pain Based on Underlying Mechanisms

<table>
<thead>
<tr>
<th>Peripheral</th>
<th>Neuropathic</th>
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<td>Non-inflammatory</td>
<td>Peripheral</td>
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<td>Inflammatory</td>
<td>Central</td>
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<td>Opiates</td>
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<td>NSAIDs/acetaminophen</td>
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<td>Immunomodulators</td>
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<td>Anti-inflammatories</td>
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<td>Alpha-2-delta ligand anticonvulsants</td>
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<td>Tricyclics</td>
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<td>SNRIs</td>
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Some antidepressants effective for nociceptive pain states with central pain component (e.g., OA, LBP):

Pharmacological Management of Peripheral (Nociceptive) Pain

- Acetaminophen
- NSAIDs
- Opioids
- Mixed-action agents

NSAIDs = non-steroidal anti-inflammatory drugs

Acetaminophen vs. NSAIDs – Which to Choose As “Peripheral” Analgesic

OA of the Knee and Hip

- Acetaminophen: Pain decreased 4 points more on 1 – 100 scale than placebo, i.e., low effect size [SMD .15 - .20] of questionable significance
- Oral NSAIDs: Better at relieving pain than acetaminophen in comparator trials but still have low to modest overall effect size [SMD .3 in pooled meta-analyses]
- Primary safety advantage of acetaminophen is in risk of GI toxicity [RR 1.47 with NSAIDs compared to acetaminophen]

OA = osteoarthritis; RR = relative risk; NSAIDs = nonsteroidal anti-inflammatory drugs


Analgesics with Mixed Opioidergic and Non-Opioidergic Activity

- Tramadol - serotonin norepinephrine reuptake inhibitor and mu opioid agonist
- Tramadol with or without acetaminophen for OA. Meta-analyses included 1019 participants
  - On average, pain improved 8 points on 0 -100 scale compared to placebo
  - RR 2.3 for minor side effects and 2.6 for major side effects compared to placebo
- Tapentadol - norepinephrine reuptake inhibitor and mu opioid agonist (likely much more opioid activity than tramadol and is schedule II drug)
  - Approved for acute pain only

OA = osteoarthritis; RR = relative risk

The Use of Opioids for Chronic Non-Cancer Pain

- Chronic opioid therapy has mainly been shown to be effective for cancer pain, neuropathic pain, and pain syndromes with a strong nociceptive component (OA, RA).
- Neuropathic pain on average had 14 points better response than placebo group.
- Be aware of recently recognized side effects of opioids:
  - Opioid-induced hyperalgesia
  - Hypogonadism and other endocrinopathies.

OA = osteoarthritis; RA = rheumatoid arthritis

American Pain Society (APS) Guidelines for the Use of Opioids for Chronic Non-Cancer Pain

- Chronic opioid therapy: considered if pain is moderate to severe with significant functional status limitations and if there is no history of addiction or abuse.
- Personal or family history of drug abuse or addiction: strongest risk for subsequent addiction.
- Screener and Opioid Assessment for Patients with Pain (SOAPP) and the Opioid Risk Tool (ORT) can be helpful.
- Before starting chronic opioid therapy, informed consent should be obtained and a contract should be considered.
- Use short trial of short-acting opioids to determine if longer trial is in order — emphasize trial of opioids.


APS Guidelines for the Use of Opioids for Chronic Non-Cancer Pain

- Methadone should only be used by those familiar with its use because of inconsistent kinetics and QTc prolongation.
- Patients should be re-assessed for efficacy and progress toward agreed upon goals.
- Urine screening for individuals at high risk or suspected of abuse.

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Any of These Neurotransmitters Are Potential Targets in Central Pain

**Facilitation**
- Substance P
- Glutamate and EAA
- Nerve growth factor
- CCK

**Inhibition**
- Descending anti-nociceptive pathways
  - Norepinephrine: serotonin (5-HT2a, 3a)
  - Opioids
  - GABA
  - Cannabinoids
  - Adenosine

EAA = excitatory amino acid; CCK = Cholecystokinin; GABA = gamma-aminobutyric acid


Pharmacological Therapies for Fibromyalgia (i.e., Central Pain)

**Strong Evidence**
- Dual reuptake inhibitors such as
  - Tricyclic compounds (amitriptyline, cyclobenzaprine)*
  - Serotonin and Norepinephrine reuptake inhibitors (SNRIs, NSRIs)*
- Anticonvulsants (e.g., pregabalin, gabapentin)*

**Modest Evidence**
- Tramadol*
- Selective serotonin reuptake inhibitors (SSRIs)*
- Gamma hydroxybutyrate*
- Dopamine agonists*

**Weak Evidence**
- Growth hormone*, 5-hydroxytryptamine*, tropisetron*, S-adenosyl-L-methionine (SAMe)*
- Opioids*, corticosteroids*, non-steroidal anti-inflammatory drugs*, benzodiazepine* and non-benzodiazepine hypnotics*, guanifenesin*

**No Evidence**
- Opioids*, corticosteroids*, non-steroidal anti-inflammatory drugs*, benzodiazepine* and non-benzodiazepine hypnotics*, guanifenesin*

*Not an FDA approved indication for this agent


See supplemental bibliography for FDA information.
Treating Peripheral Pain Generators May Reduce Hyperalgesia and Central Sensitization - I

- Female patients with FM and either (a) myofascial pain (n = 68) or (b) concurrent OA (n = 56)
- Patients were randomized to receive (a) myofascial trigger point injection* vs. sham needling, or (b) steroid ionophoresis* to affected joint or sham ionophoresis
- Evaluations were repeated on days 4 and 8 on both overall pain and tenderness

*Not an FDA approved indication for this agent
FM = fibromyalgia; OA = osteoarthritis

Treating Peripheral Pain Generators May Reduce Hyperalgesia and Central Sensitization - II

- After therapy, in active – but not placebo-treated groups: number and intensity of myofascial/joint episodes and paracetamol* consumption decreased and pressure thresholds at trigger/joint increased (p < .001); FM pain intensity decreased and all thresholds increased progressively in tender points and the non-painful site (p < .0001)
- At a 3-week follow-up, FM pain was still lower than basis in patients not undergoing further therapy, and had decreased in those undergoing active therapy from day 8

*Not an FDA approved indication for this agent
FM = fibromyalgia

Symptoms of Pain, Fatigue, etc.
- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms
- Increased Distress
- Decreased activity
- Isolation
- Poor sleep
- Maladaptive illness behaviors

Dually Focused Treatment
- Pharmacological therapies to improve symptoms
- Non-pharmacological therapies to address dysfunction

Non-pharmacological Therapies are Similar to Those for Any Chronic Pain State

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<th>Strong Evidence</th>
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<tr>
<td></td>
<td>Education</td>
<td>Strength training</td>
<td>Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound</td>
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<td>Aerobic exercise</td>
<td>Hypnotherapy, biofeedback, balneotherapy</td>
<td>Tender (trigger) point injections, flexibility exercise</td>
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<td>Cognitive behavior therapy</td>
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Cognitive Behavioral Therapy (CBT) for Chronic Pain

- Shown to be effective over a wide range of pain states
- Effect sizes on function (0.4 - 0.6) are much greater than typically seen with pharmacological therapies
- Despite wide agreement that these help, barriers to implementation have been:
  - Physicians do not strongly recommend these therapies and there is no industry promoting these therapies
  - Not generally reimbursed by third parties
  - Not enough trained therapists to give one-on-one CBT to all chronic pain patients


Fibroguide.com*

- Program features 10 CBT modules:
  - Understanding Fibromyalgia
  - Being Active
  - Sleep
  - Relaxation
  - Time for You
  - Setting Goals
  - Pacing Yourself
  - Thinking Differently
  - Communicating
  - Fibro Fog

In a RCT of 118 FM patients comparing the earlier version of this website plus usual care to usual care alone, Williams demonstrated statistically significant improvements in pain (29% in the WEB group had 30% improvement in pain vs. 8% in usual care, \( p = .009 \)) and function (i.e., 31% in WEB-SM had a 0.5 SD improvement in SF-36 PF vs. 6% in standard care, \( p < .002 \)).

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Exercise to Treat Chronic Pain

- OA of knee
  - SMD of .40 for pain and .37 for physical function. Studies that involved direct supervision of 12 or more sessions somewhat more likely to lead to improvement.
- OA of the hip
  - Small improvement in pain but not function.
- Fibromyalgia
  - Aerobic exercise improves global well-being (SMD .49), function (SMD .66) and pain (SMD .65 but very wide CIs include 0)
  - Strength training may also be effective although far fewer studies have been performed

Neurostimulatory Therapies

- Peripheral
  - TENS (transcutaneous electrical nerve stimulation)
    - Conventional TENS (C-TENS) is given at high stimulation frequency with low intensity, and pain relief is almost immediate but short-lived.
    - Acupuncture-like TENS (AL-TENS) is given at low frequency and high intensity (which is uncomfortable to many individuals), and generally has a longer lasting analgesic effect.
    - AL-TENS decreased pain and joint tenderness in rheumatoid arthritis
  - Leads to improvements in both pain and function in osteoarthritis

- Central - Being shown to be effective across a broad range of chronic pain conditions
  - Applied to scalp
    - Transcranial magnetic stimulation (TMS)
    - Direct Current Stimulation (DCS)
  - Implantable
    - Spinal cord stimulation
    - Vagal nerve stimulation
    - Deep brain stimulation

References:
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Summary

- Rheumatologists and other studying musculoskeletal pain have historically considered most pain to be from peripheral nociceptive input (i.e. damage or inflammation), and data increasingly suggest this is simply not the case.
- Central nervous system factors such as diffuse hyperalgesia and deficient descending analgesia have been shown to play a major role in common chronic pain conditions such as fibromyalgia, and are present in subsets of individuals with other chronic pain states such as rheumatoid arthritis, systemic lupus erythematosus, low back pain, osteoarthritis.

Clinical Connections

- Chronic pain states may be mixed pain states with variable peripheral and central contributions in different individuals with the same clinical label.
- None of our treatments of chronic pain have anything more than modest efficacy when used as stand-alone therapy.
- There are several treatments (e.g. CBT, exercise) that can lead to significant improvement in symptoms and function that are rarely utilized in routine clinical practice.
Save the Date!

6th Annual Chair Summit
September 26-28, 2013
Westin Tampa Harbour Island
Tampa, Florida

Check out www.cmeoutfitters.com for the most recent information on Chair Summit 2013. Registration will be open soon. See you in Tampa!