"Moving On": Non-Opioid Alternatives for Chronic Pain Management

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Disclosures

- No relevant conflicts of interest to disclose
- This presentation will include discussion of non-FDA approved indications:
  - **Venlafaxine** for treatment of chronic pain, migraine prevention, hot flashes, PTSD
  - **Duloxetine** for treatment of urinary incontinence
  - **Amitriptyline** for treatment of chronic pain, fibromyalgia, insomnia, irritable bowel syndrome, migraine prevention, PTSD
  - **Nortriptyline** for treatment of chronic pain, fibromyalgia, insomnia, migraine prevention, smoking cessation
  - **Citalopram** for treatment of chronic pain
  - **Fluoxetine** for treatment of chronic pain
  - **Paroxetine** for treatment of chronic pain
  - **Gabapentin** for treatment of fibromyalgia, anxiety, restless leg syndrome, hot flashes, alcohol dependence
  - **Pregabalin** for treatment of anxiety, restless leg syndrome, hot flashes

Pharmacist Objectives

1. Describe the efficacy and safety concerns with opioid monotherapy for chronic pain
2. Interpret the evidence of non-opioid pharmacologic therapies for chronic pain
3. List non-pharmacologic alternatives for chronic pain
4. Design a patient-specific management plan, incorporating non-opioid alternatives, for a patient with chronic pain
Technician Objectives

1. Propose 2 potential concerns of opioid monotherapy for chronic pain

2. Define the following terms: chronic pain, drivers of pain, multimodal

3. List 5 non-analgesic medications that may be used in the management of chronic pain

Definitions

Chronic Pain

• Definition: Pain persisting beyond 3 months or expected healing time

Definitions

Drivers of Pain

- **Definition:** Source from which pain originates
- **Synonyms:** Etiology, Cause of pain
- **Examples:** Nociceptive somatic, Nociceptive visceral, Neuropathic, Psychogenic
- **Represents only 1 component of the “pain picture”**

Multimodal

- **Definition:** Strategy of utilizing multiple therapies to “capture the effectiveness of individual agents in optimal doses and minimize side effects from the agents”
- **Synonyms:** Synergistic therapy
- **Can refer to pharmacotherapy or holistic care**

Audience Question #1

Which of the following is NOT an example of a multimodal approach to chronic pain management?

A. Utilizing multiple non-opioid pharmacotherapies
B. Addressing pain in conjunction with mental health conditions
C. Utilizing pharmacotherapies in conjunction with non-pharmacologic therapies
D. Utilizing both extended release and immediate release opioids to ensure adequate analgesia

CDC Guidelines for Prescribing Opioids for Chronic Pain 2016
The “CDC 5” Questions

Effectiveness  Harms  Dosing Strategies  Risk Mitigation  Acute on Chronic Pain


CDC Question #1

What is the “effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long term (≥1 year) outcomes related to pain, function, and quality of life, and how effectiveness varies according to the type/cause of pain, patient demographics, and patient comorbidities”? 

Study Selection

**Inclusion**

- Randomized and observational trials controlling for confounders
- Intervention: any opioid
- Adults on opioids for chronic pain for > 3 months
- Comparators: placebo, no therapy, another drug, non-pharm, different doses
- Outcomes after > 1 year of opioid initiation

**Exclusion**

- Tramadol, parenteral opioids
- Acute pain only, addiction treatment
- Pregnancy

Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
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</table>

Results

“No study” of opioid therapy versus placebo, opioid therapy, or nonopioid therapy for chronic pain evaluated long-term (≥1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized clinical trials were ≤6 weeks in duration. Thus, the body of evidence for KQ1 is rated as insufficient (0 studies contributing).”


The “CDC 5” Questions

- Effectiveness
- Harms
- Dosing Strategies
- Risk Mitigation
- Acute on Chronic Pain

Results

Rate of opioid abuse: 0.7% – 26%

<table>
<thead>
<tr>
<th>Opioid Abuse Risk</th>
<th>Past substance abuse</th>
<th>Mental health disorders</th>
<th>Current substance abuse</th>
<th>&lt; 30 years of age</th>
<th>20-49 MED chronic therapy</th>
<th>50-99 MED chronic therapy</th>
<th>≥ 120 MED chronic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No opioids prescribed</td>
<td>0.004%</td>
<td>6.1%</td>
<td>2.14%</td>
<td>3-26%</td>
<td>1.4X</td>
<td>3.7X</td>
<td>8.9X</td>
</tr>
<tr>
<td>≤ 36 MED chronic therapy</td>
<td>0.7%</td>
<td>6.1%</td>
<td>2.14%</td>
<td>3-26%</td>
<td>1.4X</td>
<td>3.7X</td>
<td>8.9X</td>
</tr>
<tr>
<td>≥ 120 MED chronic therapy</td>
<td>6.1%</td>
<td>6.1%</td>
<td>2.14%</td>
<td>3-26%</td>
<td>1.4X</td>
<td>3.7X</td>
<td>8.9X</td>
</tr>
<tr>
<td>Pain clinic</td>
<td>6.1%</td>
<td>6.1%</td>
<td>2.14%</td>
<td>3-26%</td>
<td>1.4X</td>
<td>3.7X</td>
<td>8.9X</td>
</tr>
<tr>
<td>Primary care</td>
<td>6.1%</td>
<td>6.1%</td>
<td>2.14%</td>
<td>3-26%</td>
<td>1.4X</td>
<td>3.7X</td>
<td>8.9X</td>
</tr>
</tbody>
</table>

Risk Factor | Overdose Risk | Death Risk |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>20-49 MED chronic therapy</td>
<td>1.4X</td>
<td>1.3X</td>
</tr>
<tr>
<td>50-99 MED chronic therapy</td>
<td>3.7X</td>
<td>1.9X</td>
</tr>
<tr>
<td>≥ 120 MED chronic therapy</td>
<td>8.9X</td>
<td>2.0X</td>
</tr>
</tbody>
</table>

CDC Recommendation

“Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate. (recommendation category: A, evidence type: 3).”
Results

“No evidence shows a long-term benefit of opioids...”

“Extensive evidence shows the possible harms of opioids...”

“Extensive evidence suggests some benefits of nonpharmacologic and nonopioid treatments...”


Audience Question #2

Dr. A utilizes opioids as monotherapy to treat a large number of patients for chronic pain and feels they are effective. She doesn’t understand why the CDC has taken a hard stance against opioids. She asks for your opinion.
Audience Question #2

Think
- How would you respond to Dr. A?

Pair
- Discuss your answer with a neighbor

Share
- Discuss as a group

<table>
<thead>
<tr>
<th>Non-Pharmacologic</th>
<th>Exercise therapy</th>
<th>Cognitive Behavioral Therapy (CBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologic Non-Opioids</td>
<td>Acetaminophen</td>
<td>NSAIDs and COX-2 Inhibitors</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
<td>Interventional Approaches</td>
</tr>
<tr>
<td></td>
<td>Antidepressants</td>
<td></td>
</tr>
</tbody>
</table>
# Exercise Therapy

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Driver(s) of Pain</th>
<th>Comparator(s)</th>
<th>Primary Outcomes</th>
<th>Take-Away's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busch</td>
<td>SR of 33 RCTs</td>
<td>Fibromyalgia</td>
<td>Active program</td>
<td>Global well-being, function, physical capacity, and fibromyalgia symptoms</td>
<td></td>
</tr>
<tr>
<td>Fransen (2015)</td>
<td>SR of 54 RCTs</td>
<td>Knee OA</td>
<td>Active program</td>
<td>Joint pain, Function, Quality of life</td>
<td></td>
</tr>
<tr>
<td>Fransen (2014)</td>
<td>SR of 10 RCTs</td>
<td>Knee OA</td>
<td>Active program</td>
<td>Joint pain, Function, Quality of life</td>
<td></td>
</tr>
<tr>
<td>Hayden</td>
<td>SR of 61 RCTs</td>
<td>Low back pain</td>
<td>Active program</td>
<td>Exercise reduces pain, improves function, quality of life, Sustained benefit at 6 months</td>
<td></td>
</tr>
</tbody>
</table>

## Clinical Pearls / Things to Remember
- Active program > No active program > No exercise
- Guidelines recommend aerobic, aquatic, and/or resistance, especially for OA
- Exercise has some of the most substantial evidence for benefit

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# Cognitive Behavioral Therapy (CBT)

<table>
<thead>
<tr>
<th>First Author</th>
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<th>Comparator(s)</th>
<th>Primary Outcomes</th>
<th>Take-Away's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams</td>
<td>SR of 42 RCTs</td>
<td>Chronic pain</td>
<td>CBT</td>
<td>Pain, Disability, Mood, Catastrophic thinking, improves mood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Behavioral only</td>
<td>Small to moderate benefit, Sustained benefit only noted for mood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No CBT</td>
<td>CBT &gt; Behavioral only</td>
<td></td>
</tr>
</tbody>
</table>

## Clinical Pearls / Things to Remember
- Helps patients modify situational factors and cognitive processes that exacerbate pain
- Can incorporate CBT without “formal CBT”
  - Relaxation
  - Mindfulness
  - Biofeedback
- For those with more entrenched anxiety/fear related to pain, refer to specialist
Non-Pharmacologic Therapies

• Unique benefits from non-pharmacologic therapies:
  ▪ Sustained improvements in pain and function without apparent risks
  ▪ Increases active patient participation in care
  ▪ Addresses psychosocial contributors to pain

• Access to “active programs” is the biggest challenge
  ▪ Cost
  ▪ Availability

• One RCT found NO difference in low back pain when comparing individual physiotherapy session (specialty) vs low-cost group aerobics

• Low-cost exercise options:
  ▪ Brisk walking in public spaces
  ▪ Public recreation facilities for group exercise

Acetaminophen

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Driver(s) of Pain</th>
<th>Comparator(s)</th>
<th>Primary Outcomes</th>
<th>Take-Away’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roelofs</td>
<td>SR of 65 RCTs</td>
<td>Low back pain</td>
<td>NSAIDs, COX-2 Inhibitors, Acetaminophen, Placebo</td>
<td>Pain</td>
<td>NSAIDs and acetaminophen have similar effect</td>
</tr>
<tr>
<td>Welsch</td>
<td>SR of 10 RCTs</td>
<td>Low back pain, OA</td>
<td>Opioids, Non-opioids</td>
<td>Pain, Function</td>
<td>Pain: Non-opioids = opioids, Function: Non-opioids &gt; opioids, Tolerability: Non-opioids &gt; opioids, Non-opioids included NSAIDs, COX-2 Inhibitors, acetaminophen, anticonvulsants, antidepressants</td>
</tr>
</tbody>
</table>

Clinical Pearls / Things to Remember

• Clearly has been delineated as first-line therapy for OA and/or low back pain
• Consider scheduling acetaminophen 3-4 times/day (not PRN)
• Potentially hepatotoxic at dosages > 3-4 grams/day
  ▪ Avoid or lower dose in liver disease
  ▪ Lower dose if chronic alcohol use
## NSAIDs and COX-2 Inhibitors

<table>
<thead>
<tr>
<th>First Author</th>
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<th>Primary Outcomes</th>
<th>Take-Away’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaparro</td>
<td>SR of 15 RCTs</td>
<td>Low back pain</td>
<td>Multiple non-opioids, Opioids</td>
<td>Pain</td>
<td>Celecoxib has similar effect as tramadol (1 trial)</td>
</tr>
<tr>
<td>Roelofs</td>
<td>SR of 65 RCTs</td>
<td>Low back pain</td>
<td>NSAIDs, COX-2 Inhibitors, Acetaminophen, Placebo</td>
<td>Pain</td>
<td>NSAIDs are effective for chronic low back pain without sciatica. NSAIDs and acetaminophen have similar effect. NSAIDs have more adverse events than acetaminophen. No NSAID, including COX-2 inhibitors, found to be superior over another.</td>
</tr>
<tr>
<td>Trelle</td>
<td>SR of 31 RCTs</td>
<td>Any condition</td>
<td>NSAIDs, Placebo</td>
<td>CV safety</td>
<td>NSAIDs associated with increased risk of MI, stroke, and CV death compared to placebo.</td>
</tr>
</tbody>
</table>

### Clinical Pearls / Things to Remember
- First-line therapy for OA and/or low back pain
- Not without their flaws
  - Gastritis, PUD
  - Cardiovascular concerns including increased blood pressure
  - Renal concerns
  - Fluid retention
  - Increased bleeding
- If hands tied with comorbidities, consider
  - COX-2 Inhibitor
  - Topical NSAID
### Antidepressants

<table>
<thead>
<tr>
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<th>Primary Outcomes</th>
<th>Take-Away’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaparro</td>
<td>SR of 15 RCTs</td>
<td>Low back pain</td>
<td>Multiple non-opioids, Opioids</td>
<td>Pain</td>
<td>TCAs have similar effect as opioids (2 trials)</td>
</tr>
<tr>
<td>Collins</td>
<td>SR of 19 RCTs</td>
<td>Diabetic neuropathy, Postherpetic neuralgia</td>
<td>Antidepressants, Placebo</td>
<td>Pain</td>
<td>Diabetic neuropathy: NNT 3.4 for ≥ 50% pain relief, Postherpetic neuralgia: NNT 2.1 for ≥ 50% pain relief, Antidepressants included TCAs and SSRIs</td>
</tr>
<tr>
<td>Lunn</td>
<td>SR of 18 RCTs</td>
<td>Neuropathic pain, Unspecified drivers, Fibromyalgia</td>
<td>Duloxetine, Placebo</td>
<td>Pain</td>
<td>Duloxetine reduces pain in: Diabetic neuropathy, Fibromyalgia, Duloxetine 60 and 120 mg were effective; lower dosages were not</td>
</tr>
<tr>
<td>Saarto</td>
<td>SR of 61 RCTs</td>
<td>Neuropathic pain</td>
<td>Antidepressants, Placebo</td>
<td>Pain</td>
<td>TCAs: NNT 3.6 for moderate relief, Venlafaxine: NNT 3.1 for moderate relief</td>
</tr>
<tr>
<td>Salerno</td>
<td>SR of 9 RCTs</td>
<td>Low back pain</td>
<td>TCAs, Placebo</td>
<td>Pain, Function</td>
<td>TCAs reduce pain, but small benefit, No significant impact on function</td>
</tr>
</tbody>
</table>

**Clinical Pearls / Things to Remember**

- Please note that many of these indications are “off-label”
- TCAs and SNRIs are considered first/second-line therapy for neuropathic “drivers of pain”
- In regards to “body of evidence”: TCAs > SNRIs >>> SSRIs
- In regards to efficacy: TCAs = SNRIs >>> SSRIs
- In regards to tolerability: SSRIs > SNRIs > TCAs
- 2 Birds with 1 Stone! – Treat pain AND depression, anxiety, insomnia, migraines, PTSD, hot flashes, incontinence, IBS, smoking cessation, etc.

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## Anticonvulsants

<table>
<thead>
<tr>
<th>First Author</th>
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<tbody>
<tr>
<td>Collins</td>
<td>SR of 19 RCTs</td>
<td>Diabetic neuropathy, Postherpetic neuralgia</td>
<td>Anticonvulsants, Placebo</td>
<td>Pain</td>
<td>Diabetic neuropathy: NNT 2.7 for ≥ 50% pain relief, Postherpetic neuralgia: NNT 3.2 for ≥ 50% pain relief</td>
</tr>
<tr>
<td>Moore (2009)</td>
<td>SR of 25 RCTs</td>
<td>Diabetic neuropathy, Postherpetic neuralgia, Central neuropathy, Fibromyalgia</td>
<td>Pregabalin, Placebo</td>
<td>Pain</td>
<td>Effective for pain relief for all studied conditions, Diabetic neuropathy: NNT &lt; 6 for moderate relief, Postherpetic neuralgia: NNT &lt; 6 for moderate relief, Central neuropathy: NNT &lt; 6 for moderate relief, Fibromyalgia: NNT &gt; 7 for moderate relief, Pregabalin 300 mg, 450 mg, 600 mg were effective; 150 mg dose was not</td>
</tr>
<tr>
<td>Moore (2014)</td>
<td>SR of 37 RCTs</td>
<td>Neuropathic pain, Fibromyalgia</td>
<td>Gabapentin, Placebo</td>
<td>Pain</td>
<td>Substantially reduces pain in: Diabetic neuropathy, Postherpetic neuralgia, Insufficient evidence for all other conditions</td>
</tr>
</tbody>
</table>

### Clinical Pearls / Things to Remember
- Gabapentin/pregabalin are considered first-line therapy for neuropathic “drivers of pain”
- Carbamazepine is considered second-line therapy for neuropathic “drivers of pain”
- Unlike SNRIs, NO evidence for non-neuropathic pain
- 2 Birds with 1 Stone! – Treat pain AND anxiety, bipolar disorder (carbamazepine), restless leg, alcohol dependence

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Wait a Second...These Studies Were < 6 Months?! 

Why are we harping on opioids for “lack of evidence” if no drugs have long-term outcomes?

- After all, in trials < 3 months, opioids have substantial evidence of pain relief and functional benefit (minimal)

2 Reasons

1. “Opioids have unique effects such as tolerance and physical dependence that might influence assessments of benefit over time. These effects raise questions about whether findings on short-term effectiveness of opioid therapy can be extrapolated to estimate benefits of long-term therapy for chronic pain.”

2. “Extensive evidence shows the possible harms of opioids…”

Other Non-Opioid Therapies

Interventional Approaches

- Examples: arthrocentesis, intraarticular steroid injection, subacromial steroid injection, epidural injection
- Pros: minimal risk, effective (for OA, RA, rotator cuff disease, lumbar radiculopathy, others)
- Cons: cost, access (most require referral), temporary effect

Lidocaine (topical)

- Pros: minimal risk, effective for neuropathic drivers and possibly musculoskeletal drivers
- Cons: limited evidence
- Clinical pearl: if not covered by insurance and want to trial, consider 4% OTC patches
Other Non-Opioid Therapies

Capsaicin (topical)
- Pros: minimal risk, effective for neuropathic drivers and musculoskeletal drivers
- Cons: limited evidence, poor tolerability
- Clinical pearl: requires 2-4 weeks of use to see benefit; high risk of ADR with little reward

Skeletal muscle relaxants
- Pros: may be effective for niche indications (spasticity)
- Cons: compounding adverse events with opioids, abuse potential, essentially zero evidence in chronic pain
- Clinical pearl: avoid use in general; if used, short-term (easy to say, hard for patients to do)

Audience Question #3

KH is a 54 male with chronic low back pain, depression, diabetes type 2, diabetic neuropathy, migraines, GERD.

Current Meds:
- Morphine 10 mg Q6H prn
- Ibuprofen 200 mg Q8H prn
- Escitalopram 5 mg daily
- Gabapentin 900 mg TID
- Metformin 1000 mg BID

He ranks his pain today as 7/10 (average of 6/10 over past year) and wants to increase his morphine dose. The physician asks for your advice on other options for the patient.
Audience Question #3

Think
- What questions do you still have about this patient?
- What do you recommend to better manage this patient’s chronic pain?
- Which of your recommendations have the most evidence of support?

Pair
- Discuss your answer with a neighbor

Share
- Discuss as a group

Audience Question #4

You are counseling a patient with chronic pain secondary to knee OA about his new diclofenac gel prescription. You ask about his exercise regimen and he complains that his doctor refuses to increase his opioids and keeps referring him to physical therapy. The patient states he can’t do PT because of “I’m in too much pain to move a lot, and it didn’t work last time I tried.”
Audience Question #4

Think
- What would you say to this patient about his physical therapy referral?
- Other than drug-specific information about his new diclofenac prescription, how would you counsel this patient about expectations?

Pair
- Discuss your answer with a neighbor

Share
- Discuss as a group

Conclusions

Although imperfect, non-opioid therapy options for chronic pain exist and have been shown to be effective.

Successful chronic pain pharmacotherapy will require tailoring and multimodal therapy
- A diabetes analogy
- 2 ways to think of multimodal

A physician can’t do this alone… but neither can a pharmacist!
- PT, social worker, care managers, consults

A word on expectations

“Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function.”

“Moving On”: Non-Opioid Alternatives for Chronic Pain Management

Nicholas Cox, PharmD, BCACP
Clinical Pharmacist, Intensive Outpatient Clinic, University of Utah Health
Pharmacist, Population Health, University of Utah Medical Group