Non-Opioid Therapy for the Management of Chronic Non-Cancer Pain

Matthew Hollon, MD MPH FACP

Dr. Hollon has indicated that he does not have any relevant financial relationships or affiliations that may have a direct bearing on the subject matter of this CME activity.

Principal Causes of Chronic Pain

<table>
<thead>
<tr>
<th>Type of Chronic Pain</th>
<th>Primary Care Site (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VA (%)</td>
</tr>
<tr>
<td>Low Back</td>
<td>44</td>
</tr>
<tr>
<td>Injury Related</td>
<td>10</td>
</tr>
<tr>
<td>Diabetic Neuropathy</td>
<td>8</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>16</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
</tr>
<tr>
<td>Spinal Stenosis</td>
<td>10</td>
</tr>
<tr>
<td>Other Disorders*</td>
<td>8</td>
</tr>
</tbody>
</table>

*Avascular necrosis, quadruplegia/paraplegia, chronic abdominal pain, chronic pancreatitis, Crohn's arthropathy, phantom limb, fibromyalgia, myofascial pain, and scoliosis.

Adapted from: J Gen Intern Med 2002;17:173-179
Case 1
A 75 year old woman reports that she has grown increasingly frustrated by bilateral hand pain, particularly in her first MCPs. She's in your clinic asking you to fix her hands so she can continue to knit sweaters for her grandchildren. Her medical history is notable for hospitalization for UGI bleed 2 years prior. She also has ischemic heart disease.

Olmsted County

Which of the following provides the best balance between efficacy and risk of adverse effects?

A. Acetaminophen 1000 mg four times daily.
B. Capsaicin 0.075% cream four times daily.
C. Amitriptyline 10mg once daily at bedtime
D. Diclofenac 75mg twice daily
E. Fluoxetine 20mg once daily
F. Salsalate 1500mg twice daily
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Presented at Update In Internal Medicine
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APAP efficacy for OA

- Recommended as first line therapy (ACR guidelines for treatment OA)
- Approximately 25 RCTs in OA
  - all studies focus on hip/knee OA
- 15 high quality trials included in 2009 Cochrane review
  - APAP marginally better than placebo
  - NSAIDs superior to acetaminophen for improving knee/hip pain in OA

APAP efficacy


Effect Size

- SMD is the difference between drug and placebo divided by their standard deviation.
- Rule of thumb for SMDs:
  - 0.2 as small
  - 0.5 as medium
  - 0.8 as large.
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APAP efficacy

- vs placebo
  - SMD = 0.13
  - mean absolute change of 4 points on 0 to 100 scale
  - no harm
- vs NSAIDS less effective overall in terms of
  - pain reduction
  - global assessments
  - improvements in functional status

APAP risk

- 280 randomized to APAP 4 gm/day
- modest drinking allowed
- no lipid lowering agents
- high rates of withdrawal
- 1/3 of those withdrawing do so because of lack of efficacy

Population Based Etiologies Fulminant Liver Failure

- Adapted from: Am J Gastroenterol 2007;102:2459–2463

Intentional

Unintentional
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NSAID Risks

- Renal toxicity
  - highest in preexisting kidney disease, congestive heart failure, cirrhosis
  - significant risk with concomitant ACE inhibitor or ARB therapy
- GI toxicity
  - more than 100,000 hospital admissions and 7,000-10,000 deaths annually in the US
  - 1997 estimate of annual direct costs > $2 billion
- Cardiovascular risk
  - coxibs associated with 46,000 AMIs, 22,000 strokes in the US between 1999 and 2004

Arthritis & Rheumatism 2008;59:1058–73
Am J Gastroenterol 2009;104:718 – 28
NEJM 1999;340:1888-99
Drug Safety 2000;32:335-43

GI risk of NSAIDs

<table>
<thead>
<tr>
<th>Author, year</th>
<th>End points</th>
<th>Studies</th>
<th>GI risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabriel, 1991</td>
<td>Bleeding, perforation, hospitalization or death</td>
<td>7 cohort 9 case-control</td>
<td>2.7 (2.5-3.0)</td>
</tr>
<tr>
<td>Bollini, 1992</td>
<td>Hematemesis, melena, pyloric ulcer perforation, and related death</td>
<td>7 cohort 27 case-control</td>
<td>3.0 (1.9-4.7)</td>
</tr>
<tr>
<td>Hernandez-Diaz, 2000</td>
<td>Bleeding, perforation, ulcers (all types), hospitalization or death</td>
<td>3 cohort 15 case-control</td>
<td>3.8 (3.6-4.1)</td>
</tr>
<tr>
<td>Olman, 2002</td>
<td>Perforation, ulcers, and GI bleeds</td>
<td>23 case-control 9 cohort 16 RCTs</td>
<td>3.0 (2.5-3.7) 2.7 (2.1-3.5) 5.4 (1.8-16.0)</td>
</tr>
</tbody>
</table>

Arthritis & Rheumatism 2008;59:1058–73

Risk Factors for GI bleeding

- Hx of PUD
  - Hx of ulcer, RR = 5.9
  - Hx of UGIB, RR = 15.4
- Age
  - 50-59 RR = 1.8
  - 60-69 RR = 2.4
  - 70-79 RR = 4.5
  — > 79 RR = 9.2
- Other considerations
  - comorbid medical conditions
  - oral glucocorticoids
  - anticoagulants

Arch Int Med 2000;160:2093-2099
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Variability in GI risk

- Diclofenac, etodolac, nabumetone, meloxicam are partially selective NSAIDs.
- These agents have been reported to be less toxic to the gastric mucosa.
- Nonacetylated salicylates have not been subjected to large GI outcomes studies. Smaller RCTs have indicated superior GI safety.

Meta-Analysis of Variability in GI Complications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean rank</th>
<th>Minimum rank</th>
<th>Maximum rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2.3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>3.5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fenclofen</td>
<td>3.5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4.8</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>6.0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Naproxen</td>
<td>7.0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>8.0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>9.0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>10.3</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>11.0</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

Adapted from BMJ 1996;312:1563-6

CV risks vs GI risks

Presented at Update In Internal Medicine
Spokane, WA  February 25, 2011
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**Celecoxib and CV risk**
The Adenoma Prevention with Celecoxib Study

<table>
<thead>
<tr>
<th>End Point</th>
<th>Hazard Ratio (95% CI)</th>
<th>Absolute Risk (3 years)</th>
<th>NNH (3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CV causes</td>
<td>3.0 [1.3-8.8]</td>
<td>6.1 (0.7-50.3)</td>
<td>0.1% 333</td>
</tr>
<tr>
<td>Combined End Point</td>
<td>2.5 [1.9-6.4]</td>
<td>3.4 (1.4-8.5)</td>
<td>0.9% 77</td>
</tr>
</tbody>
</table>

Adapted from N Engl J Med 2005;352:1071-80

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**NSAIDs and CV risk**

Circ Cardiovasc Qual Outcomes 2010;3:00-00

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**Relative Safety Opioids vs NSAIDs**

- Large claims database, identified subjects with incident use of different analgesics
- Medicare beneficiaries who qualify for pharmaceutical assistance programs for low-income older adults (mean age 80.0 yrs)
- Eligible adults with diagnoses of OA or RA on 2 separate visits excluding those with cancer or hospice care
- After propensity score matching, cohort had 12,840 members

Arch Intern Med 2010;170:1968-1978
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Safety Events Among Older Adults Initiating Prescription Analgesic Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nNSAIDs   Coxibs   Opioids</td>
</tr>
<tr>
<td>Composite CV</td>
<td>1.0        1.28 (1.01-1.62) 1.77 (1.39-2.24)</td>
</tr>
<tr>
<td>GI tract bleeding</td>
<td>1.0        0.60 (0.35-1.00) 1.07 (0.65-1.76)</td>
</tr>
<tr>
<td>Composite fracture</td>
<td>1.0        0.96 (0.62-1.49) 4.47 (3.12-6.41)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>1.0        1.12 (0.91-1.38) 1.68 (1.37-2.07)</td>
</tr>
<tr>
<td>Death related to adverse event</td>
<td>1.0        1.12 (0.62-2.02) 1.11 (0.56-2.10)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.0        1.16 (0.85-1.57) 1.87 (1.39-2.53)</td>
</tr>
</tbody>
</table>

Adapted from Arch Intern Med 2010;170:1968-1978

Salsalate

Understudied! Underutilized?

- Nonacetylated salicylate, lower prostaglandin inhibition.
- Equal efficacy vs diclofenac, vs piroxicam, vs aspirin, vs indomethacin.
- Lower GI risk in small trials.
- CV risk unstudied, unquantified.
- Tinnitus.
- Particular role in diabetes?

Salsalate and Glycemic Control

<table>
<thead>
<tr>
<th>Group</th>
<th>Plt. n</th>
<th>Pts with &gt; 0.5% HbA1c decline, n</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>26</td>
<td>2</td>
<td>0.15 (0.02-0.30)</td>
</tr>
<tr>
<td>Salsalate 3.0 g/d</td>
<td>27</td>
<td>12</td>
<td>0.44 (0.26-0.63)</td>
</tr>
<tr>
<td>Salsalate 3.5 g/d</td>
<td>26</td>
<td>14</td>
<td>0.54 (0.35-0.73)</td>
</tr>
<tr>
<td>Salsalate 4.0 g/d</td>
<td>25</td>
<td>15</td>
<td>0.40 (0.24-0.78)</td>
</tr>
</tbody>
</table>

Ann Intern Med 2010;152:346-357
Time to Assess Efficacy of Analgesics

- Four similarly designed 6-week randomized OA trials comparing rofecoxib, celecoxib, acetaminophen, and nabumetone.
- 1568 patients reported a “Good” or “Excellent” response on day six
  → 74% also had a “Good” or “Excellent” response at week 6.
- 1834 patients who did NOT report a “Good” or “Excellent” response on day six
  → 76% did NOT report a “Good” or “Excellent” response at week 6.
- Conclusion: Efficacy of drug therapy is established for the majority of OA patients within the first 6 days of therapy and this predicts efficacy during the longer term.

TCA use in elderly

- 2002 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
  – TCA’s included
- AGS Panel on the Pharmacological Management of Persistent Pain (2009)
  – TCA’s should be avoided because of higher risk for adverse effects (e.g., anticholinergic effects, cognitive impairment) (moderate quality of evidence, strong recommendation).

Fluoxetine

- Depression and OA common together
- No trials of SSRIs
- Industry sponsored trials of SNRIs with benefit

J Pain 2004;5:511-20
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Topical Capsaicin for OA of Hands

- 14 patients
- 0.075% capsaicin vs vehicle
- double blinded
- pain measured on VAS

/Arthritis 1992;21:604-607

Topical Capsaicin for OA of Knee

- 70 patients with OA and knee pain
- 0.025% capsaicin vs vehicle
- pain measured VAS
- 44% transient burning, 2 of 52 stop treatment

/Clin Ther 1991;13:383-95
Capsaicin Continued

- Trials supporting use in other conditions
  - Cochrane summary supports modest overall benefit in neuropathic pain
  - Mixed data in peripheral neuropathy
- Side effects
  - Local skin reactions disappeared or were reduced in frequency/severity after 1-2 weeks of treatment
  - 1 report contact dermatitis
  - Placebo effect

Knee OA

- Walking program
- Intra-articular therapy
- Acupuncture
- Tai Chi

Case 2

A 65 year old woman returns to see you in clinic. Three months prior she suffered an episode of moderately severe shingles in her right T7 dermatome that has been complicated by post-herpetic neuralgia. She is currently on 30mg sustained release morphine twice daily with modest pain relief but complains of constipation and drowsiness. She has a known history of coronary artery disease and ongoing tobacco use.
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Which of the following treatments will allow you to reduce her opioid dose?

A. Capsaicin 8% patch applied for one hour once every 3 months.
B. Gabapentin 600mg three times daily.
C. Lidocaine 5% patch applied for 12 hours daily.
D. Celecoxib 100mg twice daily.
E. Nortriptyline 75mg once daily.

Quetenza

- Three published clinical trials (2 PHN), largest trial:
  - 402 enrolled - 206 treatment, 196 control (low dose capsaicin)
  - stable therapies continued, intent-to-treat analysis
  - about 40% achieve > 30% reduction in pain score vs 30% in control, NNT ≈ 10
  - nearly 100% with site erythema, 50% experience pain at site of application

Lancet Neurol 2008;7:1106–12

Lidocaine patches

- Less than 10 low quality, small RCTs in CNCP:
  - heavily pharma funded
  - none longer than 12 weeks
  - host of non-RCT "clinical trials"
- 2003 review written by Endo Pharmaceuticals.
- Studied for:
  - OA (vs celecoxib), no difference, stopped early
  - carpal tunnel (vs. naproxen), no difference
  - PHN (3 studies, open label, compassionate use protocol)
  - focal peripheral neuropathic pain syndromes
- Contact dermatitis well described.
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Combination Therapies

Morphine monotherapy 45.3 mg
Morphine combination 34.4 mg
Gabapentin monotherapy 2207 mg
Gabapentin combination 1705 mg

Case 3
A 55 year old man returns to see you in clinic with persistent LBP despite naproxen 500 mg twice daily and venlafaxine 75mg daily. He's had pain for more than 5 years that has worsened in the past month but no radicular symptoms. He is not working and spends most of his day on the couch watching television. Worsening pain on a weekend prompted him to seek ED care where imaging showed only moderate degenerative changes without spinal stenosis or spondylolisthesis. He says, “if I were a horse they’d take me out behind the barn and shoot me.”
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What do you recommend next?
A. Add methadone 10 mg four times daily.
B. Increase venlafaxine to 150 mg daily.
C. Referral to a spine surgeon.
D. Enrollment in pain self-management program.
E. Both B and D.
F. Referral for injection therapy.

Surgery for Chronic LBP

• Surgical interventions (fusion or disc arthroplasty) for LBP with common degenerative changes seen on imaging are generally ineffective.
• Data suggest some beneficial effects of spinal fusion for spinal stenosis associated with lumbar spondylolisthesis.
• Surgical risks including reoperation rates substantial.

Injection Therapy for Chronic LBP

Cochrane Review 2008

• 18 trials (1179 participants) included in review
  – structure of trials widely variable
  – review does not cover epidural steroids for radiculopathy due to disc herniation
  – methodological quality of the studies limited
• Only 6/18 trials showed significant results for at least one outcome at a follow-up time point in favor treatment arms.
• 4/6 studies reported effects that could be considered to be clinically important.
• No strong evidence to support the use of any type of injection therapy (epidural, facet joint or local sites) for subacute or chronic low-back pain in patients without radicular pain.
• Rare but more serious complications of injection therapy have been reported:
  – cauda equina syndrome
  – septic facet joint arthritis
  – discitis
  – paraplegia
  – paraspinal abscesses
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Procedures for LBP

Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP)

- 12 weeks intervention with 6 month continuation phase
  - Step 1 = optimized antidepressant therapy
  - Step 2 = 6 sessions self-management program
  - Step 3 = 6-month phase of symptom monitoring and treatment reinforcement
- 250 patients with comorbid musculoskeletal pain and depression randomized
  - pain in the low back, hip, or knee; persistent for at least 3 months; at least moderate in severity
  - depression had to be of at least moderate severity PHQ-9 score ≥ 10
- BPI main outcome includes a 4-item severity scale (current pain and worst, least, and average pain in past week)

SCAMP Self-Management Program

<table>
<thead>
<tr>
<th>Table 3</th>
<th>PSM program</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview of self-management and pain</td>
<td>X</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Future-oriented pain</td>
<td>X</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Planning — goal setting</td>
<td>X</td>
<td>X X X X</td>
</tr>
<tr>
<td>Self-care and problem solving</td>
<td>X</td>
<td>X X X X</td>
</tr>
<tr>
<td>Physical activity — stretching, strengthening, walking</td>
<td>X</td>
<td>X X X</td>
</tr>
<tr>
<td>Relaxation/Deep breathing</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pain management</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dealing with low back pain with positive thinking</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Stress</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Handling pain therapies</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Working with health care providers and employers</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Evaluating medical/bedside treatments</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Good body mechanics</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tips for better sleep</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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SCAMP Main Results

- The NNT for depression response was 4.8
- Standardized effect sizes of 0.54 for BPI severity and 0.62 for BPI interference
- Intervention group much more likely to experience a reduction of > 30% in pain at 12 months with NNT of 4.1

JAMA 2009;301:2099-2110

Summary

- Placebo effect is powerful in CNCP, start with low risk therapies.
- Consider topical therapy for OA in elderly.
- If using APAP, ask about other meds.
- NSAIDS are risky, avoid in elderly, in others:
  - consider naproxen in those with CV risk
  - consider salsalate for those with GI risk (and diabetes?)
  - consider diclofenac for COX-2 selectivity
  - no improvement first week try something else
- Combination therapy studies suggest lower overall doses.
- Comprehensive depression care including self-management program works for CNCP.