Formulating Recommendations about Important Clinical Questions with Low Quality Evidence: The Case of Opioids for Chronic Pain

Jeffrey S. Harris MD, MPH, MBA
Senior Physician, The Permanente Medical Group, San Rafael
Methodologist, ACOEM and The Care Management Institute
Associate Clinical Professor of Medicine, UCSF, U of Utah

Kurt T. Hegmann MD, MPH
Chief, Division of Occupational and Environmental Health
Department of Family and Preventive Medicine, University of Utah
Editor in Chief, ACOEM Clinical Practice Guidelines
1990’s CME/Training and Marketing Messages

- No risk of addiction with Oxycontin
- *Near zero side effects*
  - Near zero respiratory depression
- *No maximum dose for opioid drugs*
- Driving on high dose opioids is very safe
- Urine drug and other testing harms the doctor-patient relationship
- OK to self-declare as a pain specialist
  - Great way to build an easy long-term cash paying practice

Greenberg DG. How Only the USA Wound Up in this Dire Situation: No Going Back to the Bad Old Days. California Medical and Pharmacy Boards’ Joint Forum to Promote Appropriate Prescribing and Dispensing, South San Francisco CA, February 2013
Clinical Observations

- Rare if any return to work if on chronic opioids
- Extended searches for “pain generators”
  - Repeated (negative) imaging
  - Failed surgeries
- Focus on pain
  - Center of life
- Apparent psychiatric overlay
The Cliff and the River: Ambulances or a Fence?

Train First Responders to Use Naloxone??
Concerning Trends

• General

• Age, gender, concurrent benzodiazepines

• Prior substance use disorders
The ACOEM Clinical Practice Guidelines

Evidence to Support Safe and Effective Practice

Methodology
Evidence to Support Practice

• **Goals**
  - Return to function
  - Improved clinical outcomes
  - Improved patient safety
  - Protect the health of the public
  - Do the right thing consistently
    - Based on quality evidence
    - Avoid “pendulum swings”
  - Provide compassionate care
  - Satisfy patient demands

• These goals do not always align
Panel Composition and Training:
- Multi-disciplinary (2 hour CME)
- Methodologist

When evidence-based best practices are not known to physicians or not used in patient care, the result is unwanted variation in care. Variance in medical care for similar conditions produces less than optimal outcomes and is an a priori indicator of poorer quality care. Despite progress in some jurisdictions, there are still significant opportunities for improvement in occupational medical care. Compared with care for similar diagnostic groups in general medical care, analyses of workers’ compensation medical care have shown up to 10-fold differences in resource use. Inappropriate use of invasive procedures and unnecessary diagnostic tests contribute to the cost and quality of care.

Jeffrey S. Harris, MD, MPH, MBA
Patricia L. Sinnott, PT, PhD, MPH
John P. Holland, MD, MPH
Julie Ording, MPH
Charles Turkelson, PhD
Michael Weiss, MD, MPH
Kurt T. Hegmann, MD, MPH

Objective: To ensure that revisions to the second edition of the American College of Occupational and Environmental Medicine’s (ACOEM) guidelines are as valid and useful as possible. Methods: The ACOEM Guideline Methodology Committee searched and synthesized the evidence-based medicine literature on systematic review and guideline development. The resulting process and tools were tested during guideline revision, and changes were made to the tools and process. Results: The methodology specifies problem formulation, literature search methods, screening of studies, quality rating, summarization of the body of literature, recommendation development, and writing. "Best practices" of medical care and other initiatives, adapted for occupational medicine.

Evidence-Based Practice Methodology Training
for ACOEM Evidence-Based Products
First Principles: Highlights

• Diagnostic Testing
  – Generally be done to confirm a clinical impression prior to invasive treatment

• Treatment
  – Relative Effectiveness
    • Evidence-based recommendations balancing benefits against harms
  – Management
    • Non-invasive before invasive
    • **Specific, objective goals, monitored within a reasonable time**
  – Invasive Treatment
    • The more invasive and permanent, the more caution ...... and the stronger the evidence of efficacy needed

• Cost-effectiveness
  – The more costly [over time], the more caution ..... and the stronger the evidence of efficacy
1. Randomization (0, 0.5, 1.0 pts.)
2. Allocation concealed (0, 0.5, 1.0)
3. Baseline comparability of groups
4. Blinding of patients
5. Blinding of provider
6. Blinding of assessor
7. Avoid co-interventions
8. Compliance Rate
9. Dropout Rate
10. Timing of Assessments
11. Intention to Treat Analysis

Low Quality: 0 - 3.5 points
Moderate Quality: 4.0-7.5 points
High Quality: 8.0 + points
**Strength of Evidence Ratings**

**A: Strong Evidence:**  
Two or more high-quality studies

**B: Moderate Evidence:**  
At least one high-quality study or multiple moderate-quality studies.

**C: Limited Evidence:**  
At least one study of moderate quality.

**I: Insufficient Evidence:**  
Evidence of insufficient quality or irreconcilable studies  
Doesn’t mean that no evidence was used.

High Quality: For therapy and prevention, well designed randomized controlled trials (RCTs) and crossover trials. For diagnosis and screening, cross sectional studies using independent gold standards. For prognosis, etiology or harms, prospective cohort studies with minimal heterogeneity.

Moderate Quality: Moderate quality studies in the same categories as above.
<table>
<thead>
<tr>
<th>Recommendation Level</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly Recommended</td>
<td>“A” Level Evidence</td>
</tr>
<tr>
<td>Moderately Recommended</td>
<td>“B” Level Evidence</td>
</tr>
<tr>
<td>Recommended</td>
<td>“C” Level Evidence</td>
</tr>
<tr>
<td>Insufficient Quality Evidence Recommended</td>
<td>“I” Level Evidence</td>
</tr>
<tr>
<td>Insufficient Quality Evidence No Recommendation</td>
<td>“I” Level Evidence</td>
</tr>
<tr>
<td>Insufficient Quality Evidence Not Recommended</td>
<td>“I” Level Evidence</td>
</tr>
<tr>
<td>Not Recommended</td>
<td>“C” Level Evidence</td>
</tr>
<tr>
<td>Moderately Not Recommended</td>
<td>“B” Level Evidence</td>
</tr>
<tr>
<td>Strongly Not Recommended</td>
<td>“A” Level Evidence</td>
</tr>
</tbody>
</table>
Criteria for Consensus “I” Ratings

- Invasiveness
- Adverse effects (and permanency thereof)
- Cost (total for that intervention)
  - Low <$100
  - Medium 100-500
  - High >$500
What are we treating?

Case Definition for Chronic Non-Cancer Pain
**Case Definition of Chronic Non-Cancer Pain**

- **Definitions in the literature**
  - Pain > expected tissue healing
  - > 1, 3 or 6 months

- **No anatomic or physiologic criteria or mechanism**
  - Imaging does not correlate
  - fMRI not ready for prime time

- **Not a homogeneous group**
  - “Axial spine” pain
    - Discogenic pain
  - DJD
  - “Chronic pain”
  - Chronic Pain Syndrome (psychiatric)
Definition of Pain

- Pain perception is complex. It includes
  - A sensation (central or peripheral)
  - An emotional reaction to it
    - Modulated by previous experiences, current expectations
  - Distress
    - Fear of pain, anxiety, panic, depression
  - Suffering

- Pain cannot be reduced to a biomechanical model

- Across studies, the higher the level of distress, the higher the doses of opioids used.
Evidence of Effectiveness

What Do We Know?
Selected References
### Results of Critical Appraisal

#### Number of RCTs

<table>
<thead>
<tr>
<th>Category</th>
<th>Low Quality</th>
<th>Moderate Quality</th>
<th>High Quality</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Subacute</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic</td>
<td>19</td>
<td>78</td>
<td>12</td>
<td>109</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>85</td>
<td>17</td>
<td>122</td>
</tr>
</tbody>
</table>

All trials were under 6 months, with most under 4 weeks duration, precluding statements on long-term safety.
No quality medical evidence that opioids are effective in CNCP

- Design and follow up problems
  - Heterogeneous group of diagnoses
  - Excluded patients at high risk of serious adverse events
    - Findings cannot be generalized to everyday clinical practice
  - High drop out and crossover rates
  - Non-parallel follow up and data collection
  - Studies ≤ 120 days

- Pain reduction not demonstrated
  - APS criterion was ≥ 30% relief
  - Lowered in 2009 systematic review
    - Caution – some panel members had a financial COI

- Improvement in function/return to work not demonstrated

Adverse Effects

Observational studies

(= post marketing)
WNL

We Never Looked
Adverse Effects

• Overdoses

  – Emergency Department visits

  – Hypoxic brain damage
    • Greenberg DG. How Only the USA Wound Up in this Dire Situation: No Going Back to the Bad Old Days. *California Medical and Pharmacy Boards’ Joint Forum to Promote Appropriate Prescribing and Dispensing, South San Francisco CA, February 2013*
Adverse Effects

• Prescription opioid deaths
    • More than heroin and cocaine combined

• Often in combination with other psychotropic drugs
Opioid Overdose and Mortality Risk

Death and Overdose Rates (Hazard Ratios) vs Dosage (mg/d)


• Falls
    - Vestibular effects, sedation, cognitive effects

• Fractures
    - Osteoporosis

• Myocardial infarction
Adverse Effects

• Endocrine suppression

• Muscle mass and strength
• Immune suppression: Tumor spread
  • Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. *Int J Cancer.* 2012;130:1237-1250

• Obstructive and Central Sleep Apnea
  – Hypoxia -> inflammation, vascular neogenesis, cancer risk

• Birth defects

• Addiction, dependence (4-40%)
• Purposeful over-sedation (26%)
Adverse Effects

• Hyperalgesia

• *Can* opioids work for CNCP?
• Non-medical use: recreational use = 18%
Sources of Non-Medical Opioids

People who abuse prescription painkillers get drugs from a variety of sources:

- Obtained free from friend or relative: 55%
- Prescribed by one doctor: 17.3%
- Bought from friend or relative: 11.4%
- Took from friend or relative without asking: 4.8%
- Got from drug dealer or stranger: 4.4%
- Other source: 7.1%
High utilizers use the majority of opioids

- Escalate doses over time
  
  
  
Relationship of Opioid Use to Psychiatric Comorbidity

- Rate, dose increased with
  - Former alcohol abuse and dependence
  - Active drug and alcohol use
  - Anxiety
  - Depression
  - PTSD, OCD, personality disorders...
- Increased doses over time
- Prevalence increases with age
- Less successful treatment of psychiatric problems
Evidence Re: Psychiatric Comorbidity

- **Depression**

- **Anxiety**

- **Substance Use Disorders**

- **PTSD**
Self-selection

• Self-selection
  
  – Reward center stimulation

  – Control problems in patients with anxiety/depression
  
  – Psychoactive effects of opioids
Psychiatric Diagnosis Associations
Possible Explanations

- Depressed or anxious
  - Because of pain?
  - Using opioids for depression or anxiety?
    - Anxiety about pain occurring?
  - Induced by opioid endocrinopathy?

- Opioid use mediated by anxiety or depression?

- Emotional distress?
  - Sedation (cf SF Chronicle series)
  - PTSD as a mediator?
Recommendations

Opioid Use for
Chronic Non-Cancer Pain
Routine Use of Opioids for Chronic Pain

• Routine opioid use for treatment of chronic and subacute non-malignant pain is moderately not recommended.
  – There is quality evidence that other medications and treatments are at least equivalent if not superior.
  – Quality evidence indicates safety profiles are considerably worse for opioids.
  – There are no quality trials to suggest superiority of opioids to other active treatments.

Not Recommended, Evidence B
Opioids for Treatment of Subacute or Chronic Severe Pain

• Opioids are recommended for treatment of function impaired by subacute or chronic severe pain (e.g., inability to work) due to
  – chronic severe radiculopathy
  – chronic severe peripheral neuropathies
  – complex regional pain syndrome
  – severe arthroses, and severe LBP).

• The maximum daily dose recommended for subacute or chronic pain patients is 50mg Morphine Equivalent Dose

• Therapeutic trial*
  – STOP if ineffective or unacceptable side effects

Recommended, Evidence C
AFTER other more efficacious treatments fail

- Physical restorative approaches
- Behavioral interventions
- Self-applied modalities
- Non-opioid medications
  - including NSAIDs, acetaminophen, and topical agents
- Functional restorative approaches
After other more efficacious treatments fail:

- For LBP patients
  - trial of a muscle relaxant
  - fear avoidance belief training
  - ongoing progressive aerobic exercise
  - strengthening exercises.
- For radiculopathy patients
  - epidural glucocorticoid injections
  - discectomy.
- For CRPS patients
  - progressive strengthening exercise.
- For DJD
  - NSAIDs
  - weight loss
  - aerobic and strengthening exercises.
Part of a multi-modal treatment plan

- Active exercise program and other most effective treatments should be ongoing.
- Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) should nearly always be the primary pain medication and accompany an opioid prescription.
- Lowest effective dose should be used.
- Weaker opioids should be used whenever possible.
- Where available, prescription databases should be checked for other opioid prescriptions.
• The use of an opioid treatment agreement* is recommended to document
  – Patient understanding
  – Acknowledgement of potential adverse effects
  – Agreement with the expectations of opioid use.
• Appropriate family members/significant others should be involved in this agreement

Recommended, Insufficient Evidence (I)

*model agreement in guideline
Daily consumption > 50mg MED

• Greater monitoring is recommended
  – At least monthly appointments
  – At least semiannual attempts to wean below 50mg MED
  – At least semiannual documentation of persistence of functional benefit
  – At least quarterly urine drug screening
  – At least semiannual review of medications
    • No sedating medication use (e.g., benzodiazepine, sedating anti-histamines)
    • Sleep meds?

Recommended, Evidence C
Patients should not receive opioids if they:

- use illicit substances
- use benzodiazepines
- use sedating medications
  - anti-histamines (H₁-blockers)
  - muscle relaxants
- are not working for reasons other than the pain
Indications for Discontinuation

- Lack of functional benefit
- Resolution of pain
- Improvement to the point of not requiring opioids
- Intolerance or adverse effects
- Non-compliance
- Surreptitious medication use
- Aberrant drug screening results
  - Diversion
  - Consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines).

Recommended, Insufficient Evidence I
Patient Selection

• Most guidelines: “Highly selected patients”
  • Likely to benefit
    • Pain reduction AND improved function
    • Low risk (misuse, addiction, adverse effects)
• How do you know?

I WONDER IF I SHOULD RELY MORE ON MY INTUITION TO MAKE DECISIONS.

YOU MEAN GUESSING?

NO. GUESSING IS TOTALLY DIFFERENT FROM INTUITION BECAUSE OF THE ... UM ...

THESE THINGS MAKE SENSE IN MY HEAD!

IS THERE ROOM IN THERE WITH ALL OF THE INTUITION?
Clinical Issue: Consider Risks v Benefits

• Consider risks
• Benefits
  – Unproven
• Patient selection
  – Compassion?
  – Patient demand?
• Older Adults/“Age-in”
  – Renal and hepatic clearance decline
    • Increase in effects with the same dose
  – Cognitive decline
    • Additive cognitive effects
    • Inadvertent overdose
  – Vestibular system decline
    • Falls
  – Bowel function decline
    • Gastroparesis, nausea
    • Constipation
    • Bowel obstruction
  – Immunosenescence
    • Tumor progression
    • Infection
High Risk Groups

• Adolescents
  – Misuse increased
  – “Recreational” use
    • Naïve users
    • Poly-drug use, alcohol combination
  – Life long exposure

• Pregnant women and women of child-bearing age
  – Birth defects
  – Neonatal withdrawal
  – Cognitive effects
  – Effects on bonding
High Risk Groups

• High dose patients
• Patients with psychiatric comorbidity
• Smoking
• Obesity
• Patients with a history of
  – Substance/alcohol abuse or dependence
  – Abuse as a child
    • Emotional, physical, sexual
  – Gastric bypass
• Patients with a PCP outside their immediate area
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Osteopenia, osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Testosterone deficiency</td>
</tr>
<tr>
<td></td>
<td>Thermoregulatory problems</td>
</tr>
<tr>
<td></td>
<td>Water retention</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain, unexplained</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Gastroparesis, slow transit time</td>
</tr>
<tr>
<td></td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Benign prostatic hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Ineffective birth control</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td></td>
<td>Oligomenorrhea</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Immune</td>
<td>Herpes</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Alodynia</td>
</tr>
<tr>
<td></td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Concentration problems</td>
</tr>
<tr>
<td></td>
<td>Coordination problems</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Gait problems</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Slow reaction time</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Alcohol abuse or dependence, or history of</td>
</tr>
<tr>
<td></td>
<td>Anxiety, anxiety disorder</td>
</tr>
<tr>
<td></td>
<td>ADHD</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Drug seeking behavior</td>
</tr>
<tr>
<td></td>
<td>Impulse control problems</td>
</tr>
<tr>
<td></td>
<td>Nicotine dependence</td>
</tr>
<tr>
<td></td>
<td>OCD</td>
</tr>
<tr>
<td></td>
<td>Personality disorder</td>
</tr>
<tr>
<td></td>
<td>PTSD</td>
</tr>
<tr>
<td></td>
<td>Substance abuse disorders, or history of</td>
</tr>
<tr>
<td></td>
<td>Suicidal ideation, risk</td>
</tr>
<tr>
<td></td>
<td>Thought disorders</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>COPD/emphysema</td>
</tr>
<tr>
<td></td>
<td>Central sleep apnea</td>
</tr>
<tr>
<td></td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td></td>
<td>Recurrent pneumonia</td>
</tr>
</tbody>
</table>
Policy and Educational Issues

• New starts
• Old patients
  – Taper -> improvement
• Knowledge and beliefs v evidence
• Pushback
  – Relatives of overdoses, fatalities, former advocates, psychiatrists
• Backlash
  – Advocacy groups
  – Self-selected patients
  – Threats, withdrawals re guideline panels
How Did This Happen?

Advocacy, Approval and Marketing

v. Science
In the Beginning...

- Flawed 1986 case series from NYC private practice
  - Desire to relieve pain, patient demand
  - President of APS and a director of American Pain Foundation, persuasive speaker, campaigner for Pain as 5th Vital Sign
- APS/AAPM
  - 1996 consensus statement: Little risk of addiction or overdose among pain patients
- FSMB
  - 1998: Model policy; 2004- call for penalty for under treating pain
- JCAHO
  - 2001: Pain as a 5th Vital sign, guide booklet

Catan T, Perez E. A Pain Drug Champion has Second Thoughts. *Wall Street Journal*, 12/14/12
• Opioid manufacturers supported speakers, research, policy research, ethics think tanks, surveys, FSMB Model Policy, Pain as 5th Vital Sign, lobbying, CME, American Pain Society, American Pain Foundation, some guideline developers, training materials

Bavley A. Biowtihics think tank’s ties to pain pill industry studied. *Kansas City Star*, 5/11/12
Catan T, Perez E. A Pain Drug Champion has Second Thoughts. *Wall Street Journal*, 12/14/12
• “For some patients, what their doctors don’t tell them could be hazardous to their health”
• “Honesty is essential to the doctor-patient relationship and to the quality of care.”

FDA Approval of OxyContin

- Head to head vs morphine sulfate
  - Equivalent efficacy
  - No evaluation of safety
- No evaluation against non-opioids
- No evaluation against non-pharmacologic treatment
- Unclear whether evaluation against placebo
- Small numbers
• **Marketing Strategy**
  - Ramped up detail sales force, paid incentives for sales
    - Hospital, insurance sales forces
  - Identified and recruited Physician Thought Leaders
    - Paid for > 40 expense-paid Training Camps for Thought Leaders
  - Supported multiple advocacy organizations such as the American Pain Foundation
  - Videos, brochures for physicians and patients
    - Coupons entitling new patients to free samples at participating pharmacies.
  - Free conferences, seminars (>5000), giveaways

Greenberg DG. How Only the USA Wound Up in this Dire Situation: No Going Back to the Bad Old Days. *California Medical and Pharmacy Boards' Joint Forum to Promote Appropriate Prescribing and Dispensing, South San Francisco CA, February 2013*

• Purdue Frederick fined $634 M for misbranding OxyContin
  – One year of the drug’s US sales: 2010 = $3.5 B

• Janssen Pharmaceuticals warned by FDA for making false safety claims and unsubstantiated effectiveness claims about transdermal fentanyl patches.

• The FDA warned King Pharmaceuticals that “the omission of serious and potentially fatal risks” associated with its morphine-naltrexone product was “especially egregious and alarming in its potential impact on the public health.”.
Future Scenarios

• “The arms race to build a safer painkiller is under way” ...“Pfizer has been lying in wait.”
  – Cowen & Co. – predicted 17% sales increase in pain drug sales by 2017 to $8.4 B
  – Reduce snorting, injection
  – Reduce euphoria by delayed release
    • Wall Street Journal May 6, 2012, pp B1, B4

• DEA sets quotas for component import and manufacture for “legitimate pain relief”
  – Likely 3 times that supported by evidence
Economics and Utilization

• Mean per capita healthcare costs: 1998-2002
  – Abusers of prescription, nonprescription opioids: $16,000; nonabusers: $1800

• Annual healthcare costs: 2005-2008
  – Medicare, Medicaid, commercial patients (N=49,425)
  – Users of prescription opioids: $23,049; non-users $4975
  – Utilization much higher
    • Leider HL, Dhaliwal J, Davis EJ, Kulakodlu, M, Buikema AR. Healthcare costs and non-adherence among chronic opioid users. *Am J Managed Care*, 2011; 17: 32-40

• Chronic opioid users represented 0.65% of 2004 database population
  – Filed 4.56% of all insurance claims (7 times)
  – Used 45% of all opioid analgesics
  – Much more physical and psychiatric co-morbidity
  – Women substantially over-represented (>63%)
    • Used a much greater share of all medical services than males, especially as they grew older.


