Acute Pain Management With Opioids and the Risks

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Paul W. Tisher, MD
Social Attachment
Evolutionary Antecedents

- Temperature regulation
- Pain threshold
- Place attachment

Attachment Theory

- Opioids attenuate the stress of social separation
- Opioids are released during social contact
- Low basal levels of opioids induce motivation to seek social contact
- Opioids are rewarding and induce odor and place preference

“Pain is the ultimate psychosomatic phenomenon. It is composed of both a somatic signal that something is wrong with the body and a message or interpretation of that signal involving attentional, cognitive, affective and social functions.”

Attention: Where is patient’s focus
Cognitive: What does pain mean
Affective: Depression and anxiety
Social: Sick role, disability
Neural correlates of interindividual differences in the subjective experience of pain

Robert C. Coghill, John G. McHaffie and Ye-Fen Yen

Some individuals claim that they are very sensitive to pain, whereas others say that they tolerate pain well. Yet, it is difficult to determine whether such subjective reports reflect true interindividual experiential differences. Using psychophysical ratings to define pain sensitivity and functional magnetic resonance imaging to assess brain activity, we found that highly sensitive individuals exhibited more frequent and more robust pain-induced activation of the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex than did insensitive individuals. By identifying objective neural correlates of subjective differences, these findings validate the utility of introspection and subjective reporting as a means of communicating a first-person experience.

Does Rejection Hurt? An fMRI Study of Social Exclusion
Naomi I. Eisenberger, Matthew D. Lieberman, Kipling D. Williams

A neuroimaging study examined the neural correlates of social exclusion and tested the hypothesis that the brain bases of social pain are similar to those of physical pain. Participants were scanned while playing a virtual ball-tossing game in which they were ultimately excluded. Paralleling results from physical pain studies, the anterior cingulate cortex (ACC) was more active during exclusion than during inclusion and correlated positively with self-reported distress. Right ventral prefrontal cortex (RVPFC) was active during exclusion and correlated negatively with self-reported distress. ACC changes mediated the RVPFC-distress correlation, suggesting that RVPFC regulates the distress of social exclusion by disrupting ACC activity.

The subjective experience of pain: Where expectations become reality
Tetsuo Koyama, John G. McHaffie, Paul J. Laurienti, and Robert C. Coghill

Our subjective sensory experiences are thought to be heavily shaped by interactions between expectations and incoming sensory information. However, the neural mechanisms supporting these interactions remain poorly understood. By using combined psychophysical and functional MRI techniques, brain activation related to the intensity of expected pain and experienced pain was characterized. As the magnitude of expected pain increased, activation increased in the thalamus, insula, prefrontal cortex, anterior cingulate cortex (ACC) and other brain regions. Pain-intensity-related brain activation was identified in a widely distributed set of brain regions but overlapped partially with expectation-related activation in regions, including the anterior insula and ACC. When expected pain was manipulated, expectations of decreased pain powerfully reduced both the subjective experience of pain and activation of pain-related brain regions, such as the primary somatosensory cortex, insular cortex, and ACC. These results confirm that a mental representation of an impending sensory event can significantly shape neural processes that underlie the formulation of the actual sensory experience and provide insight as to how positive expectations diminish the severity of chronic disease states.

“Changed Set Point” Model
Drug abuse alters a biological or physiological setting or baseline

• Although the nucleus accumbens is necessary to establish addiction it is not necessary for the maintenance of addiction. (Hanson, 2003)

• Pulse dosing of short acting opiates results in the permanent upregulation of the hypothalamic pituitary axis in humans vulnerable to addiction. (M.J. Kreek, 2004)
Risk of Addiction

- **Short Acting Opioids:** 1 in 3 to 1 in 4 who ever self-administer progress to addiction
- **Cocaine:** 1 in 10 to 1 in 20 who ever self-administer progress to addiction
- **Alcohol:** 1 in 10 to 1 in 20 who ever self-administer progress to addiction

Kreek et al, Nature Reviews Drug Discovery, 2002
Long-Term Outcomes

33 year follow-up of 581 heroin addicts:

- 48% - confirmed dead (284 people)
- 22% - over dose/poisoning
- 15% - liver disease
- 12% - cardiovascular
- 20% - homicide, suicide, accident
- 12% - could not be located (presumed dead)

(Hser, Hoffman, Grella & Anglin, Arch Gen Psychiatry, 2001)
## Estimates of Intergenic Opioid Addiction

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate/Description</th>
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<tbody>
<tr>
<td>Porter &amp; Jeck (1980)</td>
<td>0.03% in hospitalized patients</td>
</tr>
<tr>
<td>Portenoy &amp; Foley (1986)</td>
<td>5% in non-cancer pain</td>
</tr>
<tr>
<td>Fishbain, et al (1992)</td>
<td>18.9% review</td>
</tr>
<tr>
<td>Chabal, et al (1997)</td>
<td>27.6 prescription opioid abuse</td>
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>70% of Acadia’s patients on replacement therapy were introduced to opiates via management of non-malignant pain
Behavioral and Neurochemical Changes Induced by Oxycodone Differ Between Adolescent and Adult Mice

Yong Zhang, Roberto Picetti, Eduardo R Butelman, Stefan D Schlussman, Ann Ho and Mary Jeanne Kreek

• The Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY, USA

Neuropsychopharmacology advance online publication 10 September 2008
• In 2005, 12.4 percent of young adults aged 18 to 25 used prescription pain relievers nonmedically in the past year, and 1.7 percent met the criteria for past year prescription pain reliever dependence or abuse.

• Among young adults aged 18-25 who used prescription pain relievers nonmedically in the past year, over half (53.0 percent) obtained them from a friend or relative for free when they last used pain relievers nonmedically.

Genetic Factors

Bimodal distribution of pain tolerance
Cold Pressor
tolerant to intolerant
3-5 minute: 1 minute
Normal population 14:1
Drug abusers 1:6
2006 Edition
• Initiation And Cessation Of Opioid Therapy Has Been Linked To The Development Of Hyperalgesia In Humans
Ch. 11: Opioid Therapy for Chronic Noncancer Pain: Cautions, Concerns, Misconceptions, and Potential Myths

Michael E. Clark, PhD, Robert W. Young, Jr., PhD, and B. Eliot Cole, MD, MPA

- No Published Data From Randomized Controlled Trials Indicating That Opioid Therapy Results In Long-Term Pain Relief For Individuals With Chronic Noncancer Pain
Ch. 11: Opioid Therapy for Chronic Noncancer Pain: Cautions, Concerns, Misconceptions, and Potential Myths

Michael E. Clark, PhD, Robert W. Young, Jr., PhD, and B. Eliot Cole, MD, MPA

- Initiation And Cessation Of Opioid Therapy Has Been Linked To The Development Of Hyperalgesia In Humans
• When Tolerated, Successful Opioid Therapy For Chronic Noncancer Pain Results In Only Modest Reductions In Pain Intensity
Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction

Bridget A. Martell, MD, MA; Patrick G. O’Connor, MD, MPH; Robert D. Kerns, PhD; William C. Becker, MD; Knashawn H. Morales, ScD; Thomas R. Kosten, MD; and David A. Fiellin, MD

Background: The prevalence, efficacy, and risk for addiction for persons receiving opioids for chronic back pain are unclear.

Purpose: To determine the prevalence of opioid treatment, whether opioid medications are effective, and the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain.

Data Sources: English-language studies from MEDLINE (1966–March 2005), EMBASE (1966–March 2005), Cochrane Central Register of Controlled Clinical Trials (to 4th quarter 2004), PsychInfo (1966–March 2005), and retrieved references.

Study Selection: Articles that studied an adult, nonobstetric sample; used oral, topical, or transdermal opioids; and focused on treatment for chronic back pain.

Data Extraction: Two investigators independently extracted data and determined study quality.

Data Synthesis: Opioid prescribing varied by treatment setting (range, 3% to 66%). Meta-analysis of the 4 studies assessing the efficacy of opioids compared with placebo or a nonopioid control did not show reduced pain with opioids (g, 0.199 composite standardized mean difference [95% CI, 0.49 to 0.11]; P 0.136). Meta-analysis of the 5 studies directly comparing the efficacy of different opioids demonstrated a nonsignificant reduction in pain from baseline (g, 0.93 composite standardized mean difference [CI, 1.89 to 0.03]; P 0.055). The prevalence of lifetime substance use disorders ranged from 36% to 56%, and the estimates of the prevalence of current substance use disorders were as high as 43%. Aberrant medication-taking behaviors ranged from 5% to 24%.

Limitations: Retrieval and publication biases and poor study quality. No trial evaluating the efficacy of opioids was longer than 16 weeks.

Conclusions: Opioids are commonly prescribed for chronic back pain and may be efficacious for short-term pain relief. Long-term efficacy (16 weeks) is unclear. Substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24% of cases.

For author affiliations, see end of text.
Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction

Context
Patients with low back pain often request pain medication, and many physicians prescribe opioids despite concerns about drug dependence.

Contribution
Opioid prescribing rates in 11 studies varied widely (3% to 66%). In 4 short-term randomized trials, pain relief was similar with opioids and either active treatment or placebo. In poor-quality, heterogeneous studies, the prevalence of substance abuse disorders in patients taking long-term opioids for back pain varied from 5% to 24%.

Caution
Study quality was weak overall.

Implications
Opioids seem to have limited, if any, short-term value in chronic low back pain. Evidence about developing substance abuse is too limited to draw any conclusions.

—The Editors
Opioid Tolerance

- CNS Depression – Rapid
- Respiratory Depression – Rapid
- Constipation – Virtually Never
- Analgesia – Variable

Alford et al, Annals of Internal Medicine 2006; 144
• No Published Data From Randomized Controlled Trials Indicating That Opioid Therapy Results In Long-Term Pain Relief For Individuals With Chronic Noncancer Pain
Treatment Outcomes for Opioid Addiction
% Relapsed at 1 Year

Traditional Detox Alone – 90%

Residential/Therapeutic Community – 85%

Outpatient/Self-Help – 90%

Opioid Antagonist – 99%

Agonist – 25%

Partial Agonist Treatment - ?
Full Mu Agonist (i.e. Methadone) vs Partial Agonist (i.e. Buprenorphine) vs Antagonist (i.e. Naloxone)
Receptor Binding at Mu Receptor

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<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Agonist</td>
<td>Morphine-like effect (e.g. heroin, weak binding except for Fentanyl)</td>
</tr>
<tr>
<td>Partial Agonist</td>
<td>Weak morphine-like effects with strong receptor affinity (i.e. buprenorphine)</td>
</tr>
<tr>
<td>Antagonists</td>
<td>Strong receptor binding with no opiate effect and blocks receptor (e.g. naltrexone)</td>
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Precipitated Withdrawal

- Precipitated in a physically dependent person, by administration of either:
  - an opioid antagonist drug (e.g. naloxone, naltrexone) or
  - an opioid partial agonist drug (e.g. buprenorphine)
- Similar to spontaneous withdrawal but faster onset
- Duration depends upon half-life of drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Naloxone</td>
<td>~20 minutes</td>
<td>minutes</td>
<td>~20 minutes</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>minutes</td>
<td>minutes</td>
<td>1 - 2 days</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>minutes</td>
<td>minutes</td>
<td>1 - 2 days</td>
</tr>
</tbody>
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Buprenorphine Precipitated Withdrawal
Displaces full agonist off mu receptors
To Be Avoided in Any Patient Receiving Chronic Opioid Therapy (for pain or replacement)

Mixed Agonist / Antagonist Opioid Analgesics

- Talwin (Pentazocaine)
- Nubain (Nalbuphine)
- Stadol (Butorphanol)
Acute effects of opiates
Chronic effects of short-acting opiates (e.g. heroin addiction)

Opiate withdrawal effects
Opiate antagonist effects
Cocaine effects
Alcohol effects
Nicotine effects (?)

Chronic effects of long-acting opiate
(e.g., methadone maintenance treatment)

Suppression of HPA Axis
Activation of HPA Axis
Normalization of HPA Axis

HPA – Hypothalamic-pituitary-adrenal axis (involved in stress response)
(Kreek, 1972; 1973; 1987; 1993; 2001)
Treating Pain in the Buprenorphine Maintained Patient

• The extent of mu receptor blockade is variable – ask the patient
• Try splitting daily dose to TID or QID
• Stop buprenorphine, treat pain but monitor carefully with naloxone at bedside
Treating Moderate to Severe Pain in the Methadone Maintained Patient

- Continue usual dose of methadone
- If patient can’t take PO give 70% IM in 2-4 equal doses
- Treat pain as you would any other patient – that is ignore the methadone
Medication Reconciliation

- Any Narcotic Treatment Program is required to provide the amount and time of last dose in an emergency 24/7
- Any PCP should give you the same info regarding buprenorphine
Analgesic Properties of Maintenance Opioids

Methadone and Buprenorphine

• Analgesic 4-8 hours following a single dose
• Suppression of withdrawal 24-48 hours following single dose

Alford et al, Annals of Internal Medicine 2006; 144