Opioid-Induced Hyperalgesia

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Faculty Disclosure Information

I have no relevant financial relationships with the manufacturers of any commercial products and/or provider of commercial services in this CME activity.

I do **not** intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.
Goals

• Define OIH
• What are the underlying mechanisms?
• Why and when does OIH occur?
• Clinical evidence
• Clinical relevance for pain management with opioids
Evidence for OIH

• Compelling evidence
• Does it occur in the absence of tolerance?
• Challenge is how to diagnose it clinically and treated it?
OIH definition

• It is a syndrome of increased sensitivity to noxious stimuli, occurs after acute and chronic administration of opioids

• It has been observed in
  – Animal; models are robust
  – Humans; less rigorous
Definition

Low et al., 2012; Chu 2008

- Neuroplastic changes in the peripheral and central nervous system leading to sensitization of pronociceptive pathways

- A paradoxical response; worsening pain despite increasing opioid dose; unexplained by progression of the source condition

- Acute & chronic exposure to opioids at high and low doses

- Different type of opioids and different routes of administration
Clinical Settings

• Human volunteers
  – Secondary hyperalgesia ≠ OIH
• Perioperative pain
• Cancer pain
• Addiction
• Migraines  *Saper J, 2008*
• Musculoskeletal pain  *Crofford L, 2010*
Epidemiology

- Incidence
  - Various clinical pain conditions
  - Who is at a greater risk for developing OIH
    - Type of pain (nociceptive, neuropathic, inflammatory, etc.)
  - Opioid type, dose and duration
  - Concomitant administration of CYP inducers/inhibitors
  - Genetics
  - Mood
  - Inherent variability in pain perception
  - Does it lead to chronic pain?
Clinical Diagnosis

• Clinical distinguishing

  Tolerance vs. OIH

• Increased pain and hyperalgesia despite increase opioid dose. In absence of disease progression

• Mechanism(s)?
N F Sethna, MD  Boston Children’s Hospital

**OIH vs. Tolerance**

- **Initial equilibrium** (homeostasis)
  - Increased NRS
  - Stable disease state
  - Opioid **effective**

- **New equilibrium** (allostasis)
  - Increased NRS
  - Stable disease state
  - **Diffuse** pain & **different** quality
  - Opioid **ineffective**

- **Disequilibrium** (hyperlgesic state)
  - Increased NRS
  - Stable disease state
  - **Localized** pain & **same** quality
  - Opioid **effective**

- **Antinociception desensitized**

- **Normal D-R**
- **Tolerance**
- **OIH**
Tolerance vs. OIH

Chu et al., 2008

Desensitization of anti-nociceptive pathways

Sensitization of pro-nociceptive pathways
Mechanisms Proposed: Peripheral &/or central ?
Tompkins 2011; Lee 2011

• Neuro-anatomy
  – Sensitization of PAN &/or SON, enhanced DPF, and enhancing, releasing and diminished uptake of nociceptive neurotransmitters (ENP)

• Changes in peripheral &/or central nociceptive processing
  • Peripheral: TRP-V1 & cytokines
  • Central: Opioid-r, ionotropic NMD-r, substance-P (NK1-r), DPF (5HT3-r, CCK in RVM)

• Inherent variability in pain perception
OIH Preclinical Neurobiology: Complex & multifactorial overlapping shared mechanism with tolerance

- NMDA-r activation (neurotoxicity, apoptosis), G-proteins & intracellular systems: Calcitonin gene-related peptide (CGRP), substance P, prostaglandins, lipoxengenesis, endocannabinoids, CCK, Ca^{2+}/calmodulin-dependent protein kinase-2, 5-HT1A receptors, cytokines and others

Presynaptic: RVM
NMDA-r, CCK

Presynaptic: DRG

Post-synaptic: DHN, glial cells
Desensitization of Antinociceptive System

Nerve injury

Repeated opioids
A shared similarities between OIH and tissue injury

Spinobulbospinal circuit (up-regulation of dynorphin) contribute to inflammatory, neuropathic pain & OIH

Chronic opioids

1° hyperalgesia

2° hyperalgesia

site of injury

Substance-P
CGRP
Clinical Analgesia, Tolerance & OIH

Tissue injury / disease progression
- Nociception
- Inflammation
- Neuropathic pain

Psychological Distress
- Anxiety/depression
- Conditioned pain behavior
- Generalized allodynia

N F Sethna, MD. Boston Children’s Hospital
This is the first clear evidence that brainstem MPRF plays a key role in expression of hyperalgesia induced by opioid withdrawal, in an injury-free model of CS in humans.
Increased Sensitivity to Thermal Pain Following a Single Opiate Dose Is Influenced by the COMT val\textsuperscript{158} met Polymorphism

Karin B. Jensen\textsuperscript{1*}, Tina B. Lonsdorf\textsuperscript{1}, Martin Schalling\textsuperscript{2}, Eva Kosek\textsuperscript{1}, Martin Ingvar\textsuperscript{1}  

2009

**Table 1.** Distribution of the different COMTval\textsuperscript{158} met polymorphisms for male and female subjects in the present study (n = 43).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>COMT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>met/met</td>
<td>met/val</td>
<td>val/val</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>
Increased Sensitivity to Thermal Pain Following a Single Opiate Dose Is Influenced by the COMT val^{158}met Polymorphism

Karin B. Jensen\textsuperscript{1*}, Tina B. Lonsdorf\textsuperscript{1}, Martin Schalling\textsuperscript{2}, Eva Kosek\textsuperscript{1}, Martin Ingvar\textsuperscript{1}

Reduced DPF &/or OIH

Increased DPF

Reduced μ-opioid response (animal study Zubieta 2003)
Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans

Wolfgang Koppert\textsuperscript{a}, Martin Angst\textsuperscript{b}, Monika Alsheimer\textsuperscript{a}, Reinhard Sittl\textsuperscript{a}, Sven Albrecht\textsuperscript{a}, Jürgen Schüttler\textsuperscript{a}, Martin Schmelz\textsuperscript{c,*} Pain 106 (2003) 91–99

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Drug infusion with Remifentanil or Naloxone followed by observation of ongoing pain, pinprick hyperalgesia, allodynia, and electric stimulation over time.}
\end{figure}

RCTCO: Hyperalgesia after remifentanil infusion was more pronounced than after naloxone administration. Additional receptors systems other than the endorphin system are involved.
# Opioid-induced Hyperalgesia

Werner 2012

## Table 1

PubMed search as per January 2012. OIH = opioid-induced hyperalgesia.

<table>
<thead>
<tr>
<th>Search terms</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIH</td>
<td>209</td>
</tr>
<tr>
<td>OIH AND human</td>
<td>126</td>
</tr>
<tr>
<td>OIH AND review</td>
<td>55</td>
</tr>
<tr>
<td>OIH AND editorial</td>
<td>4</td>
</tr>
</tbody>
</table>
Human studies comparisons

- Cross-sectional design
- Different indicators; may or may not reflect OIH
- Different populations
  - Volunteers, postoperative, chronic pain, addicts/former addicts, MSK, cancer, migraines
- Few prospective
Clinical Studies: Inference of OIH

• Conventional testing pain threshold
  – Electrical, mechanical, heat, cold, ischemic pain; a wide response variations

• Pain Tolerance
  – CPP, HPT, DNIC

• All tests of hyperalgesia ≠ OIH
  – Peripheral and central sensitization
  – Tolerance
  – Withdrawal hyperalgesia
  – Disease progression
Table 2  Studies in Patients Undergoing Surgery

<table>
<thead>
<tr>
<th>Reference</th>
<th>Surgery</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Opioid</td>
<td>Dose</td>
</tr>
<tr>
<td>Cooper (26)</td>
<td>Cesarean section</td>
<td>Fentanyl IT</td>
<td>0 vs. 25 µg</td>
</tr>
<tr>
<td>Chia (30)</td>
<td>Hysterectomy</td>
<td>Fentanyl IV</td>
<td>1 vs. 22 µg/kg</td>
</tr>
<tr>
<td>Lee (32)</td>
<td>Colorectal</td>
<td>Remifentanil IV</td>
<td>N2O vs. 0.17 µg/kg/min for 140 min</td>
</tr>
<tr>
<td>Crawford (29)</td>
<td>Scoliosis</td>
<td>Remifentanil IV plus MS vs. MS alone</td>
<td>0.28 µg/kg/min for 460 min</td>
</tr>
</tbody>
</table>

Conclusions: Did these patients developed acute OIH and/or tolerance? Cannot be resolved because patients’ pain sensitivity before and after the surgery was not formally assessed.

*Measurements of secondary hyperalgesia were increased (~25%↑ in mechanical pain threshold and 120%↑ in area).

*Prevented by intraoperative (0.5 mg/kg → 5 µg/kg/min) and postoperative (2 µg/kg/min for 48 hr) ketamine.

*Intraoperative MS consumption was 198 versus 237 µg/kg/min for group R and MS, respectively.

Abbreviations: IT, intrathecal; IV, intravenous; ND, not different; N, number of patients.
Intraoperative Remifenatnil Infusion

*Angst al., 2009*

![Graph showing cumulative remifentanil dose (μg / kg) for different studies.](image)

- **Cortinez 2011**: 20
- **Lee 2005**: 30
- **Guignard 2000**: 80
- **July 2005**: 120
- **Crawford 2006**: Increased postoperative pain and opioid consumption
# OIH: Chronic Nonmalignant Pain (NMP) & Cancer

*Angst et al, 2009*

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Dose</th>
<th>Mo.</th>
<th>CPP</th>
<th>DNIC</th>
<th>HP</th>
<th>IP</th>
<th>MP</th>
<th>EP</th>
<th>LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Back pain</td>
<td>6*</td>
<td>60</td>
<td>1</td>
<td>40%</td>
<td>-</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 NMP</td>
<td>40</td>
<td>250</td>
<td>46</td>
<td>60%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>3 NMP/cancer</td>
<td>110</td>
<td>100</td>
<td>20</td>
<td>ND</td>
<td>40%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 NMP</td>
<td>240</td>
<td>250</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 NMP/cancer</td>
<td>224</td>
<td>70</td>
<td>9</td>
<td>-</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 NMP/cancer</td>
<td>382</td>
<td>100</td>
<td>64</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20%</td>
</tr>
</tbody>
</table>

1. Chu 2006
2. Hay 2009
3. Ram 2008
4. Fillingim 2003
5. Reznikow 2005
### Opioid-induced Hyperalgesia

**A Qualitative Systematic Review**

Martin S. Angst, M.D.,* J. David Clark, M.D., Ph.D.†

Table 2. Studies in Patients Undergoing Surgery

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Surgery</th>
<th>Opioid</th>
<th>Dose</th>
<th>Intraoperative Data</th>
<th>Postoperative Data (High vs. Low Intraoperative Opioid Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Opioid Use</td>
</tr>
<tr>
<td>18</td>
<td>Cesarean section</td>
<td>Fentanyl IT</td>
<td>0 vs. 25 μg</td>
<td>60% ↑</td>
<td>ND</td>
</tr>
<tr>
<td>17</td>
<td>Hysterectomy</td>
<td>Fentanyl IV</td>
<td>1 vs. 22 μg/kg</td>
<td>120% ↑</td>
<td>30% ↑</td>
</tr>
<tr>
<td>16</td>
<td>Colectomy</td>
<td>Remifentanil IV</td>
<td>0.1 vs. 0.3 μg · kg⁻¹ · min⁻¹ for 260 min</td>
<td>85% ↑</td>
<td>50% ↑</td>
</tr>
<tr>
<td>19</td>
<td>Gynecologic</td>
<td>Remifentanil IV</td>
<td>0.1 vs. 0.23 μg · kg⁻¹ · min⁻¹ for 100 min</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

IT = intrathecal; IV = intravenous; ND = not different.
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Morphine gr. (n = 69)</th>
<th>Placebo gr. (n = 70)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS-Contin titration for 1 month in opioid naïve patients with uncomplicated LBP</td>
<td>78 mg/d or DLSE</td>
<td>PL pill</td>
<td></td>
</tr>
<tr>
<td>Morphine potency reduction</td>
<td>42% ↓</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Pain relief improvement (mean VAS reduction)</td>
<td>44% ↓</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Disability index improvement</td>
<td>31% ↑</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Beck depression inventory</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
</tr>
<tr>
<td>CPP (Cp 0)</td>
<td>-</td>
<td>-</td>
<td>0.56</td>
</tr>
<tr>
<td>Target-controlled Remifentanil infusion at Cp 0, 1, 2, 3, 4 ng/mL</td>
<td>CPP ↑</td>
<td>CPP Ø</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Conclusion:** development of tolerance in morphine group at 1 month but not OIH
Analgesic tolerance without demonstrable opioid-induced hyperalgesia: A double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain

Larry F. Chu*, Nicole D’Arcy, Caitlin Brady, Abigail Kathleen Zamora, Chelsea Anne Young, Julie Eunwoo Kim, Anna Marie Clemenson, Martin S. Angst, J. David Clark

Placebo infusion

N F Sethna, MD. Boston Children’s Hospital
FT infant underwent 20 surgical procedures between day 1-33 days of life, intubated and ventilated, on 34th day developed bowel ischemia, sepsis, & respiratory distress and underwent 21st procedure and developed extreme irritability, allodynia (withdrawal touch) and hyperalgesia.

Analgesic intervention:
- Morphine/fentanyl infusion rotation
- Clonidine infusion
- Hydromorphone infusion (50% of MS equivalent dose + ketamine infusion) + dexmedetomidine infusion

Infusions were d/c after:
- 30 days ketamine
- 70 days midazolam
- 46 days hydromorphone & dexmedetomidine

Fig 1. Box plot showing PAT scores vs morphine dose between days 35 and 49 of life. Opioid rotation and de-escalation were initiated on day 43 of life.
Implications of OIH

• Most scientific evidence in humans is indirect and incidence is ???
• Severe postoperative pain can prolong recovery and potential for increased postoperative complications
• A risk factor for chronic pain development??
Suggested Clinical Management

Tompkins & Campbell 2011

**TOLERANCE**
- Escalate opioid to effect
- Opioid rotation
- Long-acting opioids

**Opioid-induced Hyperalgesia**
- De-escalate opioids
  - Non-opioid therapies
    - (1) Central & peripheral NB
    - (2) Antagonists of NMDA-r & α-adrenergic, NSAIDS, gabapentin/pregabalin
    - (3) Buprenorphine

**Withdrawal Hyperalgesia**
- Slow taper
- Opioid rotation
- Long-acting opioids

Non-opioid therapies
Strategies to prevent chronic post-surgical pain and OIH

Grosu & Kock Anesthesiol Clin 2011

Box 4
Drugs or substances showing antihyperalgesic effects

- Ketamine/memantine/magnesium
- Gabapentin-pregabalin
- COX-1/2 inhibitors
- $\alpha_2$-adrenoceptor agonists (perimedullary)
- Free radical scavengers (mannitol, vitamin C, and so forth)
- $N_2O$, systemic local anesthetics
- Drugs active against glial activity (minoxidil, propentofylline)
- Diet enriched with omega-3 or others
Efficacy of NMDA-r antagonists (Ketamine & Mg\(^{+2}\)) for preventing *remifentanil-induced* increase in postoperative pain and analgesic requirement: *A meta-analysis* Liu 2012

- 29 RCT identified by end of 2010
  - Remifentanil 0.1 - 0.5 mcg/ kg/ min
- 14 RCT (n = 623) met criteria
  - Ketamine n = 10
  - Magnesium sulfate n = 4

- Poor quality vs. lack of efficacy?
- Ineffective in reducing postoperative pain scores, analgesic consumption or tolerance
Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials


Table 1 Details of studies included. MO, morphine only group; MK, morphine plus ketamine group; NS, no significant difference between the groups; P-values indicate beneficial effects for ketamine group unless otherwise specified.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Quality score</th>
<th>Surgical setting</th>
<th>Number of patients (MO/MK)</th>
<th>Analgesia regime: morphine vs morphine plus ketamine (mg ml⁻¹)</th>
<th>Pain scores</th>
<th>Reduction in morphine consumption</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelet and colleagues¹³</td>
<td>5</td>
<td>Thoracotomy for lobectomy</td>
<td>50 (25/25)</td>
<td>1 vs 1+</td>
<td>$P&lt;0.05$ at 48 and 60 h</td>
<td>$P&lt;0.05$ at 36–60 h</td>
<td>Desaturation $P&lt;0.008$; 1st and 2nd night</td>
</tr>
<tr>
<td>Burstal and colleagues⁵</td>
<td>5</td>
<td>Total abdominal hysterectomy</td>
<td>70 (33/37)</td>
<td>1 vs 1+</td>
<td>Cough $P&lt;0.03$ day 1; alldynia $P&lt;0.05$; shorter duration of PCA $P&lt;0.005$</td>
<td>$P&lt;0.05$ during first 24 h</td>
<td>Dysphoria, nausea, pruritus $P=0.006$ in the ketamine group</td>
</tr>
<tr>
<td>Nesher and colleagues¹⁶</td>
<td>5</td>
<td>Transthoracic lung and heart</td>
<td>57 (29/28)</td>
<td>1.5 vs 1+</td>
<td>$P&lt;0.05$ during 72 h; shorter duration of PCA $P&lt;0.01$</td>
<td>$P&lt;0.05$ throughout 96 h; shorter duration of PCA $P&lt;0.05$</td>
<td>Desaturation and respiratory frequency $P&lt;0.005$</td>
</tr>
<tr>
<td>Murdoch and colleagues¹⁵</td>
<td>4</td>
<td>Total abdominal hysterectomy</td>
<td>40 (19/21)</td>
<td>1 vs 1+0.75</td>
<td>NS</td>
<td>NS</td>
<td>Pruritus $P&lt;0.05$</td>
</tr>
<tr>
<td>Kollender and colleagues¹¹</td>
<td>5</td>
<td>Orthopaedic-oncological</td>
<td>57 (29/28)</td>
<td>1.5 vs 1+</td>
<td>$P&lt;0.05$ throughout 96 h; shorter duration of PCA $P&lt;0.05$</td>
<td>NS</td>
<td>Wakefulness $P&lt;0.001$; urinary catheter dependence $&gt;24$ h and performance score $P&lt;0.05$</td>
</tr>
<tr>
<td>Reeves and colleagues¹⁹</td>
<td>3</td>
<td>Major upper and lower abdominal laparotomy</td>
<td>71 (35/36)</td>
<td>1 vs 1+</td>
<td>NS</td>
<td>NS</td>
<td>Cognitive function test at 48 h $P&lt;0.05$ in the ketamine group NS</td>
</tr>
<tr>
<td>Unlițenç and colleagues²⁵</td>
<td>4</td>
<td>Major abdominal</td>
<td>58 (28/30)</td>
<td>0.4 vs 0.4+</td>
<td>$P&lt;0.001$ at 15, 30, and 60 min</td>
<td>$P&lt;0.001$ at 12 and 24 h</td>
<td>Nausea, pruritus, urinary retention $P&lt;0.05$</td>
</tr>
<tr>
<td>Javery and colleagues⁸</td>
<td>3</td>
<td>Lumbar microdiscectomy</td>
<td>42 (20/22)</td>
<td>1 vs 1+</td>
<td>$P&lt;0.001$</td>
<td>$P&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td>Sveticic and colleagues²³</td>
<td>5</td>
<td>Major orthopaedic</td>
<td>352 (176/176)</td>
<td>1.5 vs 1.5+</td>
<td>NS</td>
<td>NS</td>
<td>Desaturation $P&lt;0.01$</td>
</tr>
<tr>
<td>Nesher and colleagues¹⁷</td>
<td>5</td>
<td>Thoracotomy for coronary artery bypass and lung tumour resection</td>
<td>41 (20/21)</td>
<td>1.5 vs 1+</td>
<td>$P&lt;0.001$</td>
<td>NS</td>
<td>Less sleepiness $P&lt;0.05$; doses of antiepileptics $P&lt;0.05$</td>
</tr>
<tr>
<td>Hercock and colleagues⁶</td>
<td>5</td>
<td>Total abdominal hysterectomy</td>
<td>49 (25/24)</td>
<td>1 vs 1+</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

N F Sethna, MD. Boston Children’s Hospital
Gabapentin improves cold-pressor pain responses in methadone-maintained patients

Peggy Compton\textsuperscript{a,*}, Priscilla Kehoe\textsuperscript{a}, Karabi Sinha\textsuperscript{a}, Matt A. Torrington\textsuperscript{b}, Walter Ling\textsuperscript{b}

- RCTDB, Stable methadone-maintenance program
- 5-week gabapentin 2400mg/day
- Control n=10; Placebo n=16
Opioid Rotation Strategies

Smith 2009

Table 2  Key Points for Opioid Rotation

- Utilize an opioid equianalgesic table that is appropriate/relevant for your practice, and use it consistently.
- In deciding on an alternative opioid, consider all patient factors (e.g., What is the best route of drug delivery in this patient? Which drug is most convenient for the patient/treating team? Is cost going to be an issue? Is the new drug available in the community?).
- In rotating opioids, consider all medical factors that may be relevant (e.g., renal function, liver function, age, comorbidities), and adjust equianalgesic dose based on these factors.
- In rotating to an opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%.
- In rotating to methadone, reduce the dose by 75% to 90%.
- In rotating to transdermal fentanyl, maintain the equianalgesic dose.
- In rotating because of uncontrolled pain, consider a lesser dose reduction than usual.
- Ensure that appropriate rescue/breakthrough doses are available. Use 5% to 15% of the total daily opioid dose as a guide, and reassess and retitrate the new opioid.
### Table 2: Evidence Supporting the Preemptive Effects of Various Types of Surgical Analgesia

<table>
<thead>
<tr>
<th>Type of analgesia</th>
<th>Evidence for preemptive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural analgesia</td>
<td>Moderate</td>
</tr>
<tr>
<td>Local anesthesia</td>
<td>Weak to moderate</td>
</tr>
<tr>
<td>NMDA receptor antagonists</td>
<td>Conflicting</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>Weak to moderate</td>
</tr>
<tr>
<td>Opioids</td>
<td>Conflicting</td>
</tr>
<tr>
<td>Gabapentin</td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Weak and conflicting</td>
</tr>
</tbody>
</table>

*Abbreviation: NMDA, N-methyl-D-aspartic acid.*
# Do Opioids Induce Hyperalgesia in Humans? An Evidence-Based Structured Review

David A. Fishbain, MD, FAPA,*†§‖ Brandly Cole, PsyD,‖ John E. Lewis, PhD,* Jinrun Gao, MS, MBA,** and R. Steele Rosomoff, BSN, MBA§

<table>
<thead>
<tr>
<th>Grouping of Studies According to the Hypothesis the Study</th>
<th>No. of Reports</th>
<th>Type of Evidence</th>
<th>Average Quality</th>
<th>Overall Finding of All the Studies in the Grouping in Reference to the Hypothesis Represented by the Grouping as a % of the Studies in the Grouping</th>
<th>Strength/Consistency of the Findings According to the AHCPR Guidelines in Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothesis #1: Opioid addicts maintained on opioids will have decreased pain threshold or pain tolerance. (Table S1)</td>
<td>9</td>
<td>100%</td>
<td>Type 2</td>
<td>96.0%</td>
<td>B for supporting hypothesis utilizing pain tolerance, but B for not supporting hypothesis utilizing pain threshold. Overall findings not interpretable because of issues presented in discussion.</td>
</tr>
<tr>
<td>Hypothesis #2: Detoxing opioid addicts from opioids will increase their pain threshold or pain tolerance. (Table S2)</td>
<td>2</td>
<td>100%</td>
<td>Type 2</td>
<td>100%</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
<tr>
<td>Hypothesis #3: Stopping or decreasing an opioid or rotating to a different opioid will improve pain and/or allodynia. (Table S3)</td>
<td>21, but 2 reports not utilized because of low quality scores leaving 19 reports</td>
<td>94.7%</td>
<td>Type 5 and 5.2% Type 4.</td>
<td>For 18 reports no quality score as case reports For 1 study quality score of 92.8%.</td>
<td>Overall 123 pts. reported on. In 21 pts., alldynia reported on and improved in all cases (100%). In 114 pts., pain reported on and improved in all cases (100%).</td>
</tr>
<tr>
<td>Hypothesis #4: CPPs placed on opioids will develop decreased pain threshold and tolerance. (Table S4)</td>
<td>1</td>
<td>Type 3</td>
<td>81.8%</td>
<td>100%</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
<tr>
<td>Hypothesis #5: CPPs on opioids will have decreased pain threshold and tolerance vs chronic pain patients not on opioids. (Table S5)</td>
<td>1</td>
<td>Type 2</td>
<td>100%</td>
<td>100%</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
</tbody>
</table>

*N F Sethna, MD. Boston Children’s Hospital
Conclusion

There is not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers receiving opioid infusions.
Conclusions

Angst 2009; Low 2011

• OIH probably occurs in clinical setting

• Risk of developing OIH increases with higher doses of opioids

• Treatment
  – A trial of dose escalation/de-escalation
  – Multimodal analgesia regimens to minimize the reliance on opioids alone and reduce the potential for tolerance &/or OIH