Opioid-Induced Hyperalgesia (OIH)

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Disclosures

• Research on shifts in the hypothalamic-pituitary-adrenal system and depression during and after alcohol withdrawal sponsored by the Distilled Spirits Council of the United States (Johnson 1986)
Learning Objectives

1. Get the “big picture” about why opioid prescribing has accelerated recently, setting the environment for OIH to be commonplace
2. Know the definition of OIH
3. Know the neural mechanisms of OIH
4. Know the effect of methadone or buprenorphine maintenance on OIH
Learning Objectives 2

5. Know how long it takes to induce OIH
6. Know what to do about OIH; with addicted patients and non-addicted patients
7. Understand the surgical pain management of a patient with OIH
1. The Big Picture

- Practitioners often remark that use of opioids has become ubiquitous. The following slides show how common opioid prescribing has become, what the impetus was behind the shift in medical practice, and what are some of the unimagined consequences of a social movement that was not evidence-based. The existence of OIH has been recognized only after the impact of the right to pain treatment movement had its effect.
Opioid Use Has Exploded!

- 2009 USA, 5% of world’s population
- 56% of global morphine
- 81% of global oxycodone
- 99% of global hydrocodone

(Huxtable 2011)
# Opioid-Associated Deaths - USA

<table>
<thead>
<tr>
<th>Drug</th>
<th>1998</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>14</td>
<td>1007</td>
</tr>
<tr>
<td>Morphine</td>
<td>82</td>
<td>329</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>92</td>
<td>1245</td>
</tr>
<tr>
<td>Methadone</td>
<td>8</td>
<td>329</td>
</tr>
</tbody>
</table>

(Huxtable 2011)
“Pain Management: A Fundamental Human Right”

“Reasons for deficiencies in pain management included cultural, societal, religious and political attitudes, including acceptance of torture. Strategies for improvement include framing pain management as an ethical issue; promoting pain management as a legal right,
• Providing constitutional guarantees and statutory regulations that span negligence law, criminal law, and elder abuse; defining pain management as a fundamental human right, categorizing failure to provide pain management as professional misconduct.

• Brennan, Carr, Cousins (2007)
Dr. Portenoy helped write a landmark 1996 consensus statement by two professional pain societies that said there was little risk of addiction or overdose among pain patients. In lectures he cited the statistic that less than 1% of opioid users became addicted. Today, even proponents of opioid use say that figure was wrong. “It's obviously crazy to think that only 1% of the population is at risk for opioid addiction,” said Lynn Webster, president-elect of the American Academy of Pain Medicine, one of the publishers of the 1996 statement. “It's just not true.” Dr. Portenoy's ideas about opioids reached into mainstream medicine and attracted outspoken advocates. In a 1998 talk in Houston, Alan Spanos, a South Carolina pain specialist, said patients with chronic noncancer pain could be trusted to decide themselves how many painkillers to take without risk of overdose. According to a recording, Dr. Spanos said he understood that a patient would simply “go to sleep” before stopping breathing. “It sounds scary, but as far as I know, nobody anywhere is getting burned by doing it this way.” (WSJ 2012)
Unintentional Overdose Deaths by Major Type of Drug Involved, United States 1999-2010 *

The impact of increased prescribing of opioids by physicians on overdose deaths. Note that heroin deaths are steady during this period.

Data from Centers for Disease Control and Prevention WONDER
CDC 2009 Deaths

- Accidental overdose – 37,485
- Up 3X since 1980
- Auto fatalities – 36,284
- Half of 1980
- Practitioners will experience that patients often want opioid medications despite the existence of OIH/pain intensified by opioid maintenance. Remember that the definition of addiction is that the drug is urgently wanted despite evident harm.
2. Definition of OIH

- Exacerbation of pain caused by administration of opioid medications or, “Increased nociceptive sensitization caused by exposure to opioids.”
- Opioid medication gradually causes increased baseline pain
- “Tolerance” means that baseline pain is unchanged; amelioration just takes more opioid
- Pain is generally more widespread than initially
- Quality of pain may evolve
- Patient responds with alarm at the increase of pain, and usually requests more opioid
Opioid-Induced Hyperalgesia

• “If addiction and the relief of suffering are partners in an uneasy marriage where opiates are concerned, then OIH is the mother-in-law whose role in the union may be ambiguous but whose presence is never in doubt

• “Withdrawal from opioids provides the opportunity for underlying hyperalgesia to be revealed” (Ling 2010, OIH ed. Mao)
3. Neural Mechanisms of OIH

OIH is a 21st century concept. Just as opioid prescribing was taking off, Celerier (2001) first explained the difference between tolerance and OIH, and its neural origin. The slides that follow start with a description of the endogenous morphine (endorphin) system. Opioid medications could not work unless they used an existing set of receptors. A slide shows how they create craving. There are pain drivers that overshoot opioid medications. This concept of opponent process theory is shown in the Koob slide.
Endogenous Mu Opioid-Synthesis

There are several types of opioid receptors. Mu receptors are most important for pain relief. Mu receptors are spread throughout the central nervous system and gut. There are even mu receptors on white blood cells (picture from Wyeth library).
Mechanism of Endorphin Activity

• Central Nervous System

- Involved at inhibiting GABA and thus disinhibiting dopamine

- Receptors in:
  - Descending pain circuit: amygdala, mesencephalic reticular formation, PAG, rostral ventral medulla

Image from:
Mechanism of Endorphin Activity

Peripheral Nervous System

- Primary Afferent Neurons, Peripheral Sensory Nerve fibers, Dorsal Root Ganglia
- Inhibition of substance P and other tachykinin release
Proposed Mechanisms of Release

• 2 systems in place (Peripheral and Central)
  – Peripheral mediated by stress and ACTH co-release
    • Corticotrophs in the anterior pituitary synthesize ACTH and β-endorphin in equimolar amounts
  – Central involves innervation of the hypothalamus, midbrain, and rostral medulla
    • Cell bodies of opioidergic neurons are located in the median eminence of the hypothalamus (Sehgal 2011)
Proposed Mechanisms of Release

• Co-release with ACTH during stress reactions from anterior pituitary
• Release Mediators:
  – 5-HETE, LTA4, LTB4, and other lipoxygenase products
    • Evidence of β-endorphin in T-lymphocytes, B-lymphocytes, monocytes, and macrophages during inflammatory reactions
  – Angiotensin-II
  – 5-HT
• Process involves activation of cAMP by β-adrenoreceptor activation (Sehgal 2011)
How Opioids Cause Craving

• The next slide shows the mechanisms of dopamine release in the ventral tegmental – nucleus accumbens craving pathway. Stimulant drugs such as cocaine block the dopamine transporter. Sedating drugs such as opioids affect the gabaergic brake on dopamine release. This may be why cocaine or nicotine appear to be more “addicting” than opioids.
Brain Addiction Pathways (Johnson 2009)

Craving/Dreaming Pathways: Neurop=neuropeptides, GABA=gamma amino butyric acid
Celerier 2001, Amount of Pressure Causing Pain Response

![Graph showing the amount of pressure causing pain response over days, with comparison between saline and heroin (2.5 mg/kg) treatments.](image-url)
Many Animal Studies Clearly Demonstrate OIH

- Notice that in the Celerier slide shown previously, every dose of heroin made the rat more pain-sensitive. The hyperalgesia wore off after 12 days, but was quickly reinstated by a single dose of heroin. The next slide shows Celerier’s evidence that the glutamate system was instrumental in creating OIH. If it was blocked, OIH did not develop.
Celerier 2001: Heroin + glutamate receptor antagonist 801- No OIH
Chronic Opioid Exposure

Tolerance

Sensitization (OIH)

Pronociception

Tolerance means that it takes more opioid to produce analgesia. OIH means that the pain system is driving more nociception - Mao 2010 OIH ed. Mao
Animal Hyperalgesia

• White (2004)
• Rats implanted with morphine pellet
• Initial response to radiant heat; analgesia
• By day 4, clear hyperalgesia (on morphine!)
• Biphasic response to opiates; relief followed by more pain
For Every Action, An Equal and Opposite Reaction?

• No, there seems to be an overshoot
• If it was 10,000 years ago, and you couldn’t feel pain, you might step on a thorn and die of a bacterial infection. Blocking pain signals, the “a” process, provokes a “b” process that increases pain sensitivity. Depression and anxiety drivers also increase.
• “Over the past 15 years, compelling preclinical evidence has accumulated, indicating that hyperalgesia follows opioid administration in the absence of overt, precipitated withdrawal.” Mao 2010 OIH ed. Mao
Koob 2001. The “a” Process, Slower “b” Resetting of Drivers
Mechanisms of OIH - 1

• Glutamatergic activation
  – Activation of NMDA receptors by mu opioids
  – Inhibition of glutamate transport reuptake
  – Inhibition of calcium-regulated intracellular protein kinase C

• Spinal dynorphin A increases (Laughlin 2001)
  – Dynorphin A, an endogenous opioid that activates the kappa receptor, produces pain by interacting with NMDA glutamate receptors
  – Acts on bradykinin receptors
  – Causes a switch in G proteins to stimulatory G protein, increasing intracellular calcium
  – Release of excitatory calcitonin gene-related protein
  – Potentiation of pain/neuronal hyperalgesia
OIH – 2: Toll-like receptor (TLR) signaling on glial cells

• Docking of opioids to TLR4 results in the expression of a number of pro-inflammatory mediators, especially IL-1B and IL-6. These cytokines bind to their receptors on neurons and are pro-nociceptive. IL-1B increases extracellular glutamate by down-regulation of the glutamate transporter GLT-1. It phosphorylates the NMDA receptor leading to an increase in channel opening, allowing an influx of calcium which causes increased nitric oxide and PGE2, amplifying the excitability of pain projection neurons. (Huxtable 2011)
OIH 3 – Glutamate Activation Necessary for OIH to Develop

- Subunit of NMDA receptor involved: GluRepsilon1 (NR2A)
- Knockout mice with no NR2A receptor: Day 6 on morphine; tolerance to analgesia in wild mice, not in NR2A knockout mice: 2 – 3 X NR2A in periaqueductal grey, VTA, NAc only
- Enhanced activation of anti-opioid NMDA receptor system counterbalances/cancels morphine analgesia during chronic treatments (Ueda 2010 in OIH ed Mao)
Other Drivers of OIH

- Substance P
- Corticotrophin Releasing Hormone (CRF)
- Calcitonin gene related peptide
- Bradykinin
- Prostaglandin
- ATP
- Cytokines
- Chemokines (Sehgal 2011)
Do Animal Experiments Translate to Human OIH?

- Pain is a symptom of opioid withdrawal
- A standard way to document pain sensitivity is the “Cold Pressor Test (CPT).” A subject submerges their forearm in an icewater bath for as long as they can tolerate the pain. Many studies show shortened CPT times as a consequence of opioid maintenance.
- Prospective study of back pain patients: one month on opioids shortened CPT times (Chu 2006)
- High rather than low intraoperative opioid dose is associated with increased pain and/or opioid consumption postop (see below)
- 30 – 90 minute remifentanil dose-dependently increased skin hyperalgesia (Angst 2010)
Human Hyperalgesia

- Cold pressor test (cpt) trough:
  - 56 sec. Controls
  - 15 SECONDS ON METHADONE (white 2004)
- Hay-white 2009
  - Cpt 31 seconds - control
  - 18-20 seconds on morphine for pain, methadone for pain, methadone for addiction
- Patients maintained on methadone or morphine; whether for pain or addiction, are pain-sensitive (OIH)
Diagnosis of OIH

• Patient had been maintained on opioids AND:
  • Pain worse despite no change in source of pain OR
  • Pain-sensitive on Cold Pressor Test OR
• Increase in opioid dose results in worsening pain; the phenomenon that the dose just goes up and up, threatening accidental overdose death
Sample Cold Pressor Times (CPT)

These are the first six CPT done at University Hospital, Syracuse, New York. 95% of our normal controls can tolerate at least 35 seconds in the icewater.

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>CPT seconds</th>
<th>Pain (0-10)</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/female</td>
<td>3</td>
<td>8</td>
<td>hydrocodone</td>
</tr>
<tr>
<td>26/female</td>
<td>10</td>
<td>8</td>
<td>oxycodone 240</td>
</tr>
<tr>
<td>40/female</td>
<td>14</td>
<td>10</td>
<td>illicit painkiller</td>
</tr>
<tr>
<td>42/male</td>
<td>5</td>
<td>8</td>
<td>oxycodone 60</td>
</tr>
<tr>
<td>17/female</td>
<td>180</td>
<td>10</td>
<td>oxycodone</td>
</tr>
<tr>
<td>27/male*</td>
<td>10</td>
<td>7</td>
<td>methadone</td>
</tr>
</tbody>
</table>

*Repeated post-detox-3 minutes 0 1 week later
Does OIH Ever Go Away?

- Ren (2009) Cold Pressor Times for heroin-addicted subjects sober 5 months
  - Controls 134 seconds
  - Abstinent 85 seconds (p<0.05)

As much as we would like to imagine the brain snaps right back to its opioid-naïve state, opioids may be causing long-term hyperalgesia.
Younger (2011)

- Brain changes induced in one month on morphine up to 120mg/day prn for back pain
- Brain changes did not reverse 5 months after cessation of morphine; specifically-
  - Hypothalamic changes linked to production of hypocretin, which is responsible for attention
  - Amygdalar changes linked to learning, which is impaired by opioids
4. Methadone or Buprenorphine Maintenance Make OIH Worse

- Compton and her collaborators put heroin dependent subjects on maintenance therapy. They used the Cold Pressor Test to follow pain sensitivity. You can see that the control subjects averaged 43 seconds in the icewater before they had to withdraw their forearm due to intense pain. Hyperalgesic heroin subjects averaged 19 and 26 seconds. Blanketing the opioid receptors with methadone or buprenorphine only made things worse; 14 or 17 seconds.
What About After Opioid Subst. Therapy? (Compton 2012)
Effect of Methadone?
(Rosenblum 2003)

Effect of Duration of Methadone Therapy on Percent with Severe Chronic Pain
5. How Long Does It Take to Induce OIH?

If the dose is large enough, it can be induced in a day. On the next two slides Martin Angst (2010) shows the results of five studies where subjects were administered remifentanil during surgery. “Differences in total opioid exposure likely explain the discrepant results. Studies reporting negative results (light grey bars) administered cumulative doses 20-30 mcg/kg. Studies reporting positive results (dark grey) doses 80-120 mg/kg. These findings suggest that OIH develops in dose-dependent fashion and only becomes evident when total opioid exposure is quite high.”
Angst review; increased pain and/or opioid use after higher exposure

- Cortinez-0.1 v 0.23 mcg/kg/min X 100” GYN Surg
- Lee-nitrous oxide only v 0.17mcg/kg/min X 140” Colorectal Surgery
- Guignard-0.1 v 0.3mcg/kg/min X 260” Colectomy
- Joly-0.05 v 0.4micg/kg/min for 260” Colectomy
- Crawford-morphine only versus 0.28micg/kg/min for average 460 “ Scoliosis Surgery
- Author, remifentanyl doses, duration and type of surgery above. Higher doses of remifentanil led to more OIH-within one day-as shown by post-op pain, post-op opioid use. Angst’s graph is next-
Perioperative OIH: Left-No Pain Increase/Right-Increase

Cumulative remifentanil dose (μg/kg)

- Cortinez
- Lee
- Guignard
- Joly
- Crawford
Possible Ways to Diminish OIH During Surgery

• Intraoperative low dose ketamine infused with remifentanil (Hong 2011)
• Remifentanil increased an area of mechanical hyperalgesia by 141%; but not if propranolol infused at the same time (Chu 2012)
• Gabapentin infused with remifentanil (Aguado 2012)
6. What is the Optimal Management of OIH Patients?

• OIH is diagnosed by either increased pain without any cause of exacerbation AND/OR by shortened cold pressor time
• The patient is told that opioids are causing pain
• The patient is detoxified from opioid medications; pain will not diminish with a lower dose – the cause of increased pain is described above. Patients must be off opioids for pain to get better.
• The next slides show one study of what happened next.
Diagnoses (N=53), average 3.7 years on opioid medications for the following conditions:

- Back pain 66%
- Headache 13%
- Orthopedic injury 9%
- Fibromyalgia 8%
- Toothache 4%

The next slide shows what happened to pain scores over five days of clonidine/diazepam detox – no opioids were given.
## Change in Pain Scores During Detox – Pain Improved!

<table>
<thead>
<tr>
<th></th>
<th>Hydrocodone</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>4.76/10 pain</td>
<td>7.50/10 pain</td>
</tr>
<tr>
<td>Day 2</td>
<td>4.88/10</td>
<td>7.00/10</td>
</tr>
<tr>
<td>Day 3</td>
<td>4.72/10</td>
<td>6.08/10</td>
</tr>
<tr>
<td>Day 4</td>
<td>3.85/10</td>
<td>5.29/10</td>
</tr>
<tr>
<td>Discharge</td>
<td>2.81/10 pain</td>
<td>4.58/10 pain</td>
</tr>
</tbody>
</table>
Patients Maintained on Opioids May Be Addicted

• The hallmark of addiction is that the person urgently wants the drug – even if it is clearly harmful. Think cigarettes; lethal to 50% of users and wanted. A key question for pain treatment is, “Are you looking for the best treatment available for your pain, or are you looking for a physician who will prescribe you opioids?” As shown by the Miller study above, pain often improves when opioid maintenance is terminated. Non-addicted patients welcome improvement. Addicted patients may insist on opioids despite increased pain.
Opioid Dependence

- Tolerance
- Withdrawal
- Taken in larger amounts over a longer period than intended
- Unsuccessful attempts to cut down or control
- Much time spent obtaining, using, recovering
- Important activities given up/reduced
- Use despite knowledge of physical or psychological consequences
Chapman and colleagues (2011) compared 30 patients who had chronic pain and who were maintained on opioids (CPOP) with 25 patients who had chronic pain and were not maintained on opioids (CP). Starting on opioids before surgery led to more pain for more time after surgery. The scales at the sides of the graph seen on the next slide are the 0 – 10 pain scale.
Principles of Pain Mgmt - Opioid Maintenance Surgical Patients

- Promote adequate perioperative analgesia
- Prevent withdrawal by maintaining opioid meds
- Assist with social, psychiatric and behavioral issues – plan from preadmission
- Coordinate with other involved physicians
- Be non-judgmental but ask that patients be honest about prior opioid use; or they will not get optimal management
- Give a trial dose first; patients may be dishonest and ask for an overdose. Check on dose from primary care or other source if possible.
Principles 2

• Expect to give 2 – 3 times the dose of opioid as for an opioid-naïve patient during and after surgery
• Avoid other sedating drugs such as benzodiazepines
• If opioid tolerance was not reported before surgery, it may be evident by:
  – Elevated pain scores
  – High opioid use
  – Low side effects
Principles 3

• For methadone maintenance patients, divide the dose to TID and add short-acting opioids. Methadone may be given IM or SC

• For buprenorphine maintenance, increase the dose and give TID for minorly increased pain, stop it and give full agonist opioids for major increases in pain

• Treat insomnia with low dose mirtazapine or trazodone, not benzodiazepine agonists

(Huxtable 2011)
Summary – Opioid Induced Hyperalgesia

• The Right to Pain Treatment movement, which is emotionally based, has moved opioid prescribing up to never-before seen levels. OIH, while observed for centuries, has been given a strong evidence base by results from animal studies. The glutamate system, dynorphin, and subcortical brain structures are important in OIH, as they are in addiction. The prevalence, clinical significance and treatment implications of OIH need further elucidation.
Please Click the Link Below to Access the Post Test for the Online Module

Upon completion of the Post Test:

• You will receive an email detailing correct answers, explanations and references for each question.
• You will be directed to a module evaluation, upon completion of which you will be emailed your module Certificate of Completion.

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