Opioid Induced Hyperalgesia: Clinical Implications for the Pain Practitioner

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Disclaimer

- Speaker: Purdue, Depomed, DSI, BDSI, AZ
- Institute of Pain Management, Pompano Beach, Florida
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- Member: ASIPP, FAPM, FSIPP, ASAM, FSAM, FMA, BCMA
- Officer/Board Position: Past-President Broward County Medical Association, Past-president FSIPP, Board of Directors ASIPP, Board of Directors FSIPP
- Publications: Articles in Anesthesiology, Canadian Journal of Anesthesia, Pain Physician (Section editor Controlled Substances)
- No outside funding, no grants for this presentation
Self Assessment

1. Opioid induced hyperalgesia (OIH) is:
   1. The same as tolerance
   2. Often seen in chronic opioid therapy
   3. Related to increases in central GABA and glycine activation
   4. None of the above

2. Mechanisms of OIH include:
   1. Increases in central norepinephrine levels
   2. Enhanced descending facilitation (RVM)
   3. Enhanced production of nociceptive mediators in peripheral tissues
   4. B and C

3. Opioid rotation and use of NMDA antagonists are appropriate strategies in treating OIH
   1. True
   2. False

4. A 33 yo female presents with diffuse pain, impaired sleep, migraine, irritable bowel syndrome, and TMJ syndrome. She has been using oxycodone 30 mg Q4 hours for 6 months with no resolution of symptoms. The following statement regarding this case is false:
   1. Differential diagnosis includes fibromyalgia and somatization disorder
   2. Switching to an ER/LA opioid is appropriate
   3. She has a central hypersensitization pain syndrome
   4. This type of pain syndrome responds to treatment with gabapentin and pregabalin.

5. A 22 yo male with opioid use disorder has chronic neck and back pain from several MVAs. He has seen multiple physicians in the past and utilized oxycodone, morphine, hydromorphone, and hydrocodone. The history is that the medications work initially but eventually stop working and he is in pain. His pain diagram is filled in from head to toe. Correct statements regarding this patient include:
   1. He could be in withdrawal from opioids
   2. He has OIH
   3. He is actively abusing/using opioids
   4. All of the above

Learning Objectives

- List the definitions of opioid induced hyperalgesia (OIH)
- Explain the mechanisms of OIH
- Describe clinical and lab studies
- Identify clinical manifestations
- Describe the diagnosis of OIH
- List clinical implications to practitioners
Opioid “Baggage” (Side Effects)

- Constipation
- Nausea
- Pruritus
- Sedation
- Tolerance
- Dependence
  - Addiction
- Diversion
- Hyperalgesia

Iatrogenic Addiction: A Side Effect of Opioid Analgesic Therapy?

- Published rates of abuse and/or addiction in chronic pain populations are < 10%*

- Suggests that known risk factors for abuse or addiction in the general population would be good predictors for problematic prescription opioid use

  — History of early substance use
  — Personal/family history of substance abuse
  — Comorbid psychiatric disorders

Fishbain, 1992, 1996
Prevalence of Misuse, Abuse, and Addiction

Misuse 40%  
Abuse: 20%  
Addiction: 2% to 5%  
Total Pain Population

Hyperalgesia

- A state of the sensory nervous system in which a previously noxious stimulus is perceived as more noxious
- Molecular, peripheral, and central nervous system mechanisms contribute to the phenomenon
- Symptom of neuropathic injury (CRPS, PHN)
- Symptom of fibromyalgia
Allodynic Shift

Hyperalgesia – heightened sense of pain to noxious stimuli
Allodynia – pain resulting from normally painless stimuli

Tolerance vs OIH: Definitions and Differentiation

- The laboratory definitions of tolerance and OIH are precise
- Diagnosing tolerance and OIH clinically can be difficult
  - Increased opioid requirements: tolerance vs OIH
  - Aggravated pain: progression of underlying disease vs OIH
Opioid Withdrawal Hyperalgesia

Well-characterized in preclinical models:
- A multimodal hyperalgesia
- Following single or chronic opioid dosing
- Intensity proportionate to opioid dose
- Severity increases with intermittent or naloxone-interrupted opiate dosing
  - Involves excitatory amino acid (glutamate), as well as opioid, receptors
- Can be prevented with NMDA receptor antagonism

Opioid Induced Hyperalgesia

- Opiates, in addition to providing analgesia, set in motion antianalgesic or hyperalgesic processes
- Painfree animals made tolerant to morphine $\Leftrightarrow$ significantly decreased tolerance of pain
- Hyperalgesia demonstrated to have neuroplastic as well as conditioned components
  - Behaves essentially like opioid withdrawal hyperalgesia

1 Silverman, S. Pain Physician 2009; 12:679-684
“On the abuse of hypodermic injections of morphia,”

“At such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia, which may be an evil. Here experience is needed. Does morphia tend to encourage the very pain it pretends to relieve?”

“…..in the cases in question, I have much reason to suspect that a reliance upon hypodermic morphia only ended in that curious state of perpetuated pain”

From “What is the morphine disease?”

“He is also affected by a hypersensitiveness to pain, or a morbid intolerance of any kind of distress, and a degree of mental incompetency probably always more or less present in pronounced auto-toxemias, which render his self-control and his judgment inadequate to a rational course of action. He suffers. His suffering is actually great. To his astigmatic inner eye it seems even greater than it is.”
**Chronic Pain Syndrome**

- Chronic pain syndrome (CPS) consists of long-standing, localized or diffuse complaints of discomfort and pain (hyperalgesia) that have persisted beyond the expected healing time (if resulting from injury) and have resisted more conservative and traditional health care intervention strategies.¹
- Opioid induced hyperalgesia is a state of INCREASED pain sensitization associated with the use of opioids.²
- Buprenorphine is a kappa antagonist and may be of benefit in treating both entities.¹,²

² Silverman, SM; Opioid Induced Hyperalgesia: Clinical Implications for the Pain Practitioner; Pain Physician 2009; 12:679-684

**Addiction Results in a “Syndrome of Pain Facilitation”**

- Discomfort augmented by:
  - Subtle withdrawal syndromes
  - Intoxication or withdrawal-related sympathetic arousal, muscular tension
  - Sleep disturbance
  - Affective changes
  - Functional changes

(Savage & Schefferman, 1995)
Opponent Process Theory

Solomon developed a motivational theory based on opponent processes. Every process that has an affective valence, i.e., is pleasant or unpleasant, is followed by a secondary, “opponent process”. This opponent process sets in after the primary process is initiated. With repeated exposure, the primary process becomes weaker while the opponent process is strengthened.\(^1\)

According to opponent-process theory, drug addiction is the result of an emotional pairing of pleasure and the emotional symptoms associated with withdrawal. At the beginning of drug or any substance use, there are high levels of pleasure and low levels of withdrawal. Over time, however, as the levels of pleasure from using the drug decrease, the levels of withdrawal symptoms increase, thus providing motivation to keep using the drug despite a lack of pleasure from it.

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Opponent Process Theory Applied to Hyperalgesia

(Solomon, 1980; Koob, 1989)
Opioid Induced Hyperalgesia

- Is opioid analgesic tolerance actually an organismic expression of an opioid induced increased sensitivity to pain?
- Opioid tolerance not so much a downregulation of analgesic systems, but an upregulation of hyperalgesic systems

(Colpaert, 1996; Laulin et al., 1999)

Studies of OIH
Preclinical Laboratory Studies

- Rats show increased pain via paw withdrawal tests with infusions of opioid
- Similar findings with intrathecal opioids
- Similar findings with different opioids such as IV fentanyl, heroin

Conclusions:
- Laboratory animals can be sensitized to pain via administration of opioids

Clinical Studies

- Patients had increased postoperative pain and morphine requirements when receiving intraoperative remifentanil infusions
- Opioid addicts receiving methadone had increased pain when challenged with cold pressor tests
- A prospective trial in which long-acting morphine was given to participants with chronic low back pain demonstrated measurable hyperalgesia within 1 month of beginning therapy

References:
Pain Tolerance by \( \mu \)-Opioid Agonist Activity

High-Dose Daily Opioid Administration and Poor Functional Status Intensify Local Anesthetic Injection Pain in Cancer Patients

- Eighty-two cancer patients including 20 patients not taking opioids (non-opioid group) and 62 taking opioids (opioid group) who were scheduled for an interventional procedure were enrolled in this study.
- Patients received a standardized subcutaneous injection of lidocaine prior to a full dose of local anesthetic (LA).
- Before the injection, patients completed the Brief Pain Inventory (BPI) questionnaire and were asked to rate their current pain using numeric rating scales.
- Immediately following the injection, LA injection-specific pain was evaluated using pain intensity, unpleasantness, and behavior pain scores.
- LA injection-specific pain intensity, unpleasantness, and behavior pain score were significantly higher in the opioid group compared with the non-opioid group (\( P < 0.001 \)).
- In the opioid group, these post-injection pain scores were higher in patients taking high-dose opioids than those taking low doses (\( P < 0.05 \)).
- There was a strong correlation between the baseline BPI pain interference score and the LA injection-specific pain score (\( r = 0.695, \ P < 0.001 \)).
Mechanisms of OIH

1. Enhanced projection neuron sensitivity – central glutamate, LTP (long term potentiation)
2. Enhanced descending facilitation (RVM)
3. Glial activation
4. Enhanced production of primary afferent neurotransmitters (spinal dynorphin)
5. Enhanced production of nociceptive mediators in peripheral tissues
6. Demographics, genetics, epigenetics, and environmental factors

OIH and Tolerance: Sites of Modulation

1. Enhanced projection neuron sensitivity – central glutamate, LTP (long term potentiation)
2. Enhanced descending facilitation (RVM)
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5. Enhanced production of nociceptive mediators in peripheral tissues
6. Demographics, genetics, epigenetics, and environmental factors
Peripheral Sensitization

- Inflammatory response
  - Release of intracellular contents
  - Peripheral terminals release mediators
  - Increased excitability, induces vasodilation, extravasation of proteins
  - Inflammatory soup
  - High threshold low threshold
  - Low intensity stimulus now painful
Central Sensitization

- Increased spontaneous discharges
- Repeated stimulation of C fibers causes cumulative increase in their firing rate (windup)

Central Glutaminergic System

- Glutamate is a major stimulator neurotransmitter in the CNS
- Effects are mediated through NMDA (N-methyl-D aspartate) receptors
  1. NMDA receptors become activated and when inhibited, prevent the development of tolerance and OIH
  2. The glutamate transporter system is inhibited, therefore increasing the amount of glutamate available to NMDA receptors.
  3. Calcium regulated intracellular protein kinase C is likely a link between cellular mechanisms of tolerance and OIH
  4. Cross talk of neural mechanisms of pain and tolerance may exist. Prolonged morphine administration induces neurotoxicity via NMDA receptor mediated apoptotic cell death in the dorsal horn

Neuroimmune Alterations at the Dorsal Horn

**OIH: Sites of Modulation**

*Enhanced Postsynaptic Neurotransmitter Action*

The intrathecal injection of glutamate or SP to mice chronically treated with morphine leads to enhanced nociceptive responses.

![Graph](image)

Xiangqi Li, MD, and J. David Clark, MD, PhD; Hyperalgesia During Opioid Abstinence: Mediation by Glutamate and Substance P, Anesth Analg 2002;95:979–84

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**OIH and Tolerance: Sites of Modulation**

*Enhanced Postsynaptic Neurotransmitter Action*

- Chronic opioid exposure leads to enhanced responses to spinal nociceptive neurotransmitters.
- Increased NK-1 receptor expression supports pain; blockade or deletion prevents tolerance.
- Increased AMPA and NMDA receptor expression support pain, blockade or deletion prevent tolerance.
- Postsynaptic neurons display “LTP-like” potentiation after chronic morphine exposure.
Enhanced Production of Primary Afferent Neurotransmitters (Spinal Dynorphin)

Spinal Dynorphins

- A class of opioid polypeptide
- Can modulate pain response
- Dynorphin and kappa opioid receptor stimulation in neuropathic pain
- Dynorphin could also induce pain in the spinal cord through a nonopioid p38 pathway
- Spinal dynorphin levels increase with opioid mu receptor agonists
- Concomitant increases CGRP
Role of Descending Facilitation

- Descending facilitation influence on OIH may be seen through several mechanisms
- Subsets of neurons (on and off cells) within the rostral ventromedial medulla (RVM) have a unique response to opioids
- Facilitate spinal nociceptive processing
- Lesioning of the descending pathway to the spinal cord (dorsal lateral funiculus) prevents the increase seen in excitatory neuropeptides

OIH and Tolerance: Sites of Modulation

Descending Facilitation

- Activation of descending fibers from the RVM after chronic morphine administration facilitates nociceptive neurotransmission
- RVM injections of LA or lesions of the DLF block opioid hyperalgesia and prevent tolerance
- At the level of the RVM, increased availability of CCK may mediate the enhanced descending facilitation
- At the level of the spinal cord, this descending facilitation is dynorphin and serotonin dependent
OIH and Tolerance: Sites of Modulation
Neuroinflammation

- Systemic or spinal morphine treatment activates glial cells to produce cytokines
- Blockade of spinal cytokine activity prevents tolerance and OIH
- Both microglia and astrocytes may be activated by morphine
- The TLR 4 (a toll-like receptor that is responsible for activating the innate immune system) may be responsible for the glial activation by morphine

Morphine Induces Spinal Neuroinflammation

Morphine induces proinflammatory changes in spinal cord
IL-1β, IL-6, TNF-alpha.
50 mcg etanercept blocks inflammatory changes
Opioid Adaptations: Genetic Mapping

- Genetically mapped genes (tolerance or OIH)
  - Mapped without functional confirmation (statistical association)
    - Several dozen: QTL, haplotypic mapping, sequential strategies
  - Mapped and confirmed in rodents
    - P-glycoprotein/MDR/ABCB1: controls brain levels of opioids
    - DCC: controls axonal/dendritic growth and structural organization
    - MPDZ: controls AMPA receptor subunit insertion
  - Mapped and confirmed in rodents and humans
    - Beta-2 adrenergic receptor: controls the excitability of sensory neurons
    - 5-HT3: controls sensory neuron activity and spinal nociceptive signal transmission

Treatment Strategies
OIH-Treatment Strategies

- Rational polypharmacy, opioid sparing agents
- Interventional pain medicine
- Opioid rotation
- Diagnostic challenges
  1. Increase the dose of opioid and evaluate for increased efficacy (tolerance)
  2. Reduce or eliminate the opioid and evaluate (OIH)
  3. Utilize opioids with unique properties that may mitigate OIH (methadone, tapentadol, buprenorphine, levorphanol)
  4. Utilize specific agents that are NMDA receptor antagonists

NMDA Receptor Antagonists

- Ketamine shown promise in tx CRPS and tx of OIH
- Clonidine has produced paradoxical hypersensitivity in rats, but is commonly used to tx opioid withdrawal (also used in CRPS and neuropathic pain syndromes)
- Withdrawal hyperalgesia may be similar mechanism, clonidine may have a role in tx OIH
- Dextromethorphan not much use

Methadone

- Methadone, although a pure mu receptor agonist, has properties that may prevent or reduce OIH\(^1\)
- Methadone is a racemic (D and L forms)
- D-methadone is NMDA receptor antagonist, good for neuropathic pain as well
- Anecdotal reports exist of patients who have been thought to have OIH and been treated with combinations of reducing the dose of opioid (by 40%-50%) and adding “low-dose” methadone\(^2\)

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Levorphanol

- Potent opioid has 6-10 X more affinity for mu receptor than methadone
- Has NO QT prolongation
- NOT metabolized via P450
- Is noncompetitive NMDA receptor antagonist
- Shorter T1/2 : 11-60 hrs
- About 7X more potent than morphine
## Levorphanol and Methadone

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Levorphanol</th>
<th>Methadone</th>
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<tr>
<td>Opioid agonist activity</td>
<td>µ, δ, κ</td>
<td>µ, δ</td>
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<tr>
<td>NE-metabolite inhibition</td>
<td>Weak</td>
<td>Weak</td>
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<tr>
<td>NMDA inhibition</td>
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<tbody>
<tr>
<td>Bioavailability, Oral</td>
<td>Unknown</td>
<td>20–100%</td>
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<tr>
<td>Half-life</td>
<td>11–16 hours</td>
<td>4–8 hours</td>
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<tr>
<td>Metabolic pathway</td>
<td>Phase II glucuronidation to levorphanol-0-glucuronide</td>
<td>NAc, DPH, (2S,2R)-N-depropylmethadone to EEDP</td>
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<th>Opioid chemistry</th>
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<tr>
<td>Dosing</td>
<td>4 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Oral MED of 30 mg/kg</td>
<td>1 mg (1/2 x 2-mg tablet) PO 3 or 4 times daily (maximum daily starting dose: 4 mg); titrate up by up to 25% weekly, i.e., if starting at 1 mg PO 4 times daily in the first week, increase to 1 mg PO 3 times daily at second week</td>
<td>2.5 mg (1/2 x 5-mg tablet) PO three times daily (maximum daily starting dose: 7.5 mg); titrate up by up to 25% weekly, i.e., if starting at 2.5 mg PO 3 times daily first week, increase to 2.5 mg PO 4 or 5 times daily at second week (note as dose increases, percentage of upward titration decreases due to complex pharmacokinetics)</td>
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<th>Routine monitoring</th>
<th>Levorphanol</th>
<th>Methadone</th>
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<tr>
<td>VA; ECG (collected at least annually or as clinically indicated)</td>
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## Buprenorphine

- Partial agonist at mu and antagonist at kappa
- Shown to be effective in treatment of neuropathic pain
- Buprenorphine has been shown to be intermediate in its ability to induce pain sensitivity in patients maintained on methadone and control patients not taking opioids
- Buprenorphine showed an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl

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Medically Supervised Withdrawal With SL Buprenorphine

- Need X waiver to use
- Office based
- Easy to do
- Breaks the “cycle of pain and dependency”
- OIH usually abates after short time
- Kappa antagonism may be useful
- Can use buprenorphine for analgesia

Tapentadol

- CS II mu opioid receptor agonist and NE reuptake inhibitor
- Dual action requires less opioid action
- Abrupt cessation showed very limited amount of withdrawal
- No CYP450 metabolism
- FDA approval for DPN
**Case**

- 34 yo male with history of bilateral foot pain. Patient underwent several foot surgeries and developed chronic pain in both feet. He was treated at a previous clinic with at least 5 lumbar sympathetic blocks, placement of SCS with subsequent removal secondary to lack of coverage, several medications. He was diagnosed with RSD (now CRPS). He also has diabetic neuropathy. His current complaint is much the same as it has been for 5 years: burning in the feet, toes swelling, cold, hypersensitivity. He also has anxiety for which he takes alprazolam. Sleep is interrupted by pain. He has escalated his use of opioid pain medications over the years. Current medications:
  - Xanax 0.5 mg tablet; Tablet(s); PO; QID;
  - Ritalin 10 mg tablet; Tablet(s); PO; PRN;
  - Kadian 100 mg capsule, extended release; 2-3 Capsule(s); PO; QID;
  - Cialis 5 mg tablet; 1 Tablet(s); PO; daily; Refills: 0; UOM: Tablet
  - Humalog 100 unit/mL Sub-Q; SQ; sliding scale in insulin pump.;
  - Dilaudid 8 mg tablet; 4-6 Tablet(s); PO; Q4H;
  - Methadone 10 mg tablet; 2-3 Tablet(s); PO; QID;
  - Cymbalta 40 mg tablet; 1 Tablet(s); PO; daily; Refills: 0; UOM: Tablet
  - AndroGel Transdermal
  - Fioricet 50 mg-325 mg-40 mg tablet; Tablet(s); PO; QID
  - Altace 2.5 mg tablet; 1 Tablet(s); PO; daily;

**Physical Exam**

- MS: bilateral lower extremities:
  - Neurological: motor-Overall: full strength in UE, full strength in LE.
  - Right patella: blunted at 1+. Left achilles: no reflex present (0). Right achilles: no reflex present (0).
  - Nerve root tension tests: Negative straight leg raising sign, normal Spurling sign.
  - Sensation-Left foot: Left and right increased to light touch alldynia seen plantar and dorsal surfaces bilateral
  - Pt also has diffuse myalgias by history and on Physical exam, tenderness c/w diffuse myofascial pain.
  - The Screener and Opioid Assessment for Patients with Pain -Revised (SOAPP-R) = 18. < 9 indicates low risk for opioid misuse; 10-21 indicates moderate risk of opioid misuse; > 22 indicates high risk of opioid misuse
  - Urine drug test
  - Methadone positive; THC negative; oxycodone positive; opiates positive; amphetamine negative
  - Methamphetamine positive; cocaine negative; benzodiazepines positive
• He has associated other pain problems to include migraines for which he uses Fiorcet QID, but not on a regular basis.
• He denies being tx for substance use disorder. Alprazolam used for anxiety.
• However, admits to having sweats and anxiety if Kadian dose is missed or late.
• Pt admits to occasional marijuana use, social use. Does socially consume ethanol.
• Denies any domestic violence. Currently disabled, used to own restaurant. Now winters in FL to avoid cold in NY, causes more pain in feet. He anticipates being here for about another month.
• Is also taking Ritalin to counteract effects of sedation from opioids.
• Taking androgens to counteract opioid induced hypogonadism.
• Migraines are frontal, never occipital since teenager. Pt states he has had brain MRIs and this has been worked up, but never been on other prophylactic therapy.

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**Options**

– Are there comorbidities affecting outcome
– Does the pt have addiction?
  – What is central sensitization?

• Opioid rotation
• SL buprenorphine
• No opioids at all
Summary

- Side effects/complications of opioid therapy can occur
- Be aware of OIH
- Differential diagnosis between tolerance and OIH
- Have an exit strategy
- Consider weaning, opioid rotation, medically supervised withdrawal

Self Assessment

1. Opioid induced hyperalgesia (OIH) is:
   a) The same as tolerance
   b) Often seen in chronic opioid therapy
   c) Related to increases in central GABA and glycine activation
   d) None of the above
   Answer: d

2. Mechanisms of OIH include:
   a) Increased central norepinephrine levels
   b) Enhanced descending facilitation (RVM)
   c) Enhanced production of nociceptive mediators in peripheral tissues
   d) b and c
   Answer: d

3. Opioid rotation and use of NMDA antagonists are appropriate strategies in treating OIH
   - True
   - False
   Answer: True

4. A 33 yo female presents with diffuse pain, impaired sleep, migraines, irritable bowel syndrome, and TMJ syndrome. She has been using oxycodone 20 mg Q4 hours for 6 months with no resolution of symptoms. The following statement regarding this case is false:
   a) Differential diagnosis includes fibromyalgia and somatization disorder
   b) Switching to an ER/LA opioid is appropriate
   c) She has central hypersensitization pain syndrome
   d) This type of pain syndrome responds to treatment with gabapentin and pregabalin.
   Answer: b

5. A 22 yo male with opioid use disorder has chronic neck and back pain from several MVA’s. He has seen multiple physicians in the past and utilized oxycodone, morphine, hydrocodone, and hydrocodone. He states that the medications work initially but eventually stop working and he is in pain. His pain diagram is filled in from head-to-toe. Correct statements regarding this patient include:
   a) He could be in withdrawal from opioids
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   d) All of the above
   Answer: d
Thank You
Sanford M. Silverman, MD
Comprehensive Pain Medicine

Questions & Discussion