Perioperative Treatment of the Opiate Addicted Patient

Dr. John A Costello
Matrix Anesthesia PS

GOALS

- Understand the scope of opiate addiction in the United States
- Improve understanding of opiate addiction and its consequences
- Learn about opiate genetics
- Improve understanding of opiate pharmacology
- Learn about non-opiate adjuvants for post-operative pain control
- Improve assessment and treatment of post-operative pain in the PACU through case analysis

How do Americans Obtain Their Opiates?

- 56.5% receive them for free from a friend or relative
- 81% of these friends/relatives received them from one physician
- 18% receive their opiates from a single physician while 82% physician shop
- 4% purchase from a stranger or drug dealer
- 0.5% purchased their opiates through the internet

Scope of Opiate Addiction in the United States

The Blue Mosque from the Bosphorus

**Empirical View of Opioid Dependence**

Charles Russek, PhD

ABSTRACT

BACKGROUND: The impact of opioid dependence on patients, managed care, and society is significant, imposing costs on healthcare systems and economies.

OBJECTIVE: To estimate the prevalence of opioid dependence among patients, managed care, and society.

METHODS: An estimated 4.5% of Americans in the United States abuse opioids, and approximately 2.6% use prescription opioid costs for nonmedical use. This association is an area of rapidly growing concern, affecting both the medical, economic, social, and criminal health of the abuse.

RESULTS: Among patients, opioid dependence cost society $14 billion per year. This includes the medical costs of opioid dependence, as well as the costs of crime and incarceration. The social costs of opioid dependence include lost productivity, lost time, and other costs. The economic costs of opioid dependence are estimated at $14 billion per year, including the cost of crime and incarceration. The costs associated with opioid dependence and addiction are significant. Public, private, and managed care organizations must be proactive in appropriately distributing and managing patients to further benefit society.

CONCLUSION: The costs associated with opioid dependence and addiction are significant. Public, private, and managed care organizations must be proactive in appropriately distributing and managing patients to further benefit society.

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**Rate of Opioid Prescriptions**

Figure 1 - Opioid Prescriptions Dispensed by US Retail Pharmacies

- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014

- TCA
- Fentanyl
- Hydromorphone

Empirical View of Opioid Dependence

Annual Societal Costs of Opioid Abuse

Which Opiate Users Are Likely To Overdose?

National Overdose Deaths from Prescription Drugs

Historical Price of Heroin
Historical Purity of Heroin

Prescription Opiate Deaths Vs. Cocaine and Heroin

Trend in Prevalence of Heroin Use and Deaths

Consequences of Opiate Use

Suboxone Prescriptions 2003 - 2012

Washington State Pain Medicine Rule

- Effective Jan 2, 2012 change in Standard of Care for Family Medicine Physicians: WAC 246-919-850 through 246-919-853 (enforced by Medical Quality Assurance Committee or MQAC)

- Patient Evaluation: detailed physical exam and history with indication for treatment with chronic opiates

- Monitoring Patient Conduct: photo ID and "pain contract"

- Detailed Periodic Review: annual review or semi-annual if greater than 40 mg of MED/day orally

- CME Requirement: 4 hours/year

- Pain Management Consultant requirement: if greater than 120 mg MED/day orally

- Understanding the New Washington State Pain Medication and Opioid Rules By Ronald J. Friedman
What is Opiate Addiction? The Famous Walls of Constantinople

Risk Factors For Opiate Abuse/Dependence

- National Survey on Drug Use and Health (NSDUH)
  - N = 24,348
- Daily and intermittent smokers reported a 3-fold increase in prior year opiate misuse compared to non-smokers
- Daily smokers were 5 times more likely to meet criteria for past-year opiate abuse/dependence than non-smokers
- Intermittent smokers were 3 times more likely to meet this criteria than non-smoker
- Tobacco Smoking, Nicotine Dependence, and Patterns of Prescription Opioid Misuse: Results from a Nationally Representative Sample Emily L. Zale, M.S., Michelle L. Dorfman, B.S., W. Michael Hooten, M.D., Nicotine and Tobacco Research

Substance Use Disorder = Addiction

- Tolerance: the need for an increased amount of drug to obtain the same effect either psychologically or physiologically
- Physical Dependence: the continued need of a substance to avoid withdrawal
- Withdrawal: the physical symptoms incurred by the patient after sudden cessation of a drug

Co-morbid pain and opioid addiction: Long term effect of opioid maintenance on acute pain

Amy Wachtel-1, Gerritje Comeau

A B S T R A C T

Introduction: Medication-assisted treatment for opioid dependence alters the pain experience. This study will evaluate changes in pain sensitivity and tolerance with opioid treatment and duration of this effect after treatment cessation.

Methods: 120 individuals with chronic pain were recruited in 4 groups (N=30): 1) medication for opioid addiction; 2) buprenorphine for opioid addiction; 3) history of opioid maintenance treatment for opioid addiction but with prolonged abstinence (N=121 weeks); and 4) opioid-naïve controls. Participants completed psychological assessment and a cold water test including, time to first pain (sensitivity) and time to stopping the pain task (tolerance). Analyses were performed on study data recorded at admission. Repeated-measures ANOVA was used to compare pain sensitivity and tolerance among the groups, with the duration of abstinence as the covariate.

Results: The prolonged abstinent patients had significantly increased pain sensitivity compared to the opioid naïve group (p < 0.05). Moreover, tolerance to pain among the prolonged abstinent group was significantly enhanced (p < 0.05), with the highest tolerance found among opioid-naive control group participants (p < 0.05). Correlations within the prolonged abstinent group indicated pain tolerance was significantly improved as length of opioid abstinence increased (|R = 0.27, p = 0.02|). Duration of abstinence did not alter sensitivity (p > 0.05).

Conclusion: Among individuals with a history of prolonged opioid maintenance, these appear to be long-term differences in pain sensitivity that do not resolve with discontinuation of opioid maintenance. Although pain sensitivity does not change, pain tolerance does improve after opioid maintenance cessation. Implications for creating co-morbid opioid addiction and pain (acute and chronic) are discussed.
Which of These Patients Opiate Tolerant?

- Occasional Tramadol use for OA for the past 6 months
- Former heroin user but clean for 10 years
- Six month history of oxycodone use but none in one year
- Recovering alcoholic; clean for the past 2 years
- Smoker who denies any opiate use

Opiate Review

Morphine Pharmacokinetics

Fentanyl Pharmacokinetics

Opiate Half-lives (IV)

Buprenorphine: Suboxone/Subutex

- Semi-synthetic
- Partial mu agonist and a full kappa antagonist
- Half-life 24-60 hours
- Analgesic effect is 4-8 hours (when dosed for pain control)
- Blocks opioid withdrawal for 24-48 hours
- Administered sublingually (SL) 2, 4, 8, 12 mg tablets (naloxone 0.5, 1, 2, 3 mg)
Buprenorphine Concerns:

- Ceiling effect on sedation/respiratory depression at high doses
- If injected the naloxone becomes active and immediately induces withdrawal

Methadone

- Synthetic opiate
- D binds only to the non-competitive NMDA receptor
- L binds to both mu opiate receptor and the non-competitive NMDA receptor
- Bioavailability 70-80%
- Peak plasma concentration 2.5-4 hours
- Dosed every 6 - 8 hours (analgesic effect)
- Metabolism: Liver & no active metabolites
- Elimination half-life 20-35 hours (4 - 10 days for steady state)
- Dolophine is a racemic mixture 1:1 of D & L

Methadone Concerns

- Prolonged QT Syndrome
- Phenytoin, Carbamazepine, St. John’s Wart = Increased blood levels
- Fluconazole, Fluoxetine, Paroxetine, Sertraline, Ciprofloxacin, Amitriptyline, Ketoconazole, Erythromycin, Citalopram, Desipramine, Clarithromycin = Decreased blood levels
- Conversion from other opiates to methadone is non-linear

Opiate Conversion To Morphine Equivalents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parental (mg)</th>
<th>Oral (mg)</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone*</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Demerol</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.01</td>
<td>NA</td>
</tr>
<tr>
<td>Methadone</td>
<td>1</td>
<td>#</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Buprenorphine#</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Morphine:Methadone Conversion (EDR)

<table>
<thead>
<tr>
<th>Morphine (mg/day)</th>
<th>&lt;100</th>
<th>100-300</th>
<th>301-800</th>
<th>801-1000</th>
<th>&gt;1001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine:Methadone</td>
<td>3:1</td>
<td>5:1</td>
<td>10:1</td>
<td>12:1</td>
<td>15:1</td>
</tr>
</tbody>
</table>


Post Op Pain Control with Methadone

*Intraoperative Methadone Improves Postoperative Pain Control in Patients Undergoing Complex Spine Surgery*

*Anty Gottschalk, MD* +*Maseo E. Gone, MD, PhD* +*Edward C. Herrington, MD*
Transdermal Fentanyl (TDF) conversion to Morphine Equivalents (MEQ)

- Fentanyl 25 ug/hr = 60 mg/day (range: 30 - 90)
- Fentanyl 50 ug/hr = 120 mg/day
- Fentanyl 75 ug/hr = 180 mg/day
- Fentanyl 100 ug/hr = 240 mg/day

Opiate Withdrawal

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Onset</th>
<th>Peak Intensity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapendine</td>
<td>2-6 h</td>
<td>6-12 h</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>6-16 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Morphine</td>
<td>24-48 h</td>
<td>3-21 days</td>
<td>6-7 weeks</td>
</tr>
</tbody>
</table>

Opiate Cross Tolerance

Incomplete cross tolerance and multiple mu opioid peptide receptors

Gavril W. Pasternak

Adjuvant Review

View Across the Bosporus Straight

Pharmacological Treatment Of Pain

- Ketorolac: 30 mg = 10 mg IV morphine
- Celecoxib: 400 mg p.o
- Dexamethasone: 0.1-0.2 mg/kg (4, 8, 12, 16)
- Acetaminophen (IV): 1000 mg
- Gabapentin: 1200 mg p.o
- Ketamine: 0.5 mg/kg IV
- Regional Anesthesia: peripheral nerve blocks, neuraxial blocks
Celecoxib

- Single dose oral celecoxib for acute postoperative pain in adults

Dexamethasone

- Postoperative Single Dose Systemic Dexamethasone for Postoperative Pain

Gabapentin/Pregabalin

- Analog of GABA which is an inhibitory neurotransmitter
- Block A2D subunit of voltage dependent Ca channels in the spinal dorsal horn
- Appears to prevent spinal cord “wind up” which is involved with chronic neuropathic pain
- Side effects: sedation and dizziness (may be dose dependent & time dependent)
- Use: Given both pre/post-operatively

Ketamine

- NMDA noncompetitive receptor antagonist
- Racemic formulation or (+)S (-)R
- Phencyclidine derivative (related to PCP)
- Induce general anesthesia
- Potent non-opioid with psychotomimetic activity

IV Acetaminophen Pharmacokinetics
Ketamine + Morphine PCA

Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials

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Background: Intraoperative and postoperative pain management is an integral part of postoperative care. The use of PCA (Patient Controlled Analgesia) has increased significantly over the past two decades, especially in the management of postoperative pain. The addition of ketamine to morphine PCA has been shown to improve pain relief and reduce morphine consumption. This qualitative review aimed to assess the evidence for the use of ketamine + morphine PCA in acute postoperative pain management.

Methods: We conducted a systematic search of the literature using PubMed, Embase, and Cochrane databases. Studies were analyzed for their methodology, results, and conclusions. The primary outcome measure was pain relief, and secondary outcomes included morphine consumption, patient satisfaction, and adverse effects.

Results: A total of 75 studies were identified, of which 17 were included in the qualitative analysis. The majority of studies showed improved pain relief with the addition of ketamine to morphine PCA. Morphine consumption was reduced in all studies, and patient satisfaction was generally high. Adverse effects were uncommon, with the most common being sedation and hallucinations.

Conclusion: The addition of ketamine to morphine PCA appears to be an effective and safe method of managing acute postoperative pain.

Meta-Analysis of Ketamine

A systematic review of intravenous ketamine for postoperative analgesia

Revue méthodique de l’utilisation de la kétamine intraveineuse pour l’analgesie postopératoire

Kevin Kuntowski, MD - Alina Stirling, MD - William P. McKay, MD - Hyun J. Lim, MD

Table 1: Comparison of Ketamine, Morphine, and Fentanyl

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Ketamine</th>
<th>Fentanyl</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>80.3</td>
<td>75.6</td>
<td>65.8</td>
</tr>
<tr>
<td>Sedation</td>
<td>60.1</td>
<td>70.3</td>
<td>85.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>70.9</td>
<td>80.5</td>
<td>90.1</td>
</tr>
</tbody>
</table>

Intrinsic Pain Sensitivity vs Pain Tolerance

Humans pain response in a tonic pain model: psychological determinants

Andrew C. Clark, James H. Fontaine, Jennifer E. Brown, and John Hobfoll

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The goal of this research was to investigate the relationships between pain sensitivity and pain tolerance in a tonic pain model. We conducted a series of experiments using a tonic pain model that produced prolonged pain responses. The results suggest that pain sensitivity and pain tolerance are distinct constructs and that they are influenced by different psychological factors.

Dichotomy of Pain Response in Normal Subjects

Fig. 1: Dichotomy of pain response in normal subjects, comparing pain at rest and dynamic

PCEA vs. IV PCA vs. CPNB

Effectiveness and safety of postoperative pain management: a survey of 18,925 consecutive patients between 1998 and 2006 (2nd revision); a database analysis of prospectively raised data

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The aim of this study was to evaluate the effectiveness and safety of postoperative pain management using patient-controlled anesthesia (PCA). We analyzed data from 18,925 consecutive patients who underwent major surgery at a university hospital in Germany. The results showed that patient-controlled analgesia (PCA) is a safe and effective method of pain management in the postoperative period.

Comparison PCEA, IV PCA, CNPB at Rest and Dynamic

Fig. 2: Comparison between PCEA, IV PCA, and CPNB during the two postoperative days. The figure shows the median (51st), 25th, 25th percentiles, and the other scores for each individual subject. P<0.001 using the Friedman test with Bonferroni post hoc test.
Comparison PCEA & IV_PCA in Thoracotomy, Major Abdominal Surgery, and Major Extremity Surgery

- PCEA (Patient Controlled Epidural Anesthesia)
  - Epidural Hematoma (2-3/10,000)
  - Epidural Abscess (3/10,000)
- PNB (Continuous vs. Single shot)
  - Peripheral Nerve Injury (21/10,000 vs 3-6/10,000)
- Spinal Opiates (Morphine)
  - Hematoma/Infection & Respiratory Depression
- IV PCA (Morphine, Hydromorphone, Fentanyl)
  - Multimodal

How do you rate Pain?
Is this patient in Pain?
Do you believe your patient’s reported pain level?

Less than 50% of nurses know that a patient’s self report of pain is the single most reliable indicator of pain.


Assess Pain

- Do you hurt? Do you have any pain? Are you having any pain?
- How much pain do you have?
- Where is your pain?

Consequences of Chronic Opiate Therapy/Use

- Psychological Dependence
  - Delta FosB
- Opiate induced Hyperalgesia
  - NMDA activation
- Opiate tolerance/withdrawal
  - NMDA activation
- Altered pain sensitivity
Mechanisms of Transcriptional and Epigenetic Regulation by Drugs of Abuse

Cellular Basis of Memory for Morphine Addiction

Morphine Action in Locus Coeruleus

Genetics of Opiate Addiction

- 3 opioid receptors (mu, delta & kappa)
- Delta opioid receptor (OPRD1 Chromosome 1)
- Galanin (GAL, Chromosome 11)
- P glycoprotein (ABCB1, Chromosome 7)
- Mu opioid receptor (OPRM1, Chromosome 6)
- Heritability of opioid abuse/addiction is 43 - 60%


Case #1: In-Patient Orthopedics

- 54 y/o male s/p Total Hip Arthroplasty (THA)
- History: Obesity, suspected OSA, DM 2 x 10 years, hydrocodone (8/day for 2 years). Switched to Fentanyl patch 25 ug/hr. Patch still in place.
- 40 mg/day/oral Hydrocodone = 40 mg/day/oral morphine
- 25 ug/hr Fentanyl = 60 mg/day oral morphine
- Anesthesia: Combined GA/Spinal 0.75% Hyperbaric bupivacaine 1.4 cc (10.5 mg) with Duramorph 0.2 mg
- Pt initially 0/10 pain due to spinal effect but the pain begins to escalate as spinal resolves.
- WHAT IS HIS ANTICIPATED PACU COURSE IN THE NEXT HOUR?
  - PAIN PAIN PAIN PAIN PAIN
How Do We Understand the Situation?

- Pt had potentially painful surgery but it is one of the only surgeries where we remove baseline pain
- Pt has opiate tolerance, however, his patch is in place so his baseline meds are already in place.
- Pt has chronic pain and will have altered pain sensitivity and pain tolerance
- His spinal morphine will have no effect because of his opiate tolerance except that it confuses situation with respect to respiratory sedation risk

Case #1: In-Patient Orthopedics

- By one hour post-op Pt c/o 6-7/10 pain. Response?
- Initial pain control with Fentanyl and then supplement with longer acting agents?
- Do you take the Fentanyl patch off?
- What is the role of Duramorph in this setting?
- Add multi-modal therapy: IV acetaminophen, NSAIDs
- Rescue block option? None available.
- Ketamine/Midazolam rescue option.

Case #2: Out-Patient Gynecology

- 19 y/o F s/p Laparoscopic Ovarian Cystectomy lasting 55 minutes
- History: Oxycontin/Heroin abuse. Clean for 11 months. Smoker
- Anesthetic: GA/ETT, Fentanyl 100 ug, Decadron 8 mg, Toradol 30 mg.
- PACU: Crying, inconsolable, pain 12/10
  - Switch patients, ask for a break, shoot the anesthesiologist?

How Do We Understand the Situation?

- She has had a mildly painful surgery which can have both sharp and cramp-like pain or somatic and visceral pain.
- Although we cannot quantify her prior drug use, we can assume significant opiate tolerance altered pain sensitivity. Also there is always a possibility that she has started using opiates again.
- Her intra-op Fentanyl dose is grossly inadequate for this patient.

What Are We Going To Do?

- Who wants to give Versed? Morphine? Dilaudid? Fentanyl?
- Fentanyl! What dose? How frequently?
- Is there a role for a Benzodiazepine? Haldol? Ketamine?
- Should we reframe the question, can/should we expect to discharge her home?

Schematic of Rapid Loading Dose Pharmacokinetics
Case #3: Out-Patient Orthopedics
• 68 y/o female s/p RCR, DCE, SAD, and Biceps Tenodesis
• History: smoker, occasional Xanax, and Tramadol
• Anesthetic: GA with Suprascapular block, local anesthetic by surgeon, 200 ug fentanyl, Toradol 30 mg, Decadron 8 mg
• PACU: Patient c/o 7-8/10 pain but is smiling and talking easily. HR/BP are elevated.
  • She can't be hurting that bad, right?

How Do We Understand This Situation?
• She had a painful out-patient orthopedic surgery. Many anesthesiologists would have performed a definitive block for pain control.
• She may have more tolerance to opiates and benzodiazepines than we might anticipate.
• She may appear comfortable but avoid ignoring the best assessment tool for measuring pain level.

Case #3: How Do We Respond?
• Recognize this patient is both opiate & benzodiazepine tolerant with cross-tolerance.
• Reset your expectation about length of PACU stay, quantity/type of opiates to be used, and potential for admission.
• First response: Get her pain under control which means fast acting IV drugs. Fentanyl 100 ug - 250 ug IV.
• Next: Quantify preoperative opiate use.
• Begin dosing long acting opiates (morphine/hydromorphone) simultaneously with short acting opiates.
• Reassure patient and reset expectation of appropriate level of pain that is tolerable.

Case #3: Out-Patient Orthopedics
• What do we give?
  • Fentanyl
  • Morphine/Hydromorphone
  • IV acetaminophen, Ketamine, Midazolam
  • Rescue nerve block (Supraclavicular, Interscalene)
• What do we ask/say?
  • Where are you hurting?
  • What is your baseline and what is the pain level now?
  • What type of pain is it?
  • Reassure patient

Case #4: In-Patient Nephrology
• 76 y/o Male s/p right open nephrectomy (failed robotic) lasting 6 hours
• History: Obese, OSA, metabolic syndrome, chronic back pain.
• Meds: Oxycodone 10 mg (10 -14/day), Gabapentin, Despiramine, (Didn’t take any meds today)
  • 100 - 140 mg/day X 1.5 = 150 - 210 mg/Morphine/day
  • 210 mg/dayloral = 70 mg/day/IV Morphine
• Anesthesia: GA, fentanyl 250 ug, Toradol 30 mg, Ketamine 25 mg, Dilaudid 2 mg given in last 1 hour.
  • 2 mg Dilaudid = 2 X 6.67 = 13.3 mg IV Morphine
  • How do we get out of this situation?

Case #4: Two Different Clinical Courses
• OSA dominates
  • Pt cycles between arousable/complaining of pain and unarousable/desaturating.
  • What if patient were described as not arousable to voice and barely responsive to painful stimulation?
• Chronic Pain/Opiate Tolerance dominantes
  • Pt complains of 10/10 pain
Treatment of Opiate Induced Excessive Sedation

- Time
- Naloxone
  - Intermittent bolus: start with 10-40 ug every 2 mins
  - Infusion: rarely used
    - used for Methadone situations
    - high risk patient e.g. OSA & Metabolic Syndrome

Salient Points

- Opiate use/addiction is prevalent throughout society
- Take an opiate history from each patient
- Make some attempt to quantify how much opiate a patient has received on day of surgery
- Opiate use/tolerance requires opiate treatment
- Reframe your expectations for PACU stay
- Adjuvants can help