Acute Pain Management in Patients with Substance Use Disorder

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Conflict of Interest Disclosure

• Conflicts of interest for contributors:
  • Kathleen Broglio has no conflicts related to this presentation
  • Maureen F Cooney has no conflicts related to this presentation

A conflict of interest is a particular financial or non-financial circumstance that might compromise, or appear to compromise, professional judgment. Anything that fits this should be included. Examples are owning stock in a company whose product is being evaluated, being a consultant or employee of a company whose product is being evaluated, etc.


Objectives

• Discuss the current challenges related to substance use disorder that impact pain management
• Discuss the effects of substances that may impact the individual in the acute care setting
• Describe opioid tolerance and its impact on pain management in the acute pain setting
• Identify strategies to provide effective acute pain management for the patient with substance use disorder
Where are we now?

Clarifying Terminology

- Substance use disorder (SUD) - use of alcohol or another substances for non-medical reasons - result in impairment in daily life or noticeable distress
- Addiction - neurobiological disease - compulsive craving and use despite the risk for harm
- Physical dependence - altered physiologic state caused by repeated administration of a drug that necessitates the continued administration of the drug to prevent the appearance of withdrawal or abstinence syndromes characteristic for that drug, DOES NOT necessarily constitute addiction
- Tolerance - state in which, after repeated administration of a drug, a given dose produces a decreased effect or a decreased side effect or in which increasingly larger doses are needed to obtain the same effect as that of the original dose


In 2014......

- In 2014, 27 million (one in ten Americans) ages 12 or older used an illicit drug in the past month.
- Marijuana the most commonly used drug – 22.2 million
- Non-medical use of pain relievers (opioids) second most commonly used class of drugs – 4.3 million

2014 – Illicit drug use past month 12 years and older

In 2014, 21.5 million people aged 12 or older had a substance use disorder (SUD) in past year:
- 17.0 million people alcohol use disorder
- 7.1 million with an illicit drug use disorder
- 2.6 million alcohol use and illicit drug use disorder

SUD in people 12 or older: 2014
Effects of opioid availability.....

- Increase in morbidity and mortality from prescription opioids associated with increased availability\(^1\)
- Abuse of prescription opioids plateaued in 2012
  - Percentage in 2013-2014 (1.6%) lower than percentage from 2002-2012\(^2\)
  - Changes in prescribing and availability

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Opioid Prescriptions Dispensed in US

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Opioid Overdose Deaths

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National Opioid Overdose Deaths—Number of Deaths from Prescription Opioid Pain Relievers. The figure above is a bar chart showing the total number of U.S. overdose deaths involving opioid pain relievers from 2001 to 2014. The chart is overlaid by a line graph showing the number of deaths by females and males. From 2001 to 2014 there was a 3.4-fold increase in the total number of deaths.
Heroin- Emerging Concern

• Non medical use of prescription opioids risk factor for heroin use
• 145% increase in heroin use from 2007-2014
• Heroin overdose mortality
  – 2000: 1,842 to 2014: 10,574
• BUT – No clear association of efforts to curb prescription drug abuse and increased heroin use
  – Increase started before changes in opioid policies

Heroin Overdose Deaths

Heroin Overdose Deaths

Synthetic Fentanyl Overdoses...

- Emerging problem
- Number of overdose deaths from synthetic opioids (fentanyl) increasing
  - Deaths increased by 79% from 3105 in 2013 to 5544 in 2014
  - Eight high burden states (MA, ME, NH, OH, FL, KY, MD, NC)
Synthetic Fentanyl Overdose Deaths

Benzodiazepine use

- In 2011 > 100,000 Emergency room visits related to benzodiazepines and opioids in combination compared to about 32,000 in 2004
  - Percentage of overdose deaths opioids with benzodiazepines increased from 0.6/100,000 in 2004 to 1.7/100,000 in 2011


Benzodiazepine Overdose deaths

*Note: Overdose Deaths—Number of Deaths from Benzodiazepines. The figure above is a bar chart showing the total number of U.S. overdose deaths involving benzodiazepines from 2011 to 2015. The chart is overlaid by a line graph showing the number of deaths by females and males. From 2011 to 2015 there was a steady increase in the total number of deaths.*
Other Challenges...

- Continued use of amphetamines, cocaine, hallucinogens, barbiturates, and date rape drugs
- Evolution of newer synthetic medications which have unpredictable effects

Cocaine Overdose Deaths

CONCERNS RELATED TO SPECIFIC SUBSTANCES....
Alcohol Use
- Increased risk for aspiration due to impaired airway reflexes and decreased gastric motility
- Withdrawal from alcohol starts 6 to 24 hours after the last drink
  - Minor alcohol withdrawal syndrome characterized by tremulousness, insomnia, and irritability.
  - Autonomic nervous system imbalance can cause tachycardia, hypertension, and cardiac dysrhythmias.
- Severe withdrawal syndrome characterized by restlessness, disorientation, tremulousness, and hallucinations.
  - Diaphoresis, hyperpyrexia, tachycardia, and hypertension are seen due to activation of sympathetic nervous system.
- Seizures occur about 24 hours after the last drink.
- Delirium can occur between 24 to 38 hours after the last drink.

CNS Sedative Hypnotics
- Intermittent benzodiazepine use may precipitate withdrawal effects.
- Long term benzodiazepine treatment increases the risk of life-threatening acute withdrawal seizures, precipitated 24 to 48 hours after discontinuation.

CNS SYMPATHOMIMETICS
- Effects of stimulant use are dependent on agent/dose.
- Inhibit the reuptake of the catecholamines - norepinephrine and dopamine.
- Anesthetic implications related to the potential for cardiovascular complications due to the potential for arrhythmias, hypertension, and myocardial ischemia.
HALLUCINOGENS

- Many chemically diverse hallucinogens exist
- Dimethyltryptamine (DMT) can produce increases in blood pressure and heart rate. The effects of mescaline are not known. Salvia divinorum generally does not increase blood pressure or heart rate. Methylenedioxymethamphetamine (MDMA or Ecstasy) can increase blood pressure and the heart rate
- No significant drug-drug interactions between hallucinogens and medications commonly used in the perioperative setting

DISASSOCIATIVE AGENTS

- Phencyclidine (PCP), ketamine, and dextromethorphan most commonly abused dissociatives produce similar effects as hallucinogens
- PCP ingested in large doses can cause life-threatening physiologic effects such as cardiac failure, stroke, rhabdomyolysis, renal failure, coma
- Monitor patient for sympathetic activation: increased pulse, elevated blood pressure, or hyperthermia

Inhalants

- Inhalants abused for a long period of time
- Anesthetics first used as intoxicants over 200 years ago
- Use of inhalants mostly seen in teenage population
  - In 2013 > 500,000 people over age of 12 used inhalants for the first time
- Evaluate for possible use of these substances when there are signs of possible use such as ear and nose irritation, facial rashes, unexplained cough, or abnormalities in hepatic or renal laboratory tests
CANNABINOIDS

- More potential uses for cannabis have been discovered with discovery of endogenous cannabinoid receptors
- As of 2015, marijuana was legal in 22 states for ‘medicinal use’.
- Concern is the emergence of K2, K3, Spice and Dream – synthetic cannabinoid products (SCP) - UNPREDICTABLE EFFECTS
  - If suspects use synthetic cannabinoid products, monitor for tachycardia, hypokalemia, and renal changes.

Opioids - Heroin

- Chronic opioid or heroin use – risk for withdrawal symptoms
- May require higher doses of opioid analgesics both to control the pain and to prevent withdrawal
  - Patients on medication assisted therapy

CURRENT CHALLENGES IN PAIN MANAGEMENT RELATED TO SUBSTANCE USE DISORDER
In the perioperative setting

- One in five patients has an alcohol use disorder, one in three patients has a nicotine use disorder, and one in 10 patients has a drug use disorder


Effects on Perioperative Outcomes

- Data from the Nationwide Inpatient Sample (2002-2011)
  - n= 15,903 of 9,307,348 patients identified with opioid abuse or dependence
- Data from National Hospital Discharge Survey (1990-2007)
  - n = 13,163 of 8,366,327 patients with a diagnosis of drug misuse
- Determine associations between opioid dependence/abuse and inpatient morbidity, mortality and resource utilization in major elective orthopedic surgery
- Results from both
  - increased patient mortality, postoperative complications, and increased lengths of stay
  - higher risks and increased resource utilization in these populations


So the bottom line is....

- Clinicians must be vigilant to the possibilities that patients for may be under the influence of/or withdrawing from substances
- Multimodal pain management will be cornerstone of effective analgesia.....
DSM-V Diagnostic Criteria for Cannabis Withdrawal

A. Abstinence or reduction in use that has been ongoing and protracted, i.e., usually daily or almost daily use over a period of at least a few months.

B. Three (or more) of the following signs or symptoms develop within approximately 1 week after Criteria A:
1. Irritability, anger, or aggression
2. Nervousness or anxiety
3. Sleep difficulty (e.g., insomnia, disturbing dreams)
4. Disturbed appetite or weight loss
5. Restlessness
6. Depressed mood
7. At least one of the following physical symptoms causing significant distress or impairment in social, occupational, or other important areas of functioning: abdominal pain, diarrhea, vomiting, steer, chills, or headache

C. The signs or symptoms in Criterion B occur clinically significant decrease in or impairment in social, occupational, or other important areas of functioning.

The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including nicotine or withdrawal from another substance.

Treatment of Cannabis Withdrawal

- Gabapentin
- THC
- Alpha 2 agonist
- N-acetylcystine (glutamatergic modulator)
- SNRIs
- Anxiolytics
- Mood stabilizers

From: Kuehn BM. Scientists Probe Ways to Curb Opioid Abuse Without Hindering Pain Treatment.
The Challenge

- The presence of acute pain seems to decrease the euphoric properties of opioids
- The presence of addictive disease seems to worsen the experience of acute pain

Ballantyne & Stannard. PAIN 2013 Dec;21:1-7

29yo male postop after completion of RLE BKA: PACU Pain Rating 10/10
- Intraop
  - Fentanyl 700 mcg
  - Hydromorphone 2 mg
- PACU
  - Morphine 16mg IV
  - Hydromorphone 6 mg IV
  - PCA hydromorphone: 0.4mg, 10 min
  - Versed 2 mg IVP

What we learned...
- On MMT 130 mg po daily
- active heroin use-1 bundle +/day
- Active benzodiazepine use: alprazolam 10-12mg/day
- Daily marijuana use
Challenges in Managing Acute Pain in Patients with Opioid Use Disorder

- Opioid tolerance
- Opioid induced hyperalgesia
- Anxiety, Other co-morbidities
- Withdrawal
- Unrealistic pain goals

Effects of Prolonged Opioid Therapy

Who is probably Opioid Tolerant?

- Those receiving 60 mg of oral morphine equivalents daily for at least 2 weeks (FDA)¹
  - Chronic Pain
  - Active opioid use disorder (OUD)
  - Former active opioid use disorder

¹ US Food and Drug Administration. 2009.
Types of Opioid Tolerance

• Acute tolerance – after single dose or a few doses over a short period of time.

• Chronic tolerance – drug administration over a longer period of time produces reduced drug effects.

Types of Opioid Tolerance

• Associative (learned) tolerance - Related to environmental and psychological factor

• Non-Associative (adaptive) tolerance- Occurs at the cellular level

Cellular Mechanisms of Tolerance

• Traditional theory: Tolerance caused by receptor desensitization and internalization.

• Evolving view: opioids may activate microglia which release brain derived neurotrophic factor (BDNF) which signals NMDA expression
**N-methyl-D-aspartate**

- receptors for endogenous excitatory amino acid transmitters
- NMDA receptor antagonists may prevent morphine tolerance


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**Opioid Induced Hyperalgesia**

- Abnormal sensitivity to pain
- May be associated with long term use of opioids
- Pro-nociceptive process
- Mechanism: glutaminergic system-NMDA activation
- Along with tolerance can lead to escalating doses of opioids


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**Opioid-tolerant vs. matched controls**

- Higher pain scores
- Use more post-op opioid analgesia (“greater than a mere replacement dose”)
- Fewer side effects (except sedation)
- Required more anxiolytics

“Opioid tolerant, pain intolerant” Peng et al. 1995

OUD and Acute Pain Management

- Thorough assessment to establish pain diagnosis, concurrent psych conditions, and SUD
- Recognition and Avoidance of Withdrawal Symptoms
- Symptomatic Treatment of Psych. Affective disorders (Anxiety)
- Involve pain specialist and addiction specialist

Opioid Withdrawal Symptoms

- dysphoric moods
- nausea or vomiting
- muscle aches
- lacrimation or rhinorrhea
- pupillary dilation, piloerection, or sweating
- diarrhea
- yawning
- fever
- insomnia


CLINICAL OPIOID WITHDRAWAL SCALE (COWS)

Wesson & Ling, J Psychoactive Drugs, 2000; 20: 203-209
Challenges in Clinical Practice
Acute Pain in Opioid Use Disorder

- Active Opioid Use
- Maintenance or Substitution Therapy:
  - Methadone Maintenance Treatment (MMT)
  - Buprenorphine
  - Naltrexone
- In recovery

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Active OUD and Acute Pain

“[T]he immediate perioperative period is not the optimal time to attempt detoxification or rehabilitation management for any patient abusing opioids.” Mitra & Sinatra, Anesthesiology, 2004

Think post-discharge consultation

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Active OUD and Acute Pain

- Multimodal Analgesia
- Will require opioid therapy
- Use of PCA to quantify requirements
- Scheduled, not prn opioids
- Clonidine/anxiolytics
- Close monitoring: Opioid related risks still exist!
Active OUD and Acute Pain

- Prudent use of short-acting opioids for initial acute pain
- Intravenous or epidural PCA for short-term analgesia to minimize triggering the CNS reward system
- Long-acting opioids for discharge, especially those with lower abuse potential (e.g., tamper-resistant or abuse-deterrent formulations).
- Co-management with addiction specialist

Oliver et al., Pain Management Nursing, 2012; 13(3), 169-83

Active OUD and Acute Pain

- Consider urine drug tests during inpatient hospitalization as needed to monitor for use of outside substances.
- Formulate with and educate patient regarding discharge plan.
- Ensure adherence monitoring for outpatient medications.
  - Appropriate weaning of opioids if necessary before discharge to prevent withdrawal.
  - Consider referral to emotional-expressive therapy.

Oliver et al., Pain Management Nursing, 2012; 13(3), 169-83

Opioid Agonist Therapy

Misconceptions:

- Maintenance opioid agonist confers analgesia
- Use of μ opioids to treat pain may cause addiction relapse
- μ opioids will cause respiratory depression
- Pain complaint may be manipulation to get more medications

Alford, Compton, & Samet, Annals of Internal Medicine, 2006, 144(2), 127-134
Pain Sensitivity and Tolerance

- Methadone or Buprenorphine maintenance, & active heroin use patients have increased pain sensitivity and lower tolerance for pain than opioid naïve.†
- History of prolonged abstinence have continued hyperalgesia, but pain tolerance slowly improves after cessation of maintenance treatment.†


Acute Pain and MMT

- Methadone analgesic effect only lasts 4-8 hrs
- Cross-tolerance to other mu agonists
- 80% oral bioavailability
- S-isomer: mu and delta mu agonist
- Reduces craving and euphoric effect of other opioids
- CYP450 metabolism; QT/QTc prolongation risk
- Half life 24hrs +

Sen et al., Curr Pain Headache Rep 2016, 20:16
Acute Pain and MMT

- Administer baseline dose after verification
- Use a MMA approach
- Oral to IV conversion: start with 2:1
- Short acting opioids at higher doses (1.5 x), shorter intervals
- Scheduled doses rather than prn

Postoperative

- Anticipate higher pain score, greater frequency, and greater opioid use than “usual” for this type of surgery
- Consider anxiolytics: Monitor closely
- Monitored bed may be required
- Patient comfort and safety cannot be overshadowed by a goal of rapid turnover
- Focus on function as well as pain score

Buprenorphine

- Partial mu agonist, partially activates the receptor; analgesia at lower doses
- Ceiling effect at higher doses (32mg/d); blocks full mu effect and prevents effect from other agonists
- Poor GI bioavailability, fair sublingual (P450 3A4)

Bryson, Current Opinion in Anesthesiology, 2014; 27(3), 256-264.
Buprenorphine

- Formulations for OUD treatment:
  - Sublingual tablet
  - Film (+/- naloxone)
  - 6 month implant

*Not to be confused with:*
- Weekly low dose patch for analgesia
- LA buccal film for analgesia

Elective Admission: various protocols

Protocol 1:
1. Some wean for weeks (↓by 2mg q 3days)
2. Stop 72hrs before surgery
3. If pain/intolerable withdrawal, use methadone 30mg qd

Protocol 2:
1. Continue daily buprenorphine
2. Treat pain with high affinity mu opioids at higher doses:
3. Divide buprenorphine into q 6 or q8h dosing

Buprenorphine

1. If pain resolves while hospitalized, allow mild withdrawal and reinitiate therapy
2. If expected to have pain upon discharge, coordinate plan with Buprenorphine prescriber
If Emergency Admission and Pain

• Hold Buprenorphine
• MMA approach, including regional analgesia
• PCA, expect higher doses than usual
• ICU/closely monitored setting
• Watch for decreased tolerance to opioids when buprenorphine clears (24-72h)

Bryson, Current Opinion in Anesthesiology, 2014; 27(3), 359-364

MMT vs Buprenorphine and Pregnancy

• Buprenorphine patients start treatment before or earlier in pregnancy than MMT
• Better retention with MMT
• Longer gestations with buprenorphine
• Larger infants with buprenorphine
• Less neonatal abstinence with buprenorphine

Sen et al., Curr Pain Headache Rep 2016; 20:16

Naltrexone

• μ opioid receptor antagonist for prevention of relapse to opioid dependence after detox
• New monthly IM depot injection vs. oral
• Blocks euphoric effect of opioids
• When trialed, in combo with psychosocial support, was found to reduce opioid craving and reduce relapse. Also reduces alcohol craving

Bryson, Current Opinion in Anesthesiology, 2014; 27(3), 359-364
Naltrexone

- Daily oral dose (50mg)
  - Half life 14h, D/C 72h preop
- IM depot (380mg)
  - Peaks in 2-3 days
  - Decline in 14 days; Duration
  - D/C 1 month preop

Bryson, Current Opinion in Anesthesiology, 2014; 27(3), 359-364

Naltrexone and Acute Pain

- If unplanned pain/surgery:
  - MMA, including regional anesthesia
  - If opioids needed, naltrexone blockade may be overcome with 10-20 times usual opioid dose
  - ICU setting for monitoring
- Increased opioid overdose risk if relapse after naltrexone discontinuation

Bryson, Current Opinion in Anesthesiology, 2014; 27(3), 359-364

APS 2016 Guidelines on the Management of Postoperative Pain Support the use of MMA

- Offer MMA, a variety of analgesic agents, techniques, and non-pharmacological interventions, for the treatment of postoperative pain in children and adults (strong recommendation, high-quality evidence)

Chou et al., The Journal of Pain, 2016;17(2), 131-157
Multimodal Agents

- Regional Anesthesia
- Opioids
- Local Anesthetics
- Acetaminophen
- NSAIDs, COX-2 Inhibitors
- Alpha 2-agonists
  - Clonidine
  - Dexmedetomidine
- Anticonvulsants
  - Gabapentin
  - Pregabalin
- NMDA receptor antagonists
  - Ketamine
- Adjuvants:
  - Skeletal muscle relaxants
  - SNRIs
  - TCAs

Stromer et al., Eur J Anaesthesiol 2013; 30-55-64

A Multimodal Approach Addresses the Complex Nature of Pain Transmission

Back to the case...

- Methadone increased to 160 mg/d and divided into q6h doses
- Peripheral nerve LA infusions
- APAP q6h
- Ketorolac q6h, then Celecoxib
- IV PCA hydromorphone 30-40mg/d
- Ketamine infusions postop
- Clonidine 0.2mg po q12h
- Clonazepam po 0.5mg q8h
- Gabapentin changed to Pregabalin 100mg q8h
- Duloxetine 30mg qd
- Music therapist TIW
- TENS at bedside

Stromer et al., Eur J Anaesthesiol 2013; 30-55-64
Acute Pain and Patient in Recovery

• Relapse is a major concern to both patient & caregivers
• Risk factors:
  – Drug exposure
  – Unrelieved pain
  – Anxiety
  – Interactions with professionals that negatively impact self-image
  – Lack of a support system that can adjust to increased need
• Emerging evidence that we need pay attention to this concern

Best practices

• Be open & forthright with patient
  – Provide reassurance to decrease anxiety
  – Enlist patient as active part of team
• Be aware of own biases and work to prevent them from interfering with care—process consultation helps
• For ambulatory or post-discharge planning, enlist clinical/community partners

Partnerships in Providing the Best Care Possible

Remember, complex situations require complex solutions that are best crafted by a team of experts in their field. You should never worry alone; seek out consultation for you and your patients
Questions???

APS 2016 Guidelines

- Provide acetaminophen and/or NSAIDs as part of a multimodal analgesia plan, unless contraindicated
  - Less pain, less opioid consumption
  - Combination of APAP/NSAIDs more effective than either agent alone
- Give a preoperative dose of celecoxib to adults without contraindications
  - 200-400mg 30-60 min preop


APS 2016 Guidelines

- Consider use of gabapentin or pregabalin as component of MMA
  - Preop: 600-1200mg gabapentin or 150-300mg pregabalin 1-2 hrs preoperatively
  - Postop: 600mg gabapentin as single dose or multiple doses and pregabalin 150mg or 300mg after 12 hrs

Clonidine and Dexmedetomidine

- Centrally and peripherally acting alpha₂ adrenergic agonists: modify catecholamines
- Useful in sympathetically mediated pain, persistent headaches, various neuropathic pains, intractable central pain (e.g. spinal cord injury) and some cancer pain syndromes

Clonidine and Dexmedetomidine: Alpha 2 agonists

- Blunt the signs of drug withdrawal: HTN, tachycardia, anxiety, agitation, and generalized pain)
- Analgesic
- Clonidine: intrathecal, epidural, transdermal, oral (start 0.1mg po daily-TID). Titrate
- Dexmedetomidine: 1mcg/kg; 0.2-0.7 mcg/kg/h
- SE: excessive sedation, hypotension, bradycardia, dry mouth. Use cautiously in older adults.

Ketamine

- NMDA antagonist, reduces opioid requirement
- Highly lipid soluble
- Airway, respiratory rate are preserved
- No hypotension
- Analgesia is double that of morphine
- IV administration
  - rapid onset -30 seconds
  - peak effect within one minute
  - short duration up to 60 minutes
  - half-life of 2-3 hours

Intravenous Lidocaine Infusions
Acute Postop and Neuropathic Pain

- Anti-inflammatory, analgesic, and anti-hyperalgesic
- NMDA antagonist, inhibits glutamate, blocks Na⁺ channels
- Particularly beneficial after abdominal surgeries
- Reductions in postop pain and opioid requirement; reduced ileus, LOS, and nausea/vomiting


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IV Lidocaine

- Open and lap abdominal surgery
  - Shorter duration of ileus
  - Suggested dosing
    - Intraop bolus 1.5mg/kg
    - Intraop infusion 2mg/kg/hr
    - Postop 1-1.5mg/kg/hr though use not well studied