Acute Pain Management: Patients using Buprenorphine or Methadone Maintenance Therapy

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Disclosure

- I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in the presentation.

Objectives

- Pharmacist objectives
  1. Explain the mechanistic differences between buprenorphine and methadone
  2. Describe recommendations for treating acute pain when a patient uses buprenorphine or methadone for chronic maintenance therapy
- Technician objectives
  1. Describe why acute pain management in patients using buprenorphine or methadone can be difficult for healthcare providers
  2. List the different opioid receptors within the body

Background

- FDA approval
  - methadone: 1947
  - buprenorphine: 1981 (Butrans, Subutex), 2002 (Suboxone)
- 'Uncomfortable' medications
  - Federal regulations
  - Unique pharmacokinetics/pharmacology
  - Limited clinical data
  - Limited experience

- methadone [package insert]. Columbus, OH. Roxane Laboratories, Inc; 2014.
- Suboxone [package insert]. Columbus, OH. Roxane Laboratories, Inc; 2015.
- Butrans [package insert]. Stanford, CT. Purdue Pharma LP; 2014.
- Subutex [package insert]. Richmond, VA. Reckitt Benckiser Pharmaceuticals; 2011.

Indications

buprenorphine

- Suboxone (buprenorphine/naloxone)
  - Maintenance treatment of opioid dependence
- Butrans, Subutex (buprenorphine)
  - Management of pain severe enough to require around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate

methadone

- Dolophine (methadone)
  - Maintenance treatment of opioid addiction, in conjunction with appropriate social and medical services
  - Detoxification treatment of opioid addiction
  - Management of pain severe enough to require around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate

- methadone [package insert]. Columbus, OH. Roxane Laboratories, Inc; 2014.
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Mechanism of Action

buprenorphine

Receptor	Action
μ (Mu)	**Partial agonist**
δ (Delta)	Agonist
κ (Kappa)	Antagonist
ORL-1	Partial agonist

methadone

Receptor	Action
μ (Mu)	**Agonist**
δ (Delta)	Agonist
NMDA	Antagonist

- μ-receptor primarily responsible for analgesia

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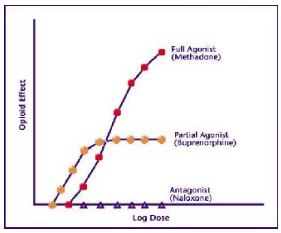
Pharmacology

- Partial Agonist
  - Possess properties of both full agonists and antagonists
  - Fully bind receptors and activate, but to lesser extent
  - Increasing effects reach maximum levels and will not increase further



o Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists. *The National Alliance of Advocates for Buprenorphine Treatment*.

o Thorough Technical Explanation of Buprenorphine. *The National Alliance of Advocates for Buprenorphine Treatment*. Available at: https://www.naabt.org/education/technical_explanation_buprenorphine.cfm.

Four Common Misconceptions

1. The maintenance opioid agonist (buprenorphine or methadone) provides adequate analgesia.
2. Use of opioids for analgesia may result in addiction relapse.
3. The additive effects of opioid analgesics in addition to opioid agonist maintenance therapy may cause respiratory and CNS depression.
4. The pain complaint may be a manipulation to obtain opioid medications, or drug-seeking, because of opioid addiction.

o Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Ann Intern Med*. 2006;144(2):127-34.

Four Common Misconceptions

1. The maintenance opioid agonist (buprenorphine or methadone) provides adequate analgesia.
   - Duration of analgesia: 4 – 8 hours
   - Suppression of opioid withdrawal: 24 – 48 hours
   - Usually dosed once daily for opioid addiction maintenance therapy
   - Tolerance can develop with chronic use
   - Cross-tolerance to other opioids
   - Hyperalgesia (increased sensitivity to painful stimuli)

o Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Ann Intern Med*. 2006;144(2):127-34.

Four Common Misconceptions

2. Use of opioids for analgesia may result in addiction relapse.
   - Lack of clinical evidence
     - Kantor TG, et al. No difference in relapse indicators between patients in MMT programs and matched controls
   - Relapse prevention theories suggest stress associated with inadequate pain management is more likely to lead to relapse.
     - Karasz A, et al. Pain played a substantial role in initiating and continuing drug use

- Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Ann Intern Med*. 2006;144(2):127-34.
- Kantor TG, Cantor R, Tom E. A study of hospitalized surgical patients on methadone maintenance. *Drug Alcohol Depend*. 1980;6:163–73.
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Four Common Misconceptions

3. The additive effects of opioid analgesics in addition to opioid agonist maintenance therapy may cause respiratory and CNS depression.
   - Theoretical risk which is unproven clinically.
   - Rapid and reliable tolerance develops for CNS and respiratory depression.

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Four Common Misconceptions

4. The pain complaint may be a manipulation to obtain opioid medications, or drug-seeking, because of opioid addiction.
   - Acute pain reports with objective findings are *less likely* drug-seeking
   - Caveat: patients may inflict self-harm to increase likelihood of obtaining medications

- Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Ann Intern Med*. 2006;144(2):127-34.

Opioid Alternatives

- New evidence!! (November 2017)
  - Single dose opioid vs non-opioid for acute extremity pain in the emergency department
  - 411 patients analyzed
  - Baseline mean NRS pain scores decreased, 2 hours post-dose
  - No statistically significant difference between analgesic medications
- Utilize non-opioids as adjunctive therapy
  - Tricyclic antidepressants
  - acetaminophen
  - NSAIDS

- Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Ann Intern Med*. 2006;144(2):127-34.
- Chang AK, Bijur PE, Esses D, et al. Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA*. 2017;318(17):1661-7. doi: 10.1001/jama.2017.16190.

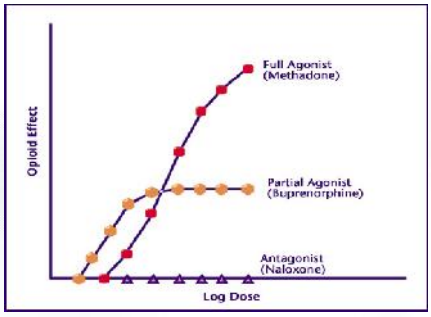
buprenorphine

General Considerations - buprenorphine

- High affinity to μ-receptor
- "Ceiling effect"
- 72-hour blockade
- Lower risk of QTc prolongation versus methadone

- Harrington CI, Zaydfudim V. Buprenorphine Maintenance Therapy Hinders Acute Pain Management in Trauma. *The American Surgeon*. 2010;76(4):397-9.
- Wedam EF, Bigelow GE, Johnson RE, et al. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med*. 2007;167(22):2469-75.
- Suboxone [package insert]. Columbus, OH. Roxane Laboratories, Inc; 2015.

"Ceiling Effect"



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Patient Case - buprenorphine

- 30 yo M
- PMH: *opiate abuse*
- CC: *motorcycle accident with 5 to 7 fractured ribs, right olecranon fracture, grade IV hepatic laceration, grade III splenic laceration*
- Hospitalization:
  - Patient agitated and experiencing acute pain
  - buprenorphine/naloxone use of 2 mg/0.5 mg daily

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Recommendations - buprenorphine (4 Options)

- Continue buprenorphine maintenance therapy and titrate a short-acting opioid analgesic to effect
- Discontinue buprenorphine therapy and treat the patient with full scheduled opioid agonist analgesic by titrating to effect
  - With resolution of the acute pain, discontinue the full opioid agonist analgesic and resume maintenance therapy with buprenorphine using an induction protocol (*buppractice* – Standard Induction Protocol)

- https://www.buppractice.com/node/12106
- Macintyre PE, Russell RA, Usher KAN, et al. Pain Relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesthesia Intensive Care*. 2013;41(2):222-30.
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Recommendations - buprenorphine (4 Options)

- Divide the daily dose of buprenorphine and administer every 6 to 8 hours to take advantage of its analgesic properties
- If the patient is hospitalized with acute pain, may convert buprenorphine to methadone at 30 to 40 mg/day
  - If opioid withdrawal persists, subsequent daily methadone doses can be increased in 5- to 10-mg increments
  - Must convert back to buprenorphine upon discharge

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Patient Case - buprenorphine

- Hospitalization
  - Buprenorphine discontinued with subsequent marked reduction in narcotic demands
  - Patient mental status and related agitation improved rapidly
  - Upon discharge, pain well-controlled with 120 mg oxycodone (sustained release) daily
  - Patient counseled on appropriate follow-up for pain management and for potential reevaluation for buprenorphine maintenance therapy

- Harrington CJ, Zaydfudim V. Buprenorphine Maintenance Therapy Hinders Acute Pain Management in Trauma. *The American Surgeon*. 2010;76(4):397-9.

methadone

General Considerations - methadone

- Duration of analgesia: 4 – 8 hours
- Half-life: 8 – 59 hours
- Maintenance methadone regimen ≠ analgesia
- Methadone accumulates with multiple doses
- Less affinity for μ-receptor versus buprenorphine
- QTc prolongation: > 45 mg

- Juba KM, Khadem TM, Hutchinson DJ, Brown JE. Methadone and Corrected QT Prolongation in Pain and Palliative Care Patients: A Case-Control Study. *Journal of Palliative Medicine*. 2017;20(7):722-8. doi: 10.1089/jpm.2016.0411.
- methadone [package insert]. Columbus, OH. Roxane Laboratories, Inc; 2014.

Patient Case - methadone

- 29 yo M
- PMH: *illicit drug abuse*
- CC: *motorcycle accident requiring below-the-knee amputation*
- Intra-Op
  - Medications: Fentanyl 700 mcg IV, hydromorphone 2 mg IV
- Post-Op
  - Pain 10/10
  - Medications (within 1-hour): hydromorphone 6 mg IV, hydromorphone PCA 0.4 mg IV with 10-minute lockout, midazolam 2 mg IV, morphine 16 mg IV
  - Reported using methadone 130 mg and alprazolam 10 mg daily

o Cooney MF, Broglio K. Acute Pain Management in Opioid-tolerant Individuals. *JNP*. 2017;13(6):394-9. doi: 10.1016/j.nurpra.2017.04.016.

Recommendations - methadone

Always

- Notify the methadone maintenance treatment program
- Verify current methadone dose and last administration
- Know the law

4 Options

- Continue methadone maintenance therapy and titrate a short-acting opioid analgesic to effect
- Divide the daily dose of methadone and administer every 6 to 8 hours to take advantage of its analgesic properties
- Slowly increase methadone dose as needed
- May use injectable methadone if unable to take orally

o Alford DP, Compton P, Samet JH. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Ann Intern Med.* 2006;144(2):127-34.

DEA "3-day rule"

- An exception to DEA registration rule for practitioners treating patients in maintenance and/or detoxification treatment programs
- Allows practitioner not registered with DEA to administer (but not prescribe) narcotic drugs to a patient for the purpose of relieving acute withdrawal symptoms
  - Not more than one day's medication may be administered or given to a patient at one time
  - This treatment may not be carried out for more than 72 hours
  - This 72-hour period cannot be renewed or extended

o Nagel, LM. Emergency Narcotic Addiction Treatment. *U.S. Department of Justice: Drug Enforcement Administration, Diversion Control Division.* April 3, 2001. Available at: https://www.deadiversion.usdoj.gov/pubs/advisories/emerg_treat.htm. Accessed January 22, 2017.

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Patient Case - methadone

- Methadone regimen altered to 40 mg every 6 hours after discussion with MMT program
- In-patient pain management regimen:
  - acetaminophen
  - ketorolac
  - pregabalin
  - ketamine
  - clonidine
  - hydromorphone PCA
  - clonazepam
  - Non-pharmacologic
- Discharge pain management regimen:
  - methadone 160 mg daily
  - celecoxib 200 mg PO q12h
  - pregabalin 150 mg PO q12h
  - hydromorphone 6 mg PO q4h prn

o Cooney MF, Broglio K. Acute Pain Management in Opioid-tolerant Individuals. *JNP*. 2017;13(6):394-9. doi: 10.1016/j.nurpra.2017.04.016.

Summary

- Acute pain management can be difficult to manage in patients using methadone or buprenorphine for maintenance therapy
- Patients will likely require higher and more frequent doses of narcotics to alleviate pain
- Common misconceptions can lead to inadequate acute pain management for patients using methadone or buprenorphine maintenance therapy
- The DEA “3-day rule” doesn’t apply when treating acute pain unrelated to withdrawal symptoms

Assessment Questions

Pharmacist 1):

For which opioid receptor is buprenorphine a partial agonist, and methadone a full agonist?

A. μ (Mu)
B. δ (Delta)
C. κ (Kappa)
D. NMDA

Assessment Questions

Pharmacist 2):

Which of the following is one option to treat acute pain when a patient uses buprenorphine?

A. Continue buprenorphine, give higher doses of additional short-acting opioids
B. Immediately stop buprenorphine, then initiate high doses of other opioids when withdrawal symptoms begin to present
C. If inpatient, convert buprenorphine to methadone 5 mg daily and titrate as needed
D. Continue buprenorphine once daily, but administer a one time loading dose to achieve analgesia

Assessment Questions

Technician 1):

Which of the following may be a reason buprenorphine and methadone can be difficult for healthcare providers?

A. Special federal regulations exist in regard to their use
B. Both medications have unique actions within the body compared to other opioid medications
C. Limited clinical data exists regarding their use compared to other pain medications
D. All of the above

Assessment Questions

Technician 2):

Which of the following is not an opioid receptor?

A. κ (Kappa)
B. α (Alpha)
C. μ (Mu)
D. δ (Delta)

References

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