NOW WHAT? MANAGING PAIN IN THE PRESENCE OF OPIOID AGONIST THERAPY

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LEARNING OBJECTIVES

- Describe clinical scenarios that may require opioid therapy concurrently with opioid agonist therapy.
- Describe management strategies for treating acute or chronic pain in conjunction with buprenorphine agonist therapy.
- Describe management strategies for treating acute or chronic pain in conjunction with methadone agonist therapy.

NOW WHAT? MY PATIENT'S ALREADY TAKING METHADONE!

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CASE 1

- GH is a 35 year old woman who is admitted to your hospital for elective surgery.
- She has a long history of heroin use but has been maintained on methadone 90 mg by mouth per day for several years now.
- She is TERRIFIED that the pain from this surgery, or the opioid therapy she will likely receive for the pain will cause her to relapse into her addiction. Thoughts?

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MISCONCEPTION #1

- The maintenance opioid agonist (methadone or buprenorphine) provides analgesia
  - Analgesic properties of maintenance opioids
    - Do not derive sustained analgesia
    - Duration of analgesic effect << dosing interval to suppress opioid withdrawal
  - Opioid Tolerance
  - Opioid-Induced hyperalgesia
    - Neuroplastic changes lead to an increase in pain sensitivity and reduced analgesic effects
    - Hyperalgesia counteracts the analgesic effects of opioids (?)

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Alford DP. Ann Int Med 2006;144:127-134.

MISCONCEPTION #2

- Use of opioids for analgesia may result in addiction relapse
  - There is no evidence that exposure to opioid analgesics in the presence of acute pain increases rate of relapse in such patients
    - Retrospective study of 74 OAT patients post-operatively
    - Small study of 6 OAT patients with cancer pain
  - The stress of unrelieved pain is more likely a trigger for relapse than adequate analgesia
    - Research has shown pain plays a substantial role in initiating and continuing drug use in OAT patients

But there is no data showing is DOESN'T lead to relapse, so extra caution is recommended (i.e., increased 12 step meetings, talking with sponsor, temporary reduction in take home doses, etc.).

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Alford DP. Ann Int Med 2006;144:127-134.

MISCONCEPTION #3

- The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression
  - Not clinically demonstrated
  - Tolerance to respiratory and CNS depressant effects of opioids occurs rapidly and reliably
    - Consider cancer patients with worsening pain; typically do not exhibit respiratory and CNS depressant effects when additional opioids are administered
  - This concern is not supported by clinical or empirical experience

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Alford DP.Ann Int Med 2006;144:127-134.

MISCONCEPTION #4

- Reporting pain may be a manipulation to obtain opioid medications, or drug-seeking, because of opioid addiction (don't play me!)
  - Pain is subjective, and assessment can be difficult
    - Try to assess pain objectively, and assess functional limitations. Consider disease process and likelihood of pain
  - Patients on OAT are often perceived by HCPs as "demanding" when experiencing pain
    - Likely due to patient distrust of the medical community
    - Drug-seeking vs. pain-relief seeking?

However, literature shows patients on methadone agonist therapy have an increased incidence of pain complaints.

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GOALS OF ACUTE PAIN MANAGEMENT IN OPIOID-TOLERANT PATIENTS

- Identify the higher-risk population – patients on long-term opioids for cancer or chronic non-cancer pain, drug abusers, recovering drug misusers on maintenance programs.
- Prevention of withdrawal symptoms and complications.
- Effective analgesic treatment in the acute pain phase.
- Involvement of multidisciplinary and/or specialist teams for treatment of psychological disorders if needed.
- Management of aberrant drug-taking behaviors, for example unapproved use of other drugs, hoarding of drugs, or altering drug prescriptions.
- Rehabilitation to suitable maintenance opioid therapy.

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Bourne N. Nursing Standard 2010:25:35-39.

GENERAL RECOMMENDATIONS ADDICTION TREATMENT ISSUES

- Reassure patient that addiction history will not prevent adequate pain management.
- Continue the usual dose (or equivalent) of OAT (for acute pain particularly).
- Methadone or buprenorphine maintenance doses should be verified by the patient's methadone maintenance clinic or prescribing physician.
- Notify the addiction treatment program or prescribing physician regarding the patient's admission and discharge from the hospital and confirm the time and amount of last maintenance opioid dose.
- Inform the addiction treatment maintenance program or prescribing physician of any medications, such as opioids and BZDs, given to the patient during hospitalization because they may show up on routine UDT.

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Alford DP. Ann Int Med 2006;144:127-134.

General Recommendations
Acute Pain Management Issues

- Relieve patient anxiety by discussing the plan for pain management in a nonjudgmental manner.
- Use conventional analgesics, including opioids, to aggressively treat the painful condition.
- Opioid cross-tolerance and patient's increased pain sensitivity will often necessitate higher opioid analgesic doses administered at shorter intervals.
- Write continuous scheduled dosing orders rather than as-needed orders.
  - PCA may be an option
- Avoid using mixed agonist-antagonist opioids because they may precipitate an acute withdrawal syndrome.

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Alford DP. Ann Int Med 2006;144:127-134.

General Recommendations
Methadone OAT Patients

- For acute pain management, there are two options:
  - Continue methadone maintenance dose
    - Oral
    - Parenteral (50-75% of oral total daily dose)
    - In divided doses
  - Use short-acting opioid analgesics

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Alford DP. Ann Int Med 2006;144:127-134.

BACK TO CASE 1

- GH is a 35 year old woman who is admitted to your hospital for elective surgery.
- She has a long history of heroin use but has been maintained on methadone 90 mg by mouth per day for several years now.
- Switch her to either:
  - Methadone 30 mg by mouth q8h or
  - Methadone 15 mg IV q8h

May need to adjust dose to account for acute pain

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WRITING FOR METHADONE?

- Any licensed prescriber may use methadone to treat acute opioid withdrawal syndrome under the "72 hour rule"
  - Methadone may be administered to a patient (but not dispensed or prescribed for unsupervised use) for up to three days.
  - Intent is to relieve suffering while appropriate transfer of care is being made
  - Applies only when opioid addiction is the primary clinical focus
- Methadone OAT patients admitted to the hospital
  - Hospitals/any prescriber can continue the methadone indefinitely while they are IN the hospital, but you cannot give them any methadone on their way out the door.
  - Only applies when patient is admitted to a medical or psychiatric reason other than drug addiction

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http://www.todayshospitalist.com/index.php?b=articles_read&cnt=776

WRITING FOR METHADONE?

- Don't believe patient's self-report of their methadone maintenance dose
  - Call the methadone clinic and verify dosing history – dose and date of last dose
  - If date of last dose is unclear, it's safe to give newly admitted patients only 30 mg of methadone as an initial dose on the first day
- If the patient has missed only one day of methadone OAT, give their regular dose
- If they have missed 3 days, give 50% of OAT dose and titrate back up
- If they have missed their methadone OAT for a week, start at 25% of the regular dose

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http://www.todayshospitalist.com/index.php?b=articles_read&cnt=776

General Recommendations
Methadone OAT Patients

- For chronic pain management (e.g., end of life) we do the following:
- If methadone is appropriate for the patient for pain control, we divide the total daily OAT dose into two or three, and now use for pain management, titrating appropriately.
- DOCUMENT carefully that this is for PAIN control.
- Let the clinic know the patient will NOT be returning to methadone clinic.
- Provide a different opioid for breakthrough pain.

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BUPRENORPHINE

- Developed in 1966 by Reckitt & Coleman in Hull, England
  - John Lewis, doctoral student under Sir Robert Robinson (identified the structure of morphine in 1925)
  - Pharmacologic profile disclosed in 1972 at College on Problems of Drug Dependency annual meeting
  - Developed as a 'safe, effective analgesic with very little physical dependence'
  - Marketed as an injectable in very low doses (ie Buprenex® 0.4mg/ml)

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BRIEF OVERVIEW – WHAT WE THOUGHT

- Buprenorphine is a semisynthetic partial μ agonist (and κ antagonist)
  - Initially used as analgesic; now 1° Maintenance Agonist Therapy (MAT)
  - Linear μ effect at lower doses
  - Morphine equivalency of ~40:1 over linear range
  - Improved safety profile due to "Ceiling Effect"
  - Available as sl mono/naloxone-combo tablet – for DATA 2000

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PHARMACOLOGY

- Derived from opium alkaloid thebain
- Terminal Elimination $t_{½}$~24-60 hours but:
  - Analgesic Duration of Action is ~6-8 hrs
  - MAT Duration of Action is ~24 – 48 hrs
- Poor oral bioavailability but well absorbed by sublingual / parenteral / transdermal route
- CYP 450 3A4 (lesser 2C8) metabolism through N-dealkylation (like methadone)

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PHARMACOLOGY

- Very high receptor affinity
  - Once attached, remains until the receptor is recycled
  - Less than complete receptor occupancy needed to effect MAT action
    - Will NOT prevent analgesic effects of other high potency opioids
  - Can precipitate withdrawal in full μ dependent users
    - But can always add full μ agonist to patient on buprenorphine without fear of inducing withdrawal

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BUPRENORPHINE REDUX

- The partial μ agonist role is under review*
  - Evidence *suggests* that the molecule may be a full agonist in the role of analgesic
    - While being a partial agonist in terms of respiratory depression
- Buprenorphine is thought to have antinociceptive effects through ORL-1 receptors°
  - ORL-1 *may* play a role in apparent ceiling effect of the drug
- Buprenorphine is complicated!

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*Pergolizzi et al, Pain Practice 2010 10(5):428-450
°Lutfy and Cowan, Curr Neuropharm 2004 2(4): 395-402

BUPRENORPHINE AVAILABLE FORMS

- Buprenorphine *was* available only as an injectable
- More recently, as sublingual and transdermal formulations
  - Buprenorphine 'mono-product' (Subutex®)
    - SL tablets of buprenorphine HCl
  - Buprenorphine 'combination-product' (Suboxone®)
    - SL tablets of buprenorphine HCl / Naloxone 4:1
  - Buprenorphine Transdermal System
    - 7 day matrix patch (Butrans® 5, 10, 20µ/hr)
    - 4 day matrix patch (Transtec® 35, 52.5, 70µ/hr)
  - Buprenorphine trans-buccal q12h dosing (Belbuca®)

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CONVERSION FROM HIGH-DOSE FULL-OPIOID AGONISTS TO SUBLINGUAL BUPRENORPHINE

- 2 papers outline the use of SL buprenorphine conversion in physically dependent pain patients – both were observational reports based on retrospective chart analysis
  - Jonathan Daitch et al Pain Physician 2012 15:ES59-66
  - Jonathan Daitch et al Pain Medicine 2014 15(12); 2087-2094

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CONVERSION OF CHRONIC PAIN PATIENTS CONT

- Results show a significant decrease in pain scores and in the second study, improvements in quality of life
  - Overall decrease of 51% in pain scores before/after conversion with no statistical difference between initial pain ratings of 0-7 vs 8-10
  - QoL improved from 6.1 before conversion to 7.1 (P=0.005)
    - As well, the greater QoL improvements were seen in those converting from the higher doses of opioids
  - Average dose of buprenorphine SL was 28.11±5.94mg
    - (far greater than typically seen in analgesia! – more commonly seen in maintenance agonist treatment)

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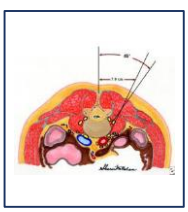
PATIENT 1

- 73 year old man with CKD III and severe peripheral vascular disease (PVD) presents with left leg pain (7/10) and early gangrene left lateral foot and toes.
- The surgeon assesses the extent of disease and finds no surgical option and offers amputation.
- The patient refuses.
- You are consulted for pain
- How will you manage his pain?

PATIENT 1 - PAIN AND PATHOPHYSIOLOGY

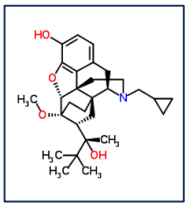
- Pain is caused by an distal axonopathy-neuropathic
- Secondary alterations in muscle and oxidative stress
- Pain is worse at night (limb is no longer in a dependent position)
- Wakens patients from sleep
- Risk of phantom pain syndrome s/p amputation

PATIENT 1



- Lumbar sympathectomy – Yes
- Spinal cord stimulation - inconclusive
- Lidocaine IV> morphine – problems with portability
- Ketamine 0.6mg/kg > placebo (NNT 5) - problems with portability and side effects

PATIENT 1



- Gabapentin- single arm, 15/17 responded (NRS 9/10 to 5/10 over 28 days)
- Buprenorphine added to epidural morphine/ local anesthetic in 2 RCT- improved pain > morphine alone, less morphine needed and better sleep

PATIENT 1

Palliation

- Gabapentin
- Buprenorphine +/- spinal analgesia
- Ketamine IV
- Lidocaine IV
- Lumbar sympathectomy

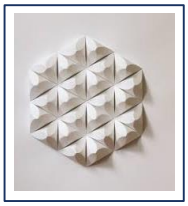
PATIENT 2

- A 35-year-old woman is on buprenorphine opioid substitution therapy (BOST) at 8 mg twice daily.
- She has a breast cancer and recently developed bone metastases to T6, the right acetabulum and critically at the left femur which requires repair.
- She is in moderate pain (NRS 5 /10).
- You are asked to see her for perioperative analgesic management.
- What would you do?

MYTHS

- Maintenance therapy with buprenorphine and or methadone provides analgesia
- Additional opioids for analgesia may cause addiction relapse
- Additional opioids may cause respiratory and CNS depression
- PCA opioid therapy is inadequate for postoperative analgesia in opioid tolerant individuals

FACTS



- Buprenorphine and methadone analgesia are shorter than its benefits for opioid withdrawal and craving
- Individuals who are opioid tolerant pre operatively will require on average 2-4 times higher postoperative short-acting potent opioids for analgesia
- There is a higher risk of developing opioid induced hyperalgesia in the perioperative.
- Opioid tolerant individuals will have a greater on pleasant nested pain from procedures

MYTHS

- There is no data that perioperative opioids increase the risk of addiction relapse and in fact uncontrolled pain is more likely to do so

FACTS

- Few guidelines and no large RCTs for guidance
- Inadequately controlled pain leads to pulmonary and cardiovascular complications and increased length of stay.
- Adequately controlled pain accelerated recovery and reduces chronic postoperative pain.
- Most anesthesiologists would maintain the perioperative chronic opioid maintenance therapy.
- There should be an emphasis on regional anesthesia in the post operative period.

FACTS

- Spinal local anesthetics may reduce opioid requirements in the perioperative period
- Judicial use of NSAIDS, gabapentinoids and ketamine may be modestly opioid sparing.
- PCA demand only potent opioids while continuing the BOST/ MOST but realizing that demand doses will need to be 2-4 times that of opioid naive patients
- Some would divide the buprenorphine or methadone dose in hopes of also providing analgesia

COUNTER ARGUMENT

- Some suggest switching to methadone from buprenorphine for painful procedures
- Buprenorphine has a high affinity for mu receptors and a long dwell time on the receptor surface.
- It is assumed that buprenorphine is a "partial agonist" and blocks potent opioid activation of the mu receptor and blunt analgesic responses
- Buprenorphine has a long half-life and so the rotation to methadone or wean off buprenorphine should occur pre-operatively

BOST AND PERIOPERATIVE POTENT OPIOID ANALGESIA

- D - Retrospective study
- P - Patients on BOST (n=51) provided PCA potent opioid therapy in the postoperative setting while maintained on BOST
- O - No difference in pains scores between BOST and MOST, no difference in morphine equivalents. Those individuals who had stopped BOST in the preoperative setting required more morphine in the perioperative period

CONCERNS ABOUT MOST/BOST

- There was greater sedation with maintenance therapy than in the opioid naïve and a concern for respiratory depression
- This concern is amplified if there is a rapid titration of potent opioids on top of maintenance therapy as a result of severe pain arising from a surgical complications

PATIENT 4

A 45-year-old with chronic low back pain, hepatitis-C and a history of opioid abuse is on buprenorphine – naloxone (Suboxone) for both pain in addiction maintenance. He was initially started on 2-0.5 mg twice daily and gradually titrated to 8-2 mg twice daily. His pain goes from a 6.5 (0-10 an RS) to 5.5 as an average pain intensity over 24 hours after 3 months of therapy. His urine is checked and tests positive for hydromorphone.

- Options in management

1. Switched to methadone and titrate him to 30-60 mg daily
2. switch to buprenorphine (Subutex)
3. Discontinue opioid therapy and use non –opioid analgesics

PATIENT 4

A 75-year-old with a past history of lung cancer resected by thoracotomy develops an empyema and undergoes a Clagett window procedure. He has been on buprenorphine maintenance therapy with Suboxone 16-4mg bid for 10 years. He is maintained on buprenorphine during his procedure but his pain is poorly controlled despite receiving IV hydromorphone 70 mg over 24 hours.

- Options in his management

1. Taper the Suboxone and continue the hydromorphone as needed

2. Switch to Subutex at 16mg twice daily and continue the hydromorphone as needed

3. switch to methadone 30 mg twice daily and continue the hydromorphone as needed

SUBOXONE

- There is a slightly greater buprenorphine bioavailability with generic Suboxone than Subutex
- Naloxone does not alter the bioavailability of buprenorphine

Strain E 2004
Weinhold L 1989

SUBOXONE

- There are differences between subjective responses of Suboxone and Subutex and pharmacokinetics of buprenorphine between preparations
- 50% of patients experience side effects when switched from Subutex to Suboxone
- 80% of those opioid tolerant have a bad experience when switched from Subutex to Suboxone

Simojoki K 2008

SUBOXONE

- Both naloxone and buprenorphine compete for the same conjugase (UGT-2B7)
- Buprenorphine causes a substrate inhibition of UGT-2B7
- Buprenorphine concentrations of 0.3nM prevent naloxone metabolism
- Naloxone clearance is delayed or becomes bioavailable which blocks less mu avid potent opioids from producing analgesia
- The "ceiling" analgesia or adverse effects of Suboxone may be related to altered naloxone metabolism and greater bioavailability caused by substrate competition which would be more evidence at higher doses.

Coffman B 1997