Pain Management in Patients on Buprenorphine Maintenance

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CARE
Clinical Addiction Research and Education

BOSTON MEDICAL CENTER
BOSTON UNIVERSITY SCHOOL OF MEDICINE
GENERAL INTERNAL MEDICINE

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Disclosures

- I have nothing to disclose with regards to commercial support.

- I will discuss the unlabeled use of sublingual buprenorphine for the treatment of pain.

Outline

- Pain and addiction
- Cases
- Buprenorphine as an analgesic
- Acute pain management
- Chronic pain management

Pain and Addiction

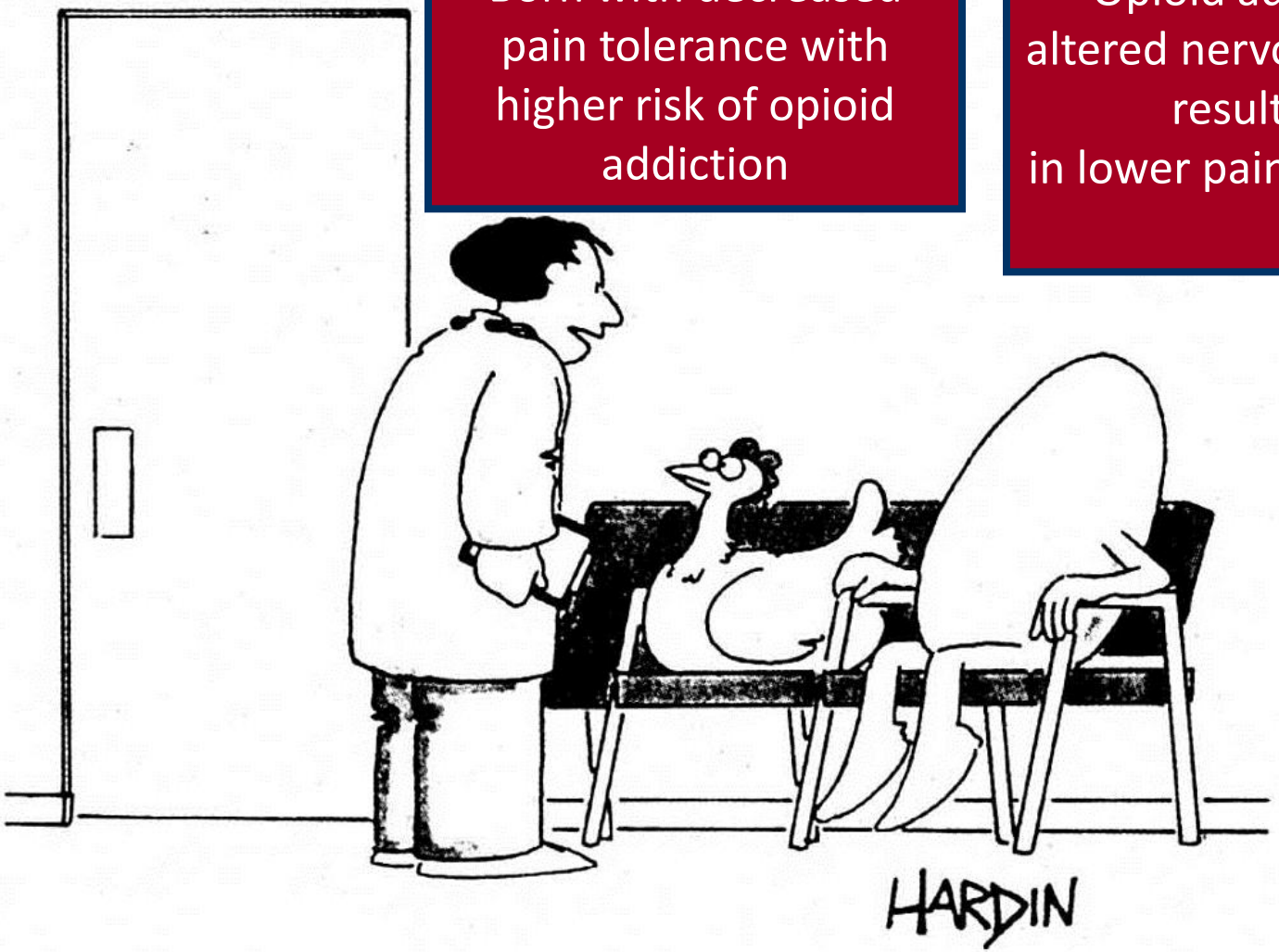
Altered Pain Experience

- Patients with opioid dependence have less pain tolerance than peers in remission or matched controls
- Patients with a history of opioid dependence have less pain tolerance than siblings without an addiction history
- Patients on opioid maintenance treatment (i.e. methadone and buprenorphine) have less pain tolerance then matched controls
- Methadone-maintained women had increased pain and required up to 70% more oxycodone equivalents after cesarean delivery

Martin J (1965), Ho and Dole V (1979), Compton P (1994, 2001), Meyer M (2007)

Born with decreased pain tolerance with higher risk of opioid addiction

Opioid addiction altered nervous system resulting in lower pain tolerance



"WHO WAS FIRST?"

Pain and Addiction

Provider Perspective

1. Physician Fear of Deception

Physicians question the "legitimacy" of need for opioid analgesics ("drug seeking" patient vs. legitimate need).

"When the patient is always seeking, there is a sort of a tone, always complaining and always trying to get more. It's that seeking behavior that puts you off, regardless of what's going on, it just puts you off."

-Junior Medical Resident

Merrill JO, et al. J Gen Intern Med. 2002

Pain and Addiction
Patient Perspective

2. No Standard Approach

The evaluation and treatment of pain and withdrawal is extremely variable among physicians and from patient to patient. There is no common approach nor are there clearly articulated standards.

"The last time, they took me to the operating room, put me to sleep, gave me pain meds, and I was in and out in two days.. . .This crew was hard! It's like the Civil War. 'He's a trooper, get out the saw'. . ."

-Patient w/ Multiple Encounters

Merrill JO, et al. J Gen Intern Med. 2002

Pain and Addiction
Patient Perspective

3. Avoidance

Physicians focused primarily on familiar acute medical problems and evaded more uncertain areas of assessing or intervening in the underlying addiction problem-particularly issues of pain and withdrawal.

<u>Patient/Resident Dialog</u>

Resident: “Good Morning”
Patient: “I’m in terrible pain.”
Resident: “This is Dr. Attending, who will take care of you.”
Patient: “I’m in terrible pain.”
Attending: “We’re going to look at your foot.”
Patient: “I’m in terrible pain.”
Resident: “Did his dressing get changed?”
Patient: “Please don’t hurt me.”

Merrill JO, et al. J Gen Intern Med. 2002

Pain and Addiction
Patient Perspective

4. Patient Fear of Mistreatment

Patients are fearful they will be punished for their drug use by poor medical care.

"I mentioned that I would need methadone, and I heard one of them chuckle. . .in a negative, condescending way. You're very sensitive because you expect problems getting adequate pain management because you have a history of drug abuse. . .He showed me that he was actually in the opposite corner, across the ring from me."

-Patient

Merrill JO, et al. J Gen Intern Med. 2002

Cases

Case 1

- *You are called by a dentist for advice on treating acute pain in the following patient…*

  46 y.o. male scheduled for extensive outpatient dental work including multiple extractions.

  He is maintained on buprenorphine 24 mg SL per day for treatment of his opioid dependence.

- *What would you recommend for pain management?*

Case 2

- *You are called by an ER physician for advice on treating acute pain in the following patient…*

  28 y.o. female with severe, 10/10, acute flank pain secondary to a kidney stone.

  She is maintained on buprenorphine 16 mg SL per day for treatment of her opioid dependence.

- *What would you recommend for pain management?*

Case 3

- *You are called by a trauma surgeon for advice on pain management of the following patient…*

  35 y.o. male is status post motor vehicle crash with a rupture spleen and femur fracture.

  He is maintained on buprenorphine 16 mg SL per day for treatment of his opioid dependence.

- *How would you manage this patient's buprenorphine and pain perioperatively?*

Case 4

- *You are called by a orthopedic surgeon for advice on pain management of the following patient…*

  65 y.o. male with right hip avascular necrosis being scheduled for an elective total hip arthroplasty.

  He is maintained on buprenorphine 16 mg SL per day for treatment of his opioid dependence.

- *How would you manage this patient's buprenorphine and pain perioperatively?*

Buprenorphine as an Analgesic

Buprenorphine Pharmacology

- Derivative of morphine alkaloid – *thebaine*
- Partial agonist at *mu* opioid receptor
- Antagonist at the *kappa* receptor
- Slow dissociation – long duration of action
- High affinity – not easily displaced by antagonists
- Sublingual peak concentration after 2 hours
- Ceiling effect on respiratory depression

Johnson RE et al. J of Pain Symptom Management 2005

Buprenorphine Duration of Action

- Suppression of opioid withdrawal and drug craving, opioid blockade for **24 - 48** hrs

- Analgesic duration of action **6 - 8** hrs

Johnson RE et al. J of Pain Symptom Management 2005

Buprenorphine as an Analgesic

- In U.S., parenteral formulation is FDA approved for pain but *not* opioid dependence treatment,
- While sublingual (SL) formulation is approved for opioid dependence but *not* pain treatment
- Small studies in Europe and Asia demonstrate analgesic efficacy of SL formulation (0.2-0.8 mg q 6-8h) in opioid naïve post-operative pain

Edge WG et al. Anaesthesia. 1979
Moa G et al. Acta Anaesthesiol Scand. 1990

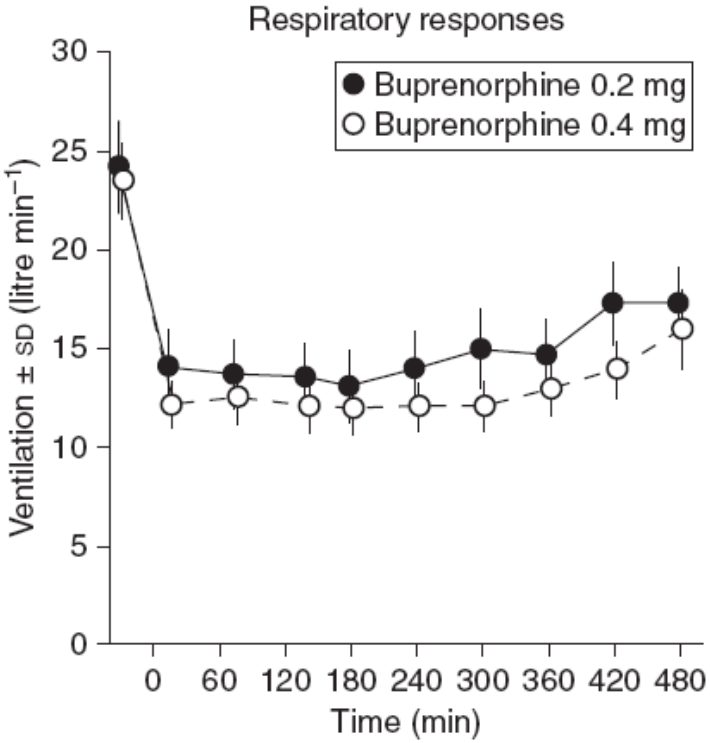
Buprenorphine as an Analgesic

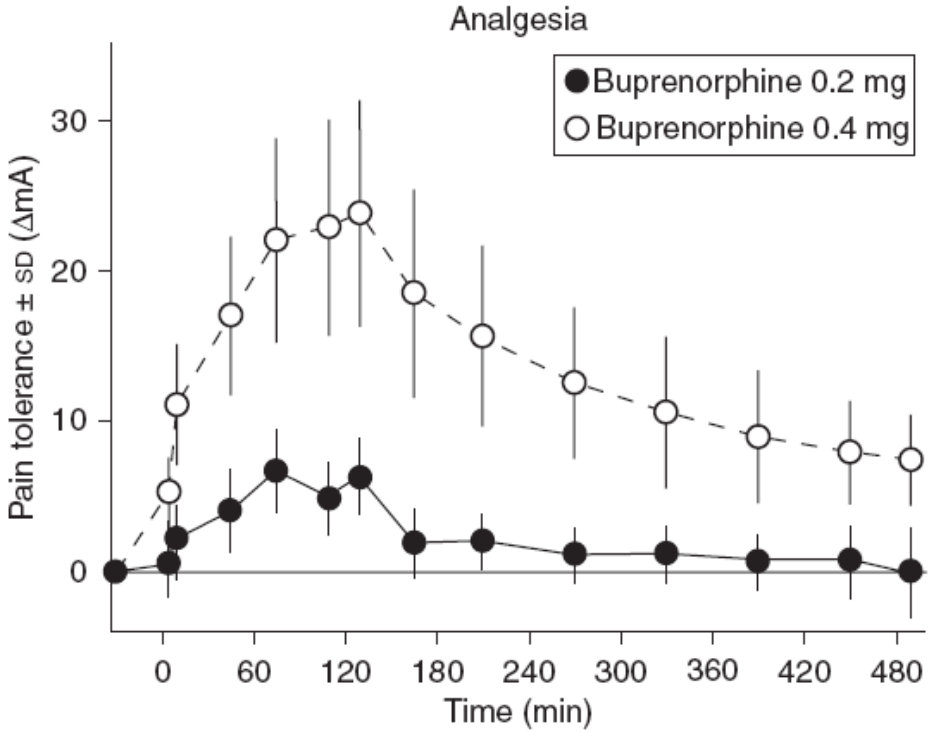
Analgesic ceiling effect is UNCERTAIN

- Differing data on analgesic ceiling effect in animal models
- **No** published data indicating an analgesic ceiling in humans
- Doubling dose resulted in dose-dependent increase in analgesia without increase in respiratory depression

Johnson RE et al. J of Pain Symptom Management 2005
Cowan A. J Addiction Medicine 2007

Buprenorphine as an Analgesic





Doubling dose increased peak analgesic effect by a factor of 3.5 while time and magnitude of respiratory depression remained unchanged

Dahan A et al. Br J Anaesh 2006

Acute Pain Management

Acute Pain Management

- Reassure patients that their addiction will not be an obstacle to aggressive pain management
- Communicate with buprenorphine prescriber
- Avoid using mixed agonist/antagonist opioids (e.g. pentazocine and butorphanol) as they may precipitate acute withdrawal
- Careful use and monitoring of combination products containing acetaminophen

Alford DP, Compton P, Samet JH. Ann Intern Med 2006

Acute Pain Management

- Buprenorphine maintenance dosed q24 does not confer analgesia (*beyond 6-8 hours*)
- Is relapse risk greater for…
  - inadequate pain management or
  - exposure to opioid analgesics?

Alford DP, Compton P, Samet JH. Ann Intern Med 2006

The "Opioid Debt"

Patients who are physically dependent on opioids (ie. buprenorphine) must be maintained on daily equivalence before ANY analgesic effect is realized with opioids used for acute pain management

Peng PW, Tumber PS, Gourlay D: Can J Anaesthesia 2005

Theoretical Concern…

Buprenorphine may…

- antagonize the effects of previously administered opioid analgesics
  - depends on proportion of receptors occupied
  - depends on time interval since last opioid analgesic dose
- block the effects of subsequent administered opioid analgesics

Interaction with Opioid Analgesics

- Experimental mouse and rat pain models
- Combination of buprenorphine and opioid analgesic (morphine, oxycodone, hydromorphone, fentanyl) resulted in additive or synergistic effects
- Receptor occupancy by buprenorphine does not appear to cause impairment of μ-opioid receptor accessibility

Kogel B, et al. European J of Pain. 2005
Englberger W et al. European J of Pharm. 2006

Case Series…

- 5 patients underwent 7 major surgeries (colectomy, knee replacement, small bowel resection, bilateral mastectomy)
- All maintained on stable doses of SL buprenorphine (2 mg – 24 mg) for chronic musculoskeletal pain – some with remote history of opioid addiction
- By chart review, postoperative pain was adequately controlled using oral or IV full agonist opioids

Kornfeld H and Manfredi L. Am J Therapeutics 2010

Accumulating Research…

- Observational study of peripartum acute pain management of buprenorphine (n=8) stabilized patients
  - Patients responded to additional opioid medication given for pain control

Jones HE et al. Am J Drug Alc Abuse 2009

- DB RCT comparing IV patient-controlled analgesia with buprenorphine and morphine alone and in combination for postoperative pain in adults undergoing abdominal surgery
  - In the combination group, buprenorphine did not appear to inhibit the analgesia provided by morphine

Oifa S et al. Clin Ther. 2009

Buprenorphine Maintenance
Acute Pain Management Five Options

1. Continue buprenorphine and titrate short-acting opioid analgesic
2. Discontinue buprenorphine, use opioid analgesic, then re-induce w/ buprenorphine
3. Divide buprenorphine to every 6-8 hours
4. Use supplemental doses of buprenorphine*
5. If inpatient, d/c buprenorphine, start ER/LA opioid (debt and pain), use IR/SA opioid analgesics, then re-induce w/ buprenorphine

Alford DP. Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence. 2010
Alford DP, Compton P, Samet JH. Ann Intern Med 2006
* Book SW, Myrick H, Malcolm R, Strain EC. Am J Psychiatry 2007

Case 1

- *You are called by a dentist for advice on treating acute pain in the following patient…*

  46 y.o. male scheduled for extensive outpatient dental work including multiple extractions.

  He is maintained on buprenorphine 24 mg SL per day for treatment of his opioid dependence.

- *What would you recommend for pain management?*

Acute Pain Management

Mild - moderate pain (e.g., dental extraction)

1) Continue buprenorphine maintenance
2) Use non-opioid analgesics
3) +/- dual mechanism opioids (tramadol, tapentadol) or IR/SA opioid analgesics

OR

1) Divide buprenorphine to q8
2) Use non-opioid analgesics
3) +/- dual mechanism opioids or IR/SA opioid analgesics

OR

1) Give supplemental buprenorphine doses 2 mg q6-8

Case 2

- *You are called by an ER physician for advice on treating acute pain in the following patient…*

  28 y.o. female with severe, 10/10, acute flank pain secondary to a kidney stone.

  She is maintained on buprenorphine 16 mg SL per day for treatment of her opioid dependence.

- *What would you recommend for pain management?*

Acute Pain Management

Moderate - severe pain (e.g., kidney stone)

1) Discontinue buprenorphine
2) Treat with opioid analgesics (e.g. combination ER/LA opioid + IR/SA opioid) until pain resolves
3) Re-induction with buprenorphine using established protocols

OR

1) Divide buprenophine dose to q8 and give supplemental SL or parenteral buprenorphine doses

Case 3

- *You are called by a trauma surgeon for advice on pain management of the following patient…*

  35 y.o. male is status post motor vehicle crash with a rupture spleen and femur fracture.

  He is maintained on buprenorphine 16 mg SL per day for treatment of his opioid dependence.

- *How would you manage this patient's buprenorphine and pain perioperatively?*

Acute Pain Management

Inpatient: Severe pain

(e.g., trauma)

1) Discontinue buprenorphine on day of surgery
2) Methadone ~ 30 mg per day (or other ER/LA opioid) for "opioid debt"
3) IR/SA opioid analgesics (including PCA) until pain resolves
4) Discontinue methadone (or other ER/LA opioid) and re-induction with buprenorphine

Case 4

- *You are called by a orthopedic surgeon for advice on pain management of the following patient…*

  65 y.o. male with right hip avascular necrosis being scheduled for an elective total hip arthroplasty.

  He is maintained on buprenorphine 16 mg SL per day for treatment of his opioid dependence.

- *How would you manage this patient's buprenorphine and pain perioperatively?*

The "Five Day" Rule
University of Michigan Protocol

- If moderate-severe post-operative pain is anticipated
  - Discontinue buprenorphine and transitioned to short-acting opioid for ≥ 5 days prior to surgery

- But this protocol…
  - Risks causing a disruption in the patient's recovery from opioid addiction by stopping buprenorphine during preoperative period
  - Has never been evaluated and is based on a theoretical concern of pharmacological principles

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Management Guidelines

Periprocedure management WITH expected need for opioid analgesics

- Take last buprenorphine dose on the morning of the day prior to the procedure
- Hold buprenorphine dose on day of surgery

- **Pre-procedure**: give single dose of ER/LA opioid (e.g., SR morphine 15 mg) on the day of procedure

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Management Guidelines

Periprocedure management WITH expected need for opioid analgesics

- **Post-procedure**: Opioids analgesics should be started using standard dosing protocols but pain management should be carefully monitored since patients with opioid dependence often have decreased pain tolerance and cross-tolerance to opioid analgesics resulting in a need higher opioid doses and shorter dosing intervals
- Because of it high affinity at the opioid receptor Fentanyl should be the opioid of choice for analgesia during surgery and in PACU for these patients

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Management Guidelines

Post-procedure **INPATIENT** analgesia with opioids

- Continue to hold buprenorphine
- All patients should be placed on an ER/LA opioids (e.g., SR morphine 15 mg bid) to address the patients baseline opioid requirements and for sustained pain control
- If patient also requires parenteral analgesia for breakthrough pain control use PCA (fentanyl, dilaudid or morphine) with NO basal dose. Continue ER/LA opioid
- If patient does not require parenteral analgesia for breakthrough pain control use IR/SA opioids e.g.,oxycodone, morphine. Continue ER/LA opioid.

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Management Guidelines

Post-procedure **OUTPATIENT** analgesia with opioids

- Continue to hold buprenorphine
- All patients should be continued on ER/LA opioid
- Treat patient's breakthrough pain with IR/SA opioids e.g.,oxycodone, morphine.
- Schedule patient to seen by their buprenorphine provider within 1 week to be considered for restarting buprenorphine maintenance

Chronic Pain Management

Chronic Pain Management
If Opioid Analgesics Are Required

- Buprenorphine-maintained patients may not benefit from concurrent opioid analgesics due to high μ-opioid receptor affinity
- Due to its inherent analgesic properties, buprenorphine could be dosed every 6-8 hours to treat both opioid dependence (*on-label* indication) and pain (*off-label* indication)

Chronic Pain Management

- Open-labeled study of 95 patients with chronic pain who failed long-term opioids and were converted to sublingual buprenorphine
- Mean buprenorphine dose 8mg/d (4-16mg) in divided doses
- Mean duration of treatment ~9 months
- 86% had moderate to substantial pain relief along with improved mood and function
- 6% discontinued therapy due to side effects or worsening pain

Malinoff HL, Barkin R, Wilson G. Am J of Thera 2005

Chronic Pain in "High-Risk" Patients

- Study to develop (by panel of experts) and pilot a clinical protocol for safe transition from full opioid agonist to SL bup/nx
- 12 patients with moderate to severe chronic pain, receiving long-term full opioid agonists with ≥1 aberrant medication taking behavior and no opioid use disorder
- Results
  - 3 patients on highest baseline opioid dose and 3 patients on lowest opioid dose had early AE and did not complete trial
  - Remaining 6, 1 withdrew due to AE, 1 responded well then withdrew, and 4 completed 3-month trial
    - Controlling for dropouts, average and worst pain significantly decreased after switch to bup/nx

Rosenblum A et al. J Opioid Management. 2012

Chronic Pain Management

- Try non-pharmacologic and nonopioid therapies
- If pain persists, and opioid analgesics are required
  - Try splitting buprenorphine dose, if no relief…
  - Because buprenorphine may compete with concurrent long-acting opioid analgesics…
  - Buprenorphine-maintenance should be discontinued and patient's opioid dependence treated in a methadone maintenance treatment program w/ concurrent long-acting opioid analgesics

Thank you! Questions?

References.

- Alford DP. Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence. 2010
- Alford DP, Compton P, Samet JH. Ann Intern Med 2006
- Book SW, Myrick H, Malcolm R, Strain EC. Am J Psychiatry 2007
- Compton MA. J Pain Symptom Manage 1994
- Compton P et al. J Drug Alcohol Depend. 2001
- Cowan A. J Addiction Medicine 2007
- Dahan A et al. Br J Anaesh 2006
- Edge WG et al. Anaesthesia. 1979
- Englberger W et al. European J Pharm 2006
- Ho A, Dole VP. Proc Soc Exp Biol Med. 1979
- Johnson RE et al. J of Pain Symptom Management 2005
- Jones HE et al. Am J Drug Alc Abuse 2009
- Kogel B, et al. European J of Pain. 2005
- Kornfeld H and Manfredi L. Am J Therapeutics 2010
- Malinoff HL, Barkin R, Wilson G. Am J of Thera 2005
- Martin JE, Inglis J. Br J Soc Clin Pysch. 1965
- Merrill JO, et al. J Gen Intern Med. 2002
- Meyer M et al. Obstet Gynecol 2007
- Moa G et al. Acta Anaesthesiol Scand. 1990
- Ofia S et al. Clin Ther. 2009
- Peng PW, Tumber PS, Gourlay D: Can J Anaesthesia 2005
- Rosenblum A et al. J Opioid Manage. 2012