Disclosure

- I have nothing to disclose

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Objectives

- Be more confident addressing acute pain in patients on buprenorphine products for opioid use disorder and for patients on naltrexone formulations.
- Be able to list three important implications of chronic methadone use during the perioperative period
- understand the evidence-base for how to approach perioperative pain in patients on buprenorphine.

Which form of MAT is the easiest to manage preoperatively?

- ☐ A. Naltrexone
- ☐ B. Methadone
- ☒ C. Buprenorphine

Nuance

*Noun: (*n(y)o͞o ̩äns) a subtle difference in meaning or opinion or attitude

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The bottom line

Whenever possible, always continue MAT

except sometimes if it is naloxone or naltrexone

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Why Would You Want to Continue MAT?

Because stopping may put recovery at risk

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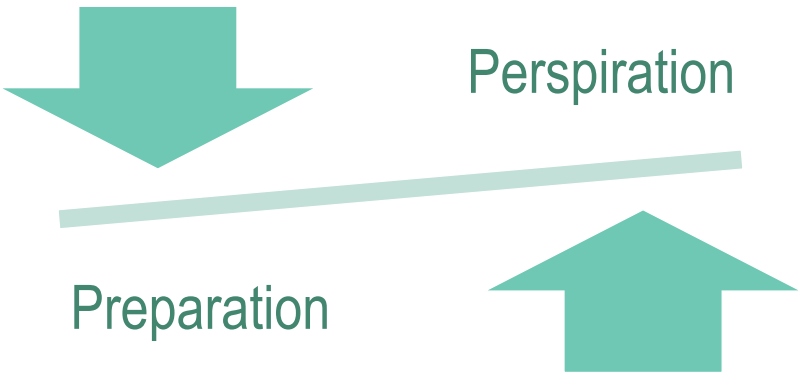
Preparation vs. Perspiration



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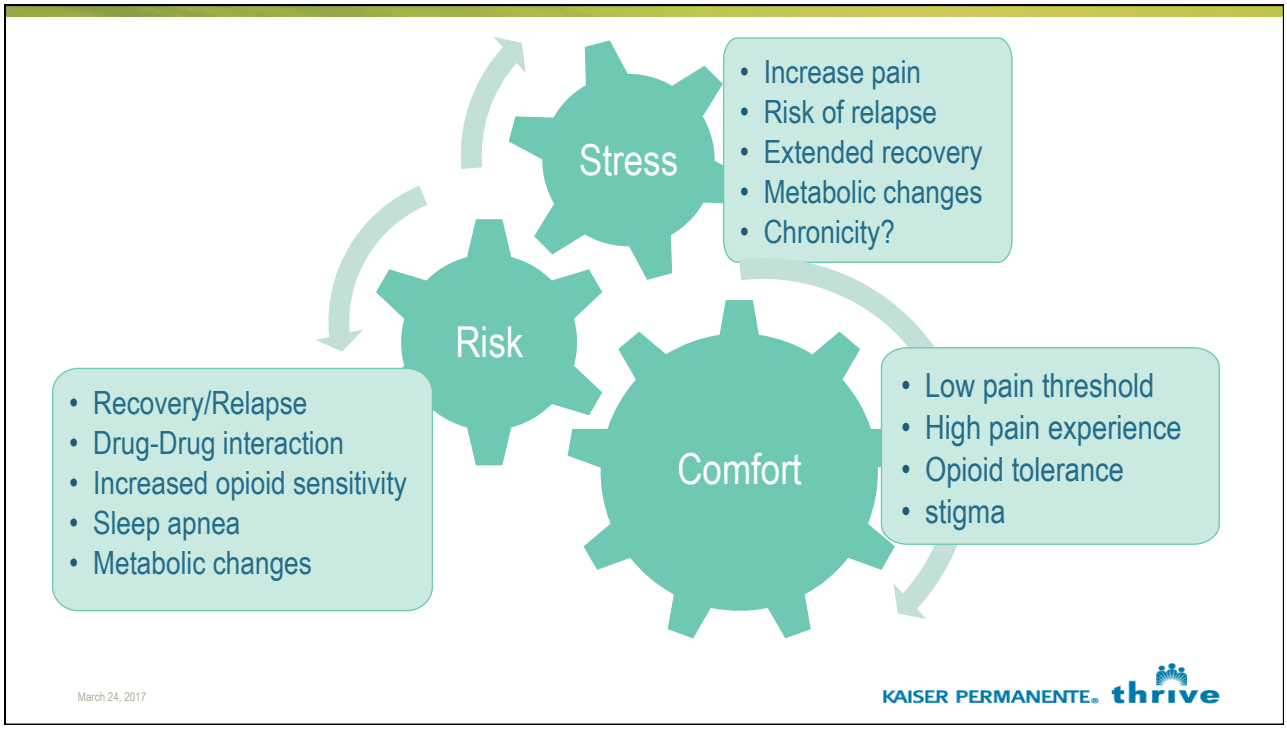

My preparation

- Have a plan and a back-up plan
- Pre-op visit with patient with written instructions
- Discussion with the surgeon
- Email or discussion with the anesthesiologist
- Note in the chart to hospitalist about the recommendations
- Who to call in case of issues
- Check in post op day 1 and post op day 3
- If MAT is stopped, close contact and a plan for restart

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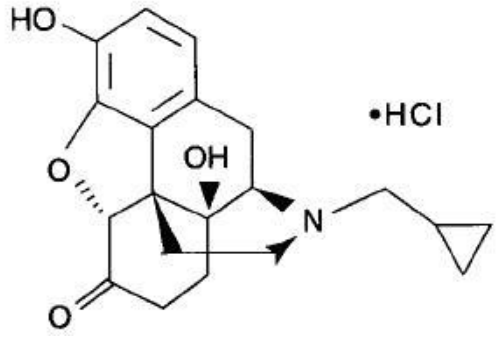

Naltrexone/Naloxone

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Naltrexone

- Opioid antagonist
- 50 mg tablets daily
- 380 mg injected IM every 4 weeks
- Binds competitively but does not activate mu receptor
- Blocks opioid analgesia
- Competitive block changes over time

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Naltrexone

- Best strategy: schedule surgery at the end of cycle if using IM
- Wait 24 hours if using oral tablets
- Opioid tolerant vs. increased opioid sensitivity
- Restart naltrexone once abstinence from postoperative opioids is *adequate*
- Always try to utilize multi-modal opioid sparing analgesia strategies
- Discuss with perioperative team what experience and options are
- Consider medic-alert bracelet
- Consider pre-op urine toxicology for non opioids (cocaine, meth etc.)

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Digression: Multi-modal Analgesia

- Ketamine (single dose vs infusion)
- Regional anesthesia
- Neuraxial analgesia spinal/ epidural
- NSAIDS
- Acetaminophen
- Membrane stabilizers
- Lidocaine infusion
- Alpha 2 agonists (dexmedetomidine, clonidine)

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Acute Pain and Naltrexone/Naloxone

- Non-steroidal anti inflammatory medications
- Acetaminophen
- Steroids
- Topical local anesthetics
- Management of expectations
- Consult with pain team

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Sticky Situations: Naltrexone/Naloxone

- What if this is not enough?
- Emergency surgery?
- Perioperative team is unaware/unfamiliar with MAT
- Extended NPO time

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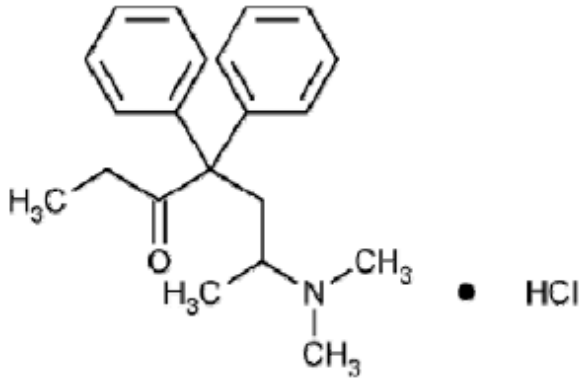

Methadone

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Which drugs prolong QT intervals

- ☐ A. Ciprofloxacin
- ☐ B. Fluoxetine
- ☐ C. Promethazine
- ☐ D. Sevoflurane
- ☒ E. All of the above

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methadone

The Fortunate

- Inexpensive
- Intrinsically long-acting for withdrawal
- High oral bioavailability
- No significant toxic metabolites
- No accumulation in renal disease
- NMDA antagonist
- Liquid or pill form
- Easy dose adjustments
- Relatively low street value (liquid)

The Unfortunate

- Highly variable metabolism related
- Unpredictable half-life
- Unpredictable equi-analgesic potency
- Variable protein binding
- Genetic difference affect metabolism
- QT prolonging
- Multiple drug-drug interactions
- Conversion is not bi-directional
- Sleep apnea

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Bottom line:

- Methadone used for MAT maintained up to surgery and throughout perioperative period
- Other opioids added on top for new acute pain and tapered off as tolerated

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If only it were that simple…

- Methadone affects QT interval
- Addition or discontinuation of other drugs can alter serum levels and therefore risk
- Some patients on take home methadone may not be using the prescribed dose
- Methadone doses are not easy to determine
- Ask about previous analgesic strategies that worked
- Low pain threshold and low high pain experience
- The methadone for MAT will not be analgesic post op

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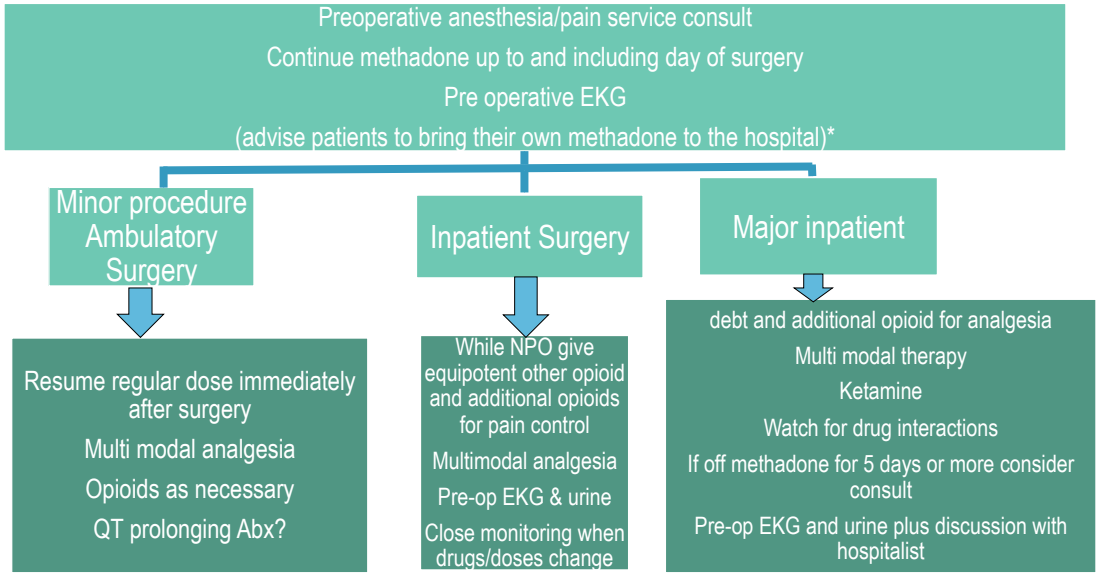

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Anaesth Intensive Care 2013; 41: 222-230

Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy

P. E. MACINTYRE*, R. A. RUSSELL†, K. A. N. USHER‡, M. GAUGHWIN§, C. A. HUXTABLE**

Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia

	All Methadone	Methadone given	Methadone not given
1st 24 hour MSE	221.2 +/-138.2	202.0 +/- 138.0	281 +/- 129.9
NSAID	44.8	36.4	71.4
Ketamine	58.6	54.5	71.4
Days APS	5.1 +/-3.4	4.0 +/-2/5	8.7 +/-3.4

Opioid Debt

Acute Pain Methadone

- Other analgesics, including opioids can be used with methadone (watch metabolism and QT)
- Close monitoring if using opioids for acute pain
- 3 day quantity of other opioid is usually enough post-op

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Sticky Situations: Methadone

- What if this is not enough?
- What if this is emergency surgery?
- What if the perioperative team is unaware of the MAT
- What if the patient is NPO

Mostly issue is changing other drugs changes methadone

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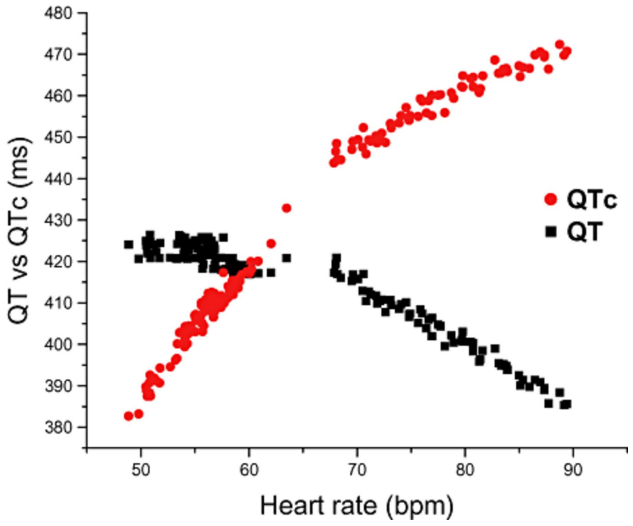
Monitoring QT intervals



Spevak, C et. al. The Clinical Significance of QT Interval Prolongation in Anesthesia and Pain Management: What You Should and Should Not Worry About. *Pain Med* 2012; 13 (8): 1072-1080.

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Table 1

Relative potency of various opioids for blocking the hERG-related potassium channel

Drug	IC50 for hERG Block	Maximum Plasma Conc. (Cmax)	Ratio IC50/Cmax
LAAM	2.2 μM	1 μM	2.2
Methadone	9.8 μM	3.6 μM	2.7
Meperidine	75 μM	1.3 μM	58
Fentanyl	1.8 μM	30 nM	60
Buprenorphine	7.5 μM	36 nM	208
Morphine	>1 mM	2.5 μM	>400
Codeine	>300 μM	0.66 μM	>455

From Katchman et al. [31].

hERG = human *ether-a-go-go*-related gene; LAAM = L-α-acetyl-methadol; conc. = concentration.

Not Worry About. *Pain*

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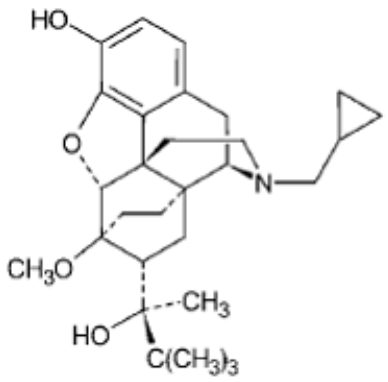

Buprenorphine

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It ain't what you don't know, it's what you know for sure that just ain't so

Attributed to Mark Twain…

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Buprenorphine/naloxone can best be described as an agonist-antagonist because

- ❑ A. Buprenorphine is the agonist and naloxone is the antagonist
- ☒ B. Buprenorphine is an agonist at mu and an antagonist at kappa
- ❑ C. Buprenorphine is an agonist up to a certain dose and then it becomes an antagonist
- ❑ D. Buprenorphine is an agonist but it is an antagonist for other opioids

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What we're sure we know

(that just ain't so)

It isn't (a very good) analgesic

It has a ceiling effect for analgesia

It blocks other opioids

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Concept #1: Analgesia

Journal of Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2014 doi: 10.1111/jcpt.12196

Commentary

The clinical analgesic efficacy of buprenorphine

R. B. Raffa* PhD, M. Haidery* PharmD, H.-M. Huang* PharmD, K. Kalladeen* PharmD, D. E. Lockstein* PharmD, H. Ono* PharmD, M. J. Shope* PharmD, O. A. Sowunmi* PharmD, J. K. Tran* PharmD and J. V. Pergolizzi†‡§ Jr MD

**Temple University School of Pharmacy, Philadelphia, PA, †Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, ‡Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, and §Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA*

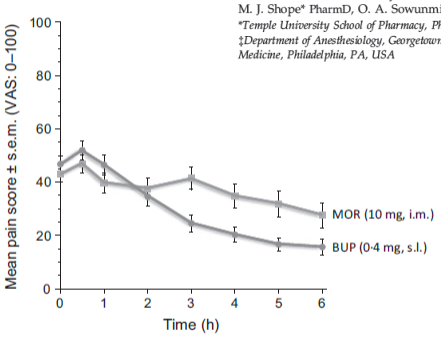

Fig. 2. The analgesic efficacy of s.l. buprenorphine (0·4 mg) was compared with that of i.m. morphine (10 mg) in a randomized, double-blind study of post-op pain of 101 patients (mean age: 40–45 years). Pain was measured using a 10-cm pain scale (0 = none, 10 = as much as imaginable). Buprenorphine produced the same pain relief as did morphine during the first 2 h and modestly greater pain relief from 2 to 6 h. Redrawn from Edge *et al.*[22]

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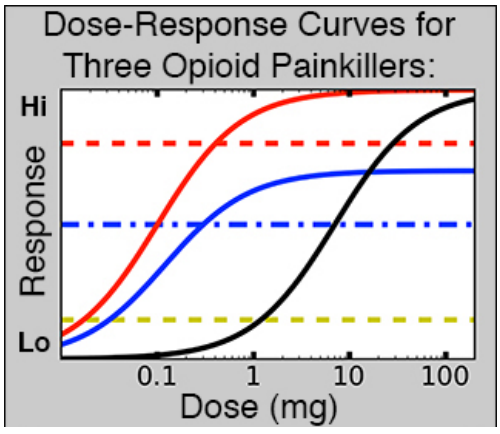
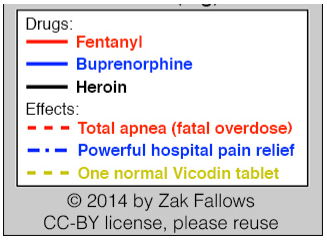
Ceiling Effect





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British Journal of Pharmacology (2009), 157, 831–843

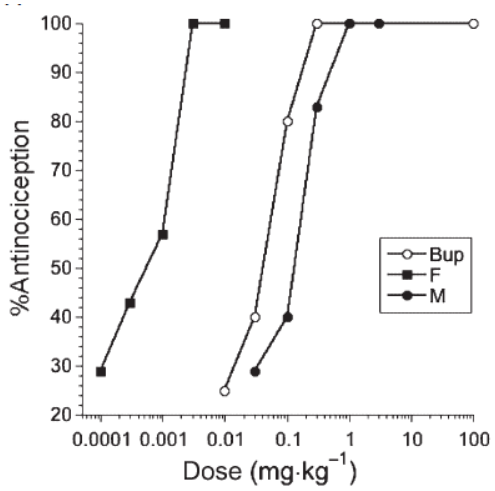
0007-1188/09
www.brjpharmacol.org

RESEARCH PAPER

Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine

Zhe Ding and Robert B Raffa

Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA



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Which of the following statements are true?

- ❑ A. In a patient on buprenorphine taking another opioid can precipitate withdrawal
- ❑ B. In a patient on buprenorphine taking another opioid will not offer additional analgesia
- ☒ C. In a patient on morphine buprenorphine can precipitate withdrawal
- ❑ D. All of the above

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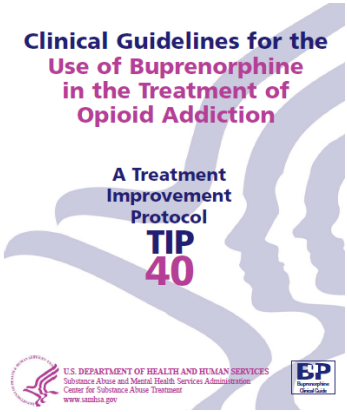
Concept: Opioid Blocking

"While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. Note that until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids."



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Apparently the government does not need to use footnotes to reference where their information comes from….

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Anaesth Intensive Care 2013; 41: 222-230

Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy

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Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia

	All Buprenorphine	Buprenorphine Given	Buprenorphine NOT given
1st 24 hour MSE	200 +/-128.6	155.2 +/-135.5	245.5 +/- 109.3
NSAID	31.8	18.2	45.5
Ketamine	63.6	27.3	100
Days APS	4.5 +/-3.3	3.0 +/-1.7	5.9 +/-3.9

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And what about naloxone…..

- Naloxone in buprenorphine is not bio-available unless injected
- It does not block other opioids when used as directed
- It is not the cause of precipitated withdrawal when taken sublingually.

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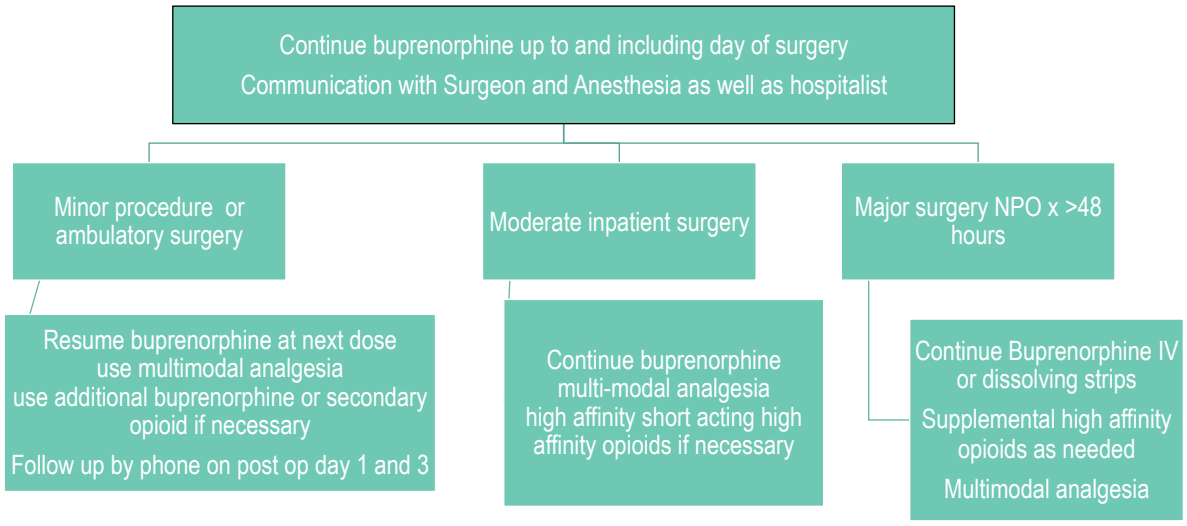
Algorithm for managing perioperative buprenorphine



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Acute Pain: Buprenorphine

- No problem with adding any appropriate drug, including opioids to a buprenorphine regimen
- Some patients can be managed with increased doses of buprenorphine in perioperative period (QID)
- Close monitoring if using opioids for acute pain
- 3 day quantity of additional opioid is usually enough

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Sticky Situations: Buprenorphine

- What if this is not enough?
- What if this is emergency surgery?
- What if the perioperative team is unaware of the MAT
- What if the patient is NPO

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Buprenorphine Maintenance Therapy Hinders Acute Pain Management in Trauma

COLIN J. HARRINGTON, M.D.,* VICTOR ZAYDFUDIM, M.D., M.P.H.†

*From the *Departments of Psychiatry and Medicine, Brown Medical School and Rhode Island Hospital, Providence, Rhode Island and the †Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee*

Sometimes the problem is not the drug…buprenorphine was restarted after a 4 day abstinence while other opioids were being given….

The patient's agitation and complaints of pain persisted. Agitation was managed with haloperidol and lorazepam. Pain was treated with high dose full agonist opiates. By postinjury day (PID) 3, the patient's analgesic needs began to decline. Additional history revealed that the patient was active in a buprenorphine maintenance program. His preadmission buprenorphine maintenance regimen of buprenorphine/naloxone (2 mg/0.5 mg) combination therapy was restarted on PID 4, with the aim of achieving better analgesia. Subsequent tapering of narcotics, however, was unsuccessful and the patient received 50 mg of morphine, 37 mg of haloperidol, 8 mg of lorazepam, and 17 mg of midazolam on PID 6.

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Binding Affinity

Volpe, DA et. al. Regulatory toxicology and pharmacology 2011; (59)3, 385-90

Drug	K_i
Sufentanil	0.136
Buprenorphine	0.27
Hydromorphone	0.36
Morphine	1.17

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Summary

- Most MAT can be maintained preoperatively with pre-planning
- Even with Pre-planning problems can arise that perioperative team may not be equipped to handle
- Each patient should be assessed for their particular MAT regimen, their surgery, their team and plans should be made accordingly

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References on Naltrexone/Naloxone

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Contact Information

Andrea Rubinstein, MD

3559 Roundbarn Blvd
Santa Rosa, CA 95403

707-571-3931
andrea.L.rubinstein@kp.org

Twitter: @rubinsteinMD

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