Why Buprenorphine is Superior for Management of Opioid Use Disorder and Pain

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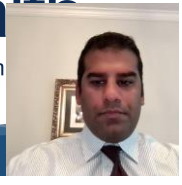

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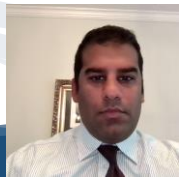
Disclosures

- None



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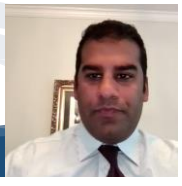
Outline

- History and Overview of PK and PD properties
- Use in OUD
  - Concurrent use in Acute Pain Management
- Use in Pain Management



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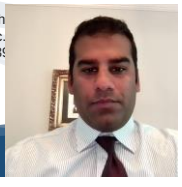
History

- Early 1920's significant "opium problem"

Brand Name	Formulation	FDA Approval Date	Indication
Buprenex	Injectable	1981	Moderate to severe pain
Subutex	Sublingual	2002	Opioid dependence
Suboxone	Sublingual, combined with naloxone	2002	Opioid dependence
Butrans	Transdermal	2010	Moderate to severe chronic pain
Zubsolv	Sublingual, combined with naloxone	2013	Opioid dependence

- Developed in 1966 mainly as an analgesic
  - Alternative to Morphine
- In 1975, the Committee on Problems of Drug Dependence,
  - proposed buprenorphine as an attractive alternative to methadone for opioid treatment because of its unique profile as a mu-opioid receptor partial agonist, producing less tolerance and less intoxicating effects.

Campbell, Nancy D., and Anne M. Lovell. "Th
of buprenorphine as an addiction therapeutic.
Academy of Sciences 1248.1 (2012): 124-13



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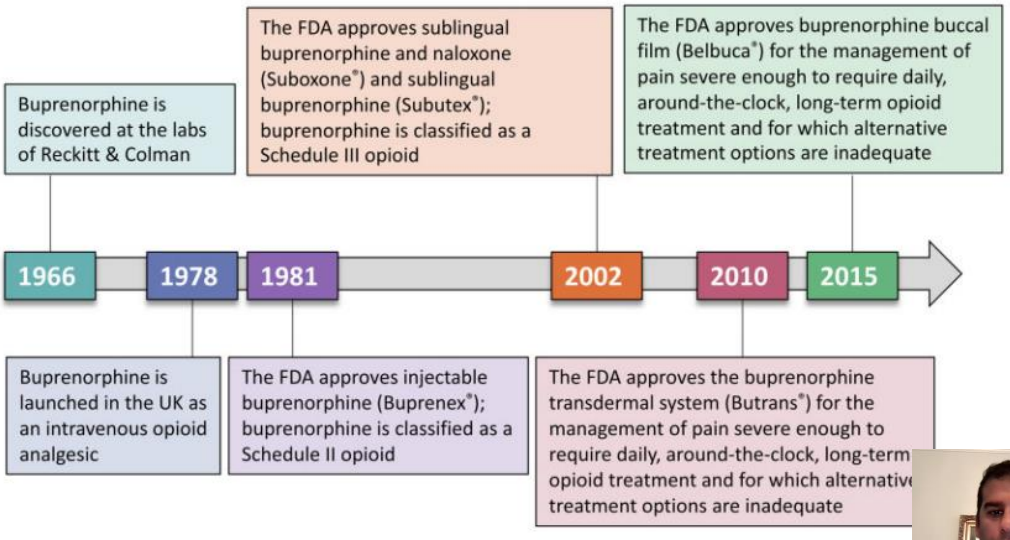

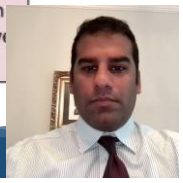

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Webster, Lynn, et al. "Understanding buprenorphine for use in chronic pain: expert opinion." *Pain Medicine* 21.4 (2020): 714-723.

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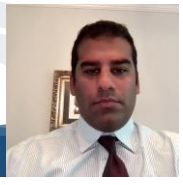
- However, it displays low intrinsic activity (agonism) in in vitro (test tube) assays, as determined by [^{35}S]GTPgammaS binding.
  - In vitro assays also given us information on Affinity and Intrinsic activity



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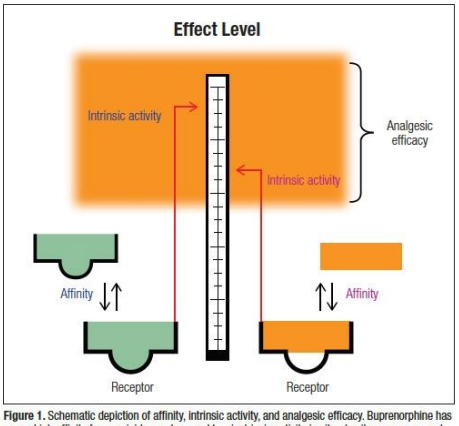
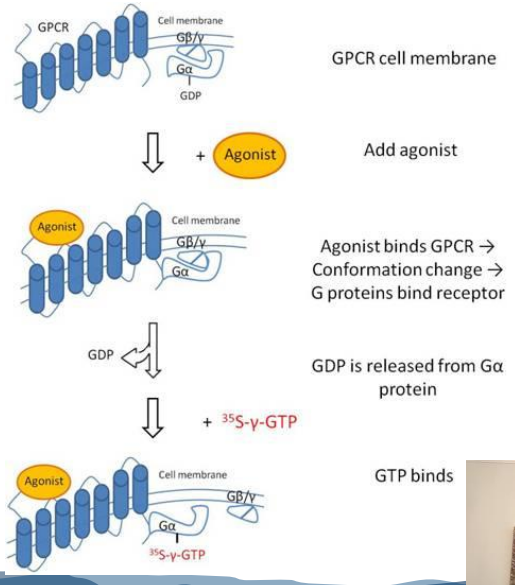
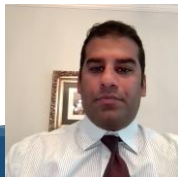


Figure 1. Schematic depiction of affinity, intrinsic activity, and analgesic efficacy. Buprenorphine has a very high affinity for μ-opioid receptors, and low instrinsic activity in vitro. In vitro assays are not good predictors of in vivo analgesic activity.





https://www.perkinelmer.com/lab-products-and-services/application-support-knowledgebase/radiometric/35s-gtp-binding-assays.html

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Partial Agonist

- According to [^{35}S]GTPγS binding assays, Morphine would also be partial agonist
- Loperamide high affinity and high intrinsic activity

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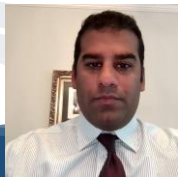

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?Full Agonist

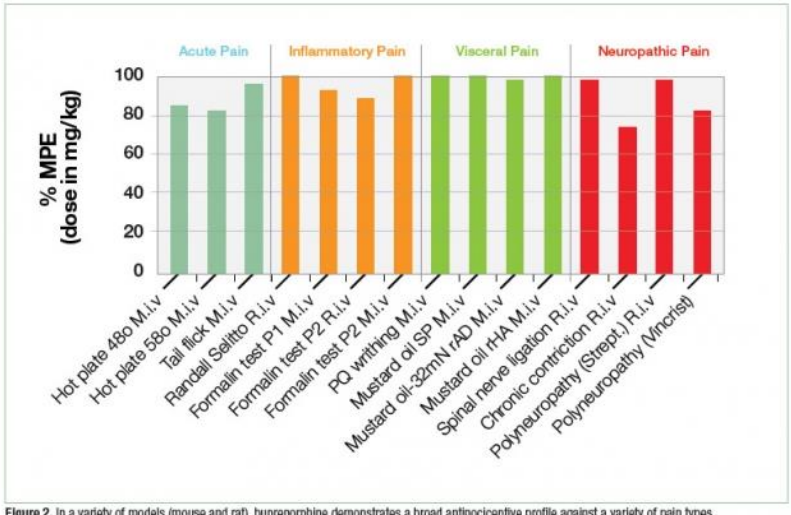

Figure 2. In a variety of models (mouse and rat), buprenorphine demonstrates a broad antinociceptive profile against a variety of pain types. **M**, mouse; **MPE**, maximum possible effect; **PQ**, phenylquinone; **R**, rat
Adapted from reference 10.

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9 https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/buprenorphine-partial-agonist-preclinical-clinical-evidence

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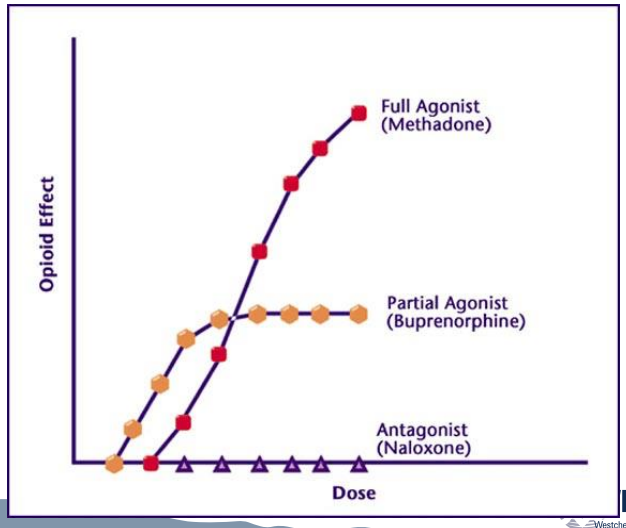
PK/PD



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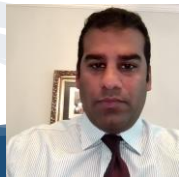

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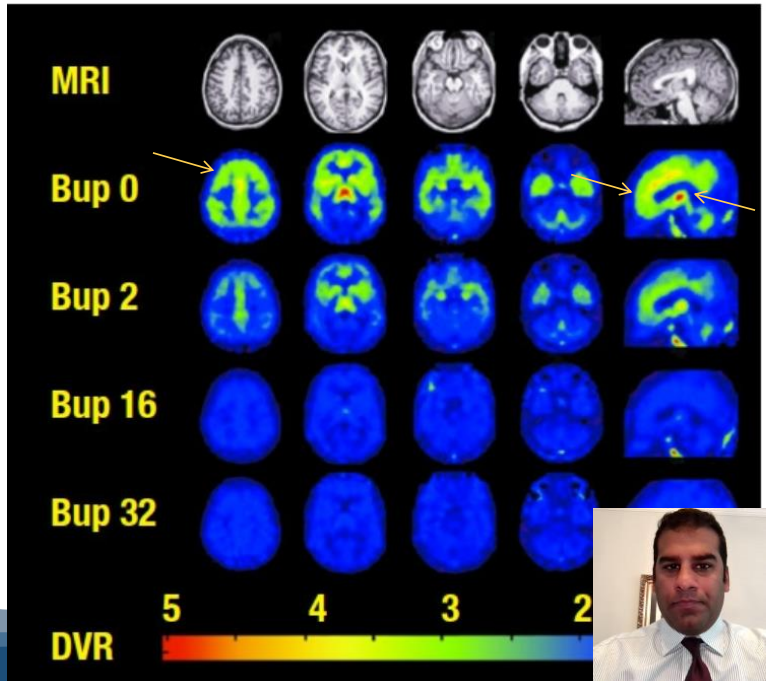
- 5 heroin addicts on different doses of Bup
- ROI
  - (prefrontal cortex, anterior cingulate, thalamus, amygdala, nucleus accumbens, caudate)



Greenwald, Mark K., et al. "Effects of buprenorphine maintenance dose on μ-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers." *Neuropsychopharmacology* 28.11 (2003): 2000-2009.

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PK/PD

- Derivative of the morphine alkaloid
- Oral bioavailability of 10%;
  - Sublingual (30%), buccal (50%), transdermal (15%), IM 70% / IV (100%).
- Onset: 15 min (IV), 30 min PO
- Peak: 1-4 hours (SL)
- Duration: not less than 6 hours
- Half-life: mean of 37 hours
- Metabolized hepatically. NO Renal excretion. Elimination in

Naloxone is essentially inert due to poor oral and sublingual bioavailability followed by first-pass metabolism and elimination

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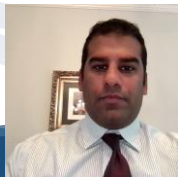
Aes/Safety

- Lower incidence of constipation vs. traditional agonists
- Does not appear to cause Oddi spasm
- TD > 20 mc/h
  - QTc interval prolongation
- No Renal dosing
- CYP3A4 / care w/ hepatic impairment / monitor LFTs
- Epilepsy?



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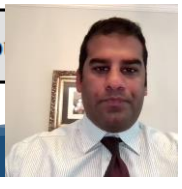
PK/PD – Clinical Potency

Opioid (strength in mg except where noted)	MME Conversion Factor
Buprenorphine, transdermal patch (MCG/HR)	12.6
Buprenorphine, tablet or film	30
Buprenorphine, film (MCG)	0.03
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl, buccal/SL tabet or lozenge/troche (MCG)	0.13
Fentanyl, film or oral spray (MCG)	0.18
Fentanyl, nasal spray (MCG)	0.16
Fentanyl, transdermal patch (MCG/HR)	7.2
Hydrocodone	1
Hydromorphone	4
Tramadol	0.1

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)	<30 mg	30-80 mg
Recommended BUTRANS Starting Dose	5 mcg/hour	10 mcg/ho



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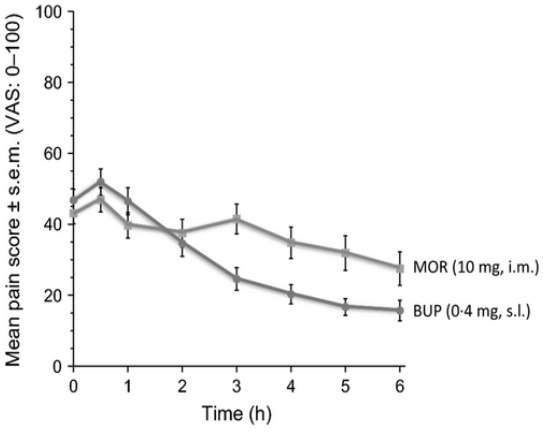
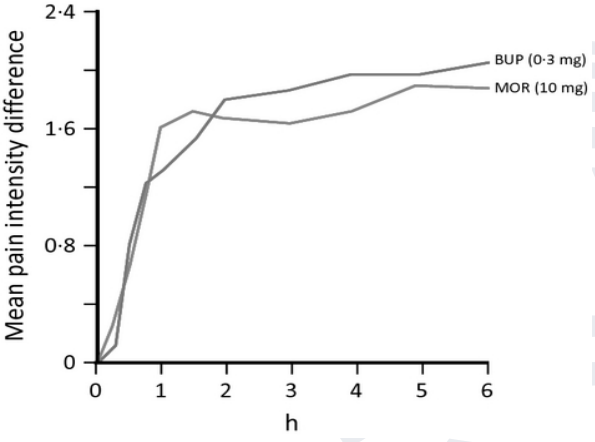


The analgesic efficacy of buprenorphine SI (0.4mg vs IM morphine in open prostatectomy in double blinded RCT study.



The analgesic efficacy of buprenorphine SI (0.3mg vs IM morphine in upper abdominal surgery in dou… RCT study. 0 = none,1 = slight, 2 = moderate severe.

Gaitini, Louis, et al. "Sublingual buprenorphine compared to morphine delivered by a patient-controlled analgesia system as postoperative analgesia after prostatectomy." *Urologia internationalis* 57.4 (1996): 227-229.

Bradley, J. P. "A comparison of morphine and buprenorphine for analg… surgery." Anaesthesia and intensive care 12.4 (1984): 303-310.

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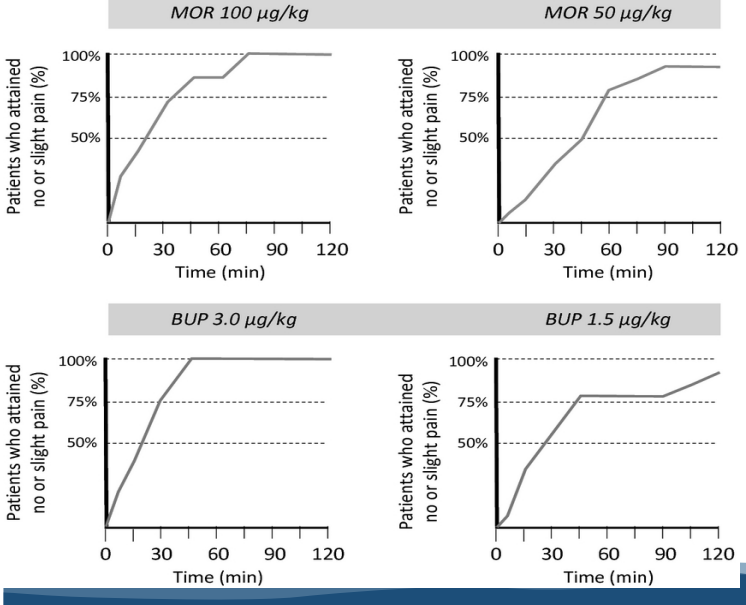

- i.v. buprenorphine (1·5 and 3·0 µg/kg) V
- i.v. morphine (50 and 100 µg/kg) for post-operative pain in a double-blind trial involving 57 children (0·5–6 years)
- Thoracotomy

Maunuksela, E-L., R. Korpela, and K. T. Olkkola. "Double-blind, multiple-dose comparison of buprenorph… postoperative pain of children." *BJA: Brit… Anaesthesia* 60.1 (1988): 48-55.

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Annals *of* Emergency Medicine
An International Journal

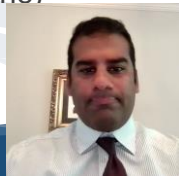
PAIN MANAGEMENT AND SEDATION/ORIGINAL RESEARCH | VOLUME 59, ISSUE 4, P276-280, APRIL 01, 2012

Sublingual Buprenorphine in Acute Pain Management: A Double-Blind Randomized Clinical Trial

Mohammad Jalili, MD • Marzieh Fathi, MD • Maziar Moradi-Lakeh, MD • Shahriar Zehtabchi, MD

Published: November 24, 2011 • DOI: https://doi.org/10.1016/j.annemergmed.2011.10.021

- Bup 0.4mg SL vs. Morphine 5mg IV
- NRS 11 scale @ 30 and 60 min
- 44 v 45 pts (acute fractures)
- No change at 2 time intervals (hypotension 4% in Bup vs. 18% in Morphine)



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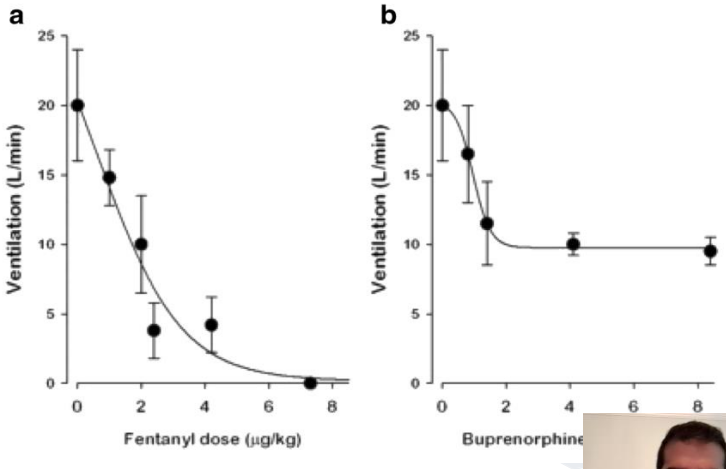
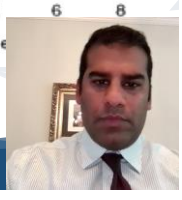
Respiratory Depression

- Fentanyl: supraspinal and spinal cord mu opioid receptor.
- Buprenorphine: mu receptor at spinal cord.





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Dahan, A., et al. "Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats." *British journal of anaesthesia* 94.6 (2005): 825-834.

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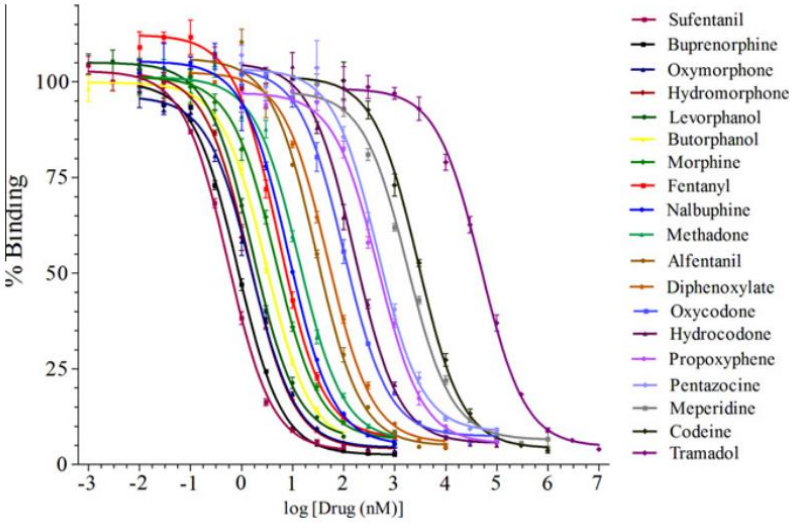

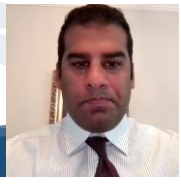

Volpe, Donna A., et al. "Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs." *Regulatory Toxicology and Pharmacology* 59.3 (2011): 385-390.

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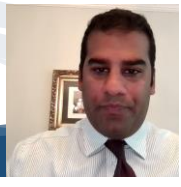
Affinity

Drug	K_i (nM)	Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Hydrocodone	41.58	Butorphanol	0.7622
Codeine	734.2	Oxycodone	25.87	Levorphanol	0.4194
Meperidine	450.1	Diphenoxylate	12.37	Oxymorphone	0.4055
Propoxyphene	120.2	Alfentanil	7.391	Hydromorphone	0.3654
Pentazocine	117.8	Methadone	3.378	Buprenorphine	0.2157
		Nalbuphine	2.118	Sufentanil	0.1380
		Fentanyl	1.346		
		Morphine	1.168		



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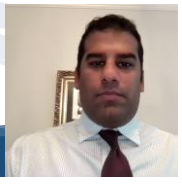
Summary

- High affinity for the mu-opioid receptor in humans
  - low intrinsic activity in test tube assay
- Acts on all opioid receptors: mu, delta, ORL-1 and κ-antagonism
  - KOR activation produces dysphoria
  - KOR activation: depression, drug-craving and seeking behavior.
  - Modulates ORL-1(aka Norciceptin Opioid Receptor)
  - Anti-nociceptive effect



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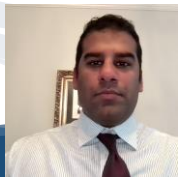
Summary

- Opioid action at the level of spinal cord ONLY: favorable tolerability.
- No plateau on the dose-response curve in **clinical dosage**.



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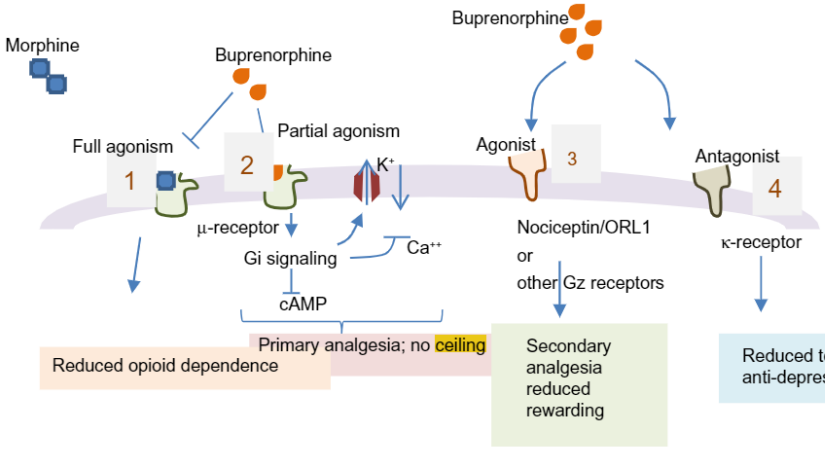

Khanna, Ish K., and Sivaram Pillarisetti. "Buprenorphine–an attractive opioid with underutilized potential in treatment of chronic pain." *Journal of pain research* 8 (2015): 859.

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PK/PD

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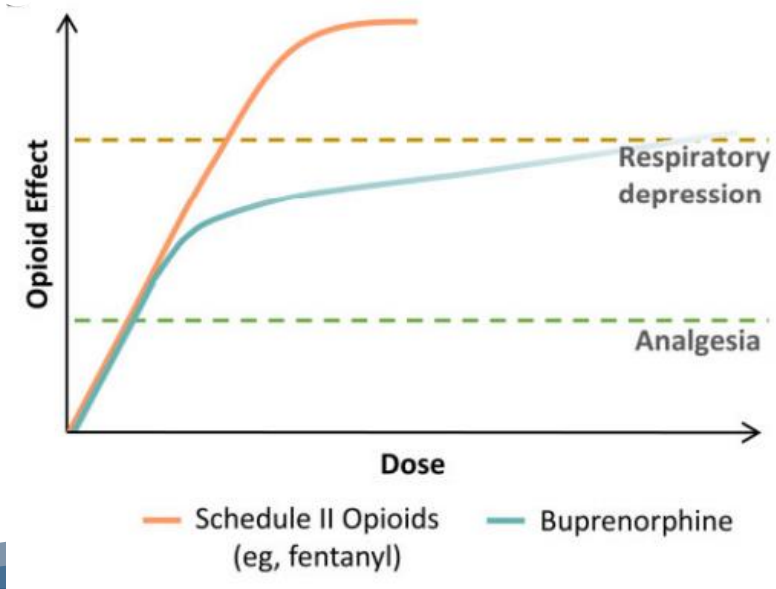

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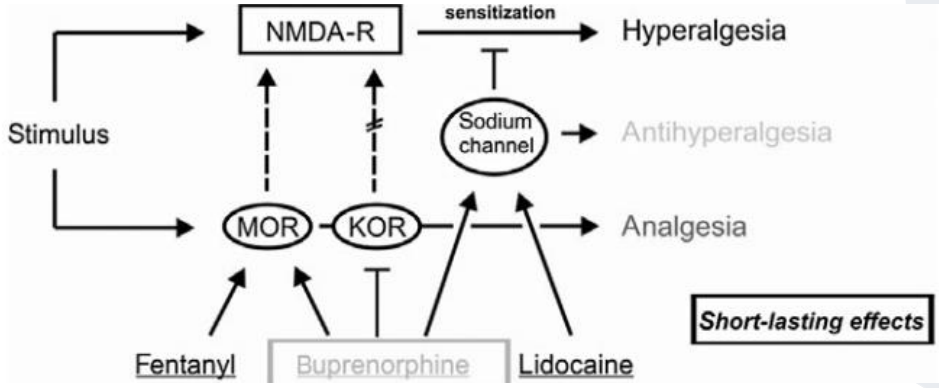
Anti-Hyperalagesia



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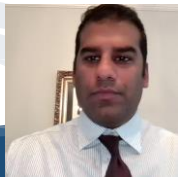
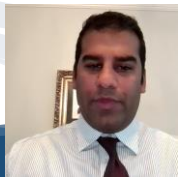
Drugs Currently Approved for OUD

- Methadone
  - Methadone was the first medication for MAT
- Naltrexone
- Buprenorphine



Methadone

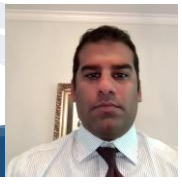
- In the U.S., methadone is limited by federal law to specially licensed, closely regulated clinics that must operate under strict guidelines
  - Possibly requiring that patients attend the clinic daily at the outset for observed dosing
  - Many barriers to methadone which leads to less likely enrollment



Deck, Dennis, and Matthew J. Carlson. "Access to publicly funded methadone maintenance treatment in two western states." *The journal of behavioral health services & research* 31.2 (2004): 164-177.

Bup for OUD

- SL Buprenorphine first adopted by France in the 1990's
  - Ongoing problem at the time
  - Made almost all practioners able to Rx
  - Would help to wean to Naltrexone
- FDA/USA in 2002
  - Subutex
  - Suboxone



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Shulman, Matisyahu, Jonathan M. Wai, and Edward V. Nunes. "Buprenorphine treatment for opioid use disorder: An overview." *CNS drugs* (2019): 1-14.

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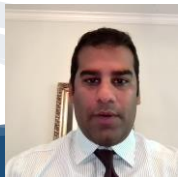
DATA 2000

- **Drug Addiction Treatment Act of 2000 (DATA 2000)**
  - **Part of the Children's Health Act of 2000**
  - **Allowed for practioners who were trained to prescribe narcotic medications for opioid dependency outside OTPs**
- **Can treat up to 100 patients**
- **EXCEPTION if using buprenorphine in hospital setting in accordance with the opioid withdrawal facility approved order set**
  - **72 hr rule**
- **Allows you to treat 30 patients with buprenorphine in year 1, and 100 patients starting in year 2**



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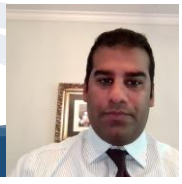

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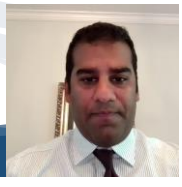
The Comprehensive Addiction and Recovery Act of 2016

- CARA
  - Signed into law by President Obama on July 22, 2016
  - $181 Million to aid in OUD
  - Expanded prescribing authority for buprenorphine
  - Practioners could apply for increase from 100 patients to 275



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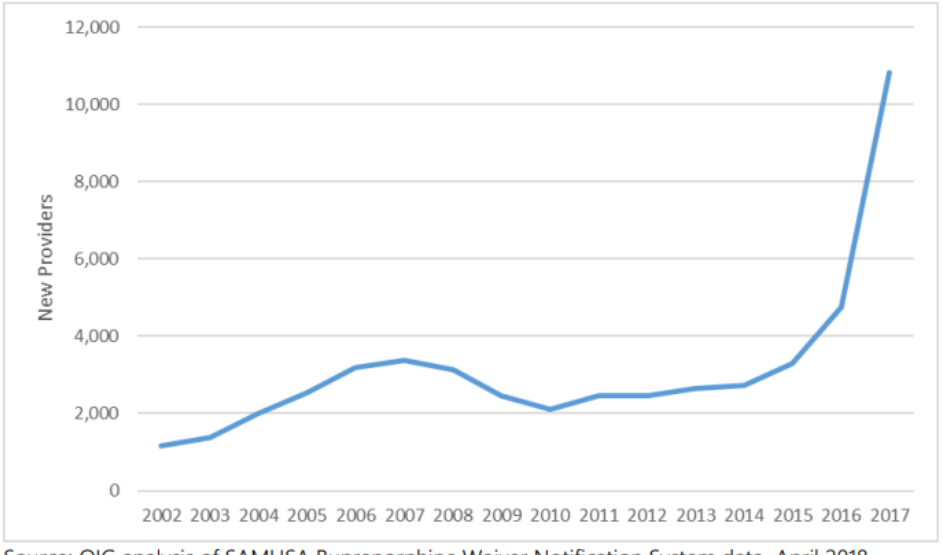
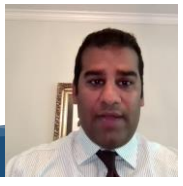


Source: OIG analysis of SAMHSA Buprenorphine Waiver Notification System data, April 2018.



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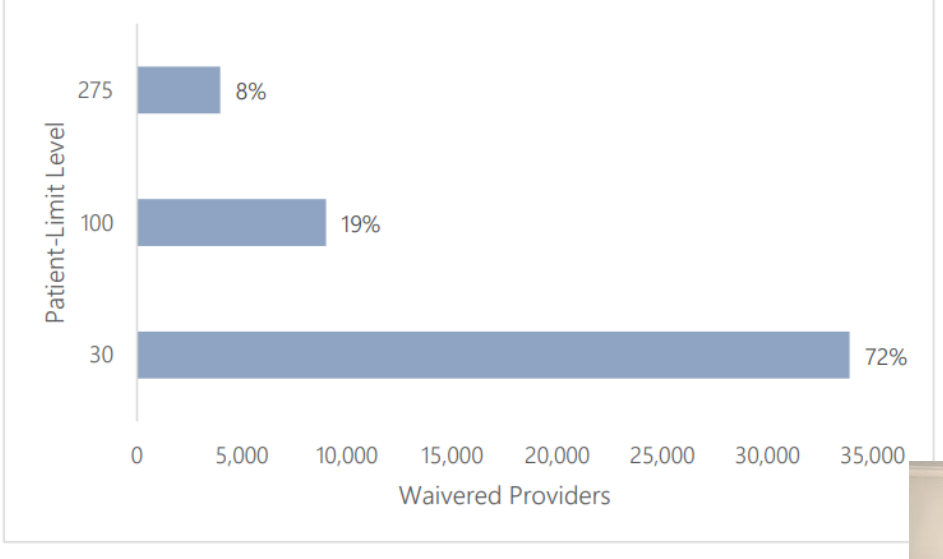

Source: OIG analysis of SAMHSA Buprenorphine Waiver Notification System data, April 2018.

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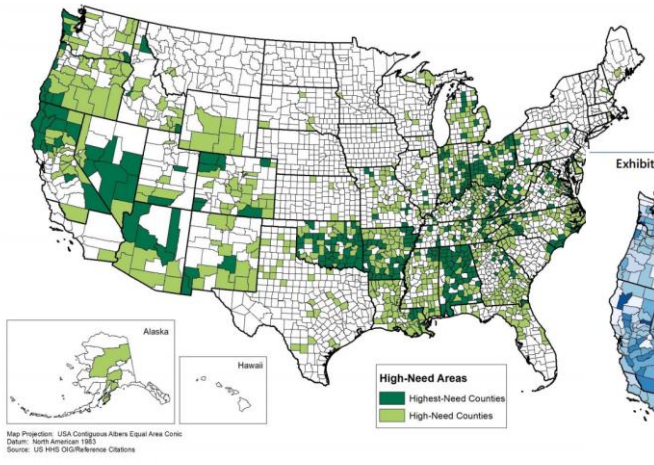
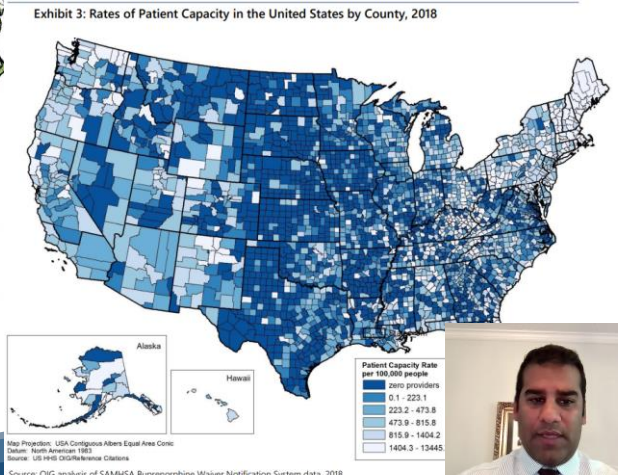
Exhibit 4: Counties With High Need for Treatment Services, 2018



Source: OIG analysis of CDC and SAMHSA data, 2018

Exhibit 3: Rates of Patient Capacity in the United States by County, 2018



Source: OIG analysis of SAMHSA Buprenorphine Waiver Notification System data, 2018
Note: All counties with patient capacity rates less than or equal to 473.8 are considered to have low-to-no patient

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Bup vs. Methadone

Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in A Multi-site Trial

Yih-Ing Hser, Ph.D.[1], **Andrew J. Saxon, M.D.**[2], **David Huang, Ph.D.**[1], **Al Hasson, M.S.W.**[1], **Christie Thomas, M.P.H.**[1], **Maureen Hillhouse, Ph.D.**[1], **Petra Jacobs, M.D.**[3], **Cheryl Teruya, Ph.D.**[1], **Paul McLaughlin, M.A.**[4], **Katharina Wiest, Ph.D.**[5], **Allan Cohen, M.A.**[6], and **Walter Ling, M.D.**[1]

[1]University of California, Los Angeles

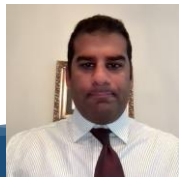
[2]Veterans Affairs Puget Sound Health Care System

[3]National Institute on Drug Abuse

[4]Hartford Dispensary, CT

[5]CODA, Inc., OR

[6]Bay Area Addiction Research and Treatment, CA



Hser, Yih-Ing, et al. "Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial." *Addiction* 109.1 (2014): 79-87.

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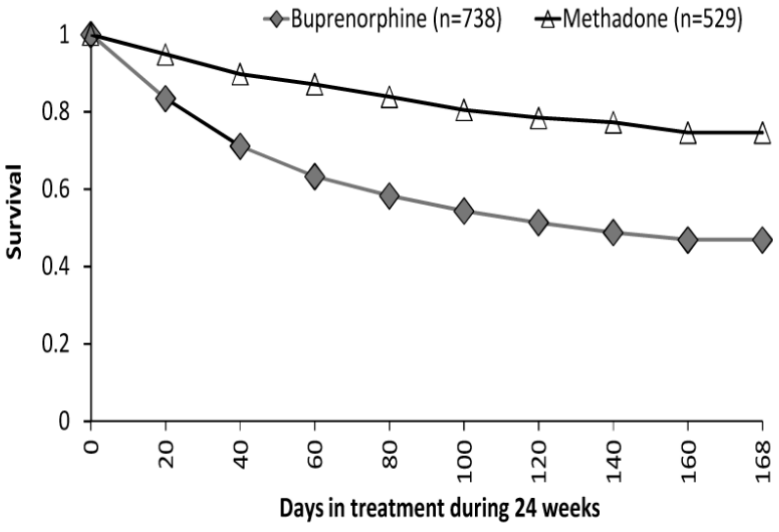

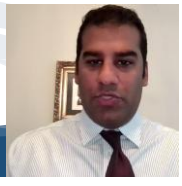

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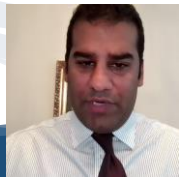
- Treatment completion rate
  - 74% Met vs. 46% BUP
  - Completion rate for BUP was linear with dosing (32mg)



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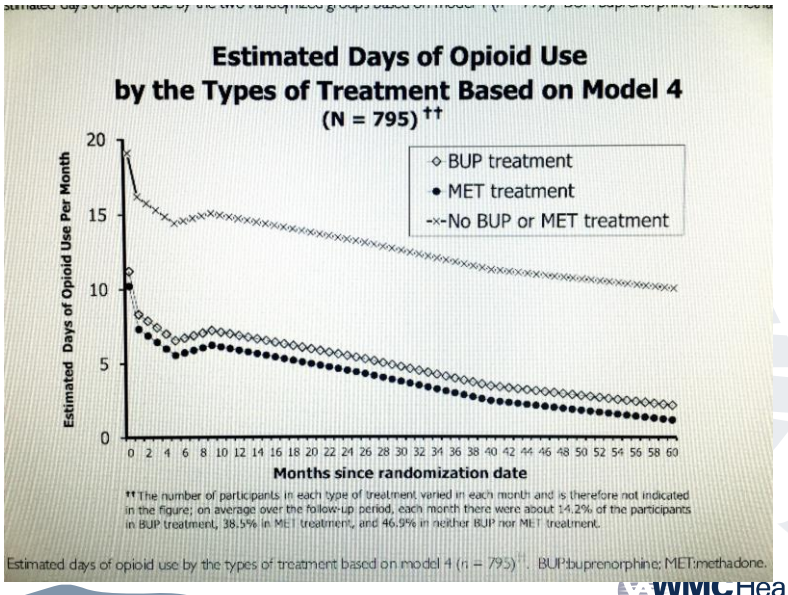
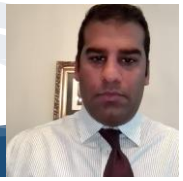


Estimated days of opioid use by the types of treatment based on model 4 (n = 795)††. BUP:buprenorphine; MET:methadone.



Hser Y, Evans E, Huang D, et al (2015). Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction*;111:695-705.

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Coronavirus (COVID-19) resources

Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

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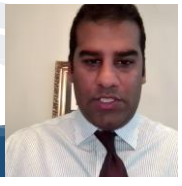
- *…compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses. If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness*



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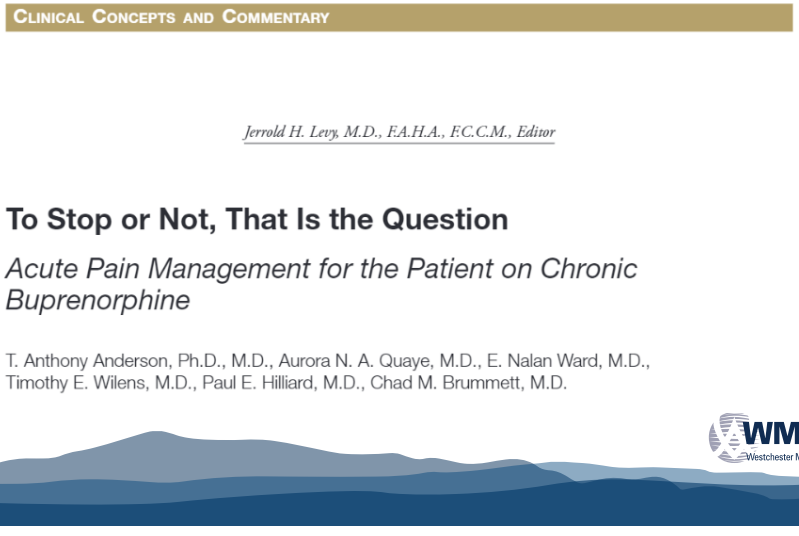
Emergency Pain and Periop?

- 3 years ago –stop all Bup and maximize non-opioid analgesics



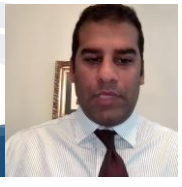
CLINICAL CONCEPTS AND COMMENTARY

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

To Stop or Not, That Is the Question

Acute Pain Management for the Patient on Chronic Buprenorphine

T. Anthony Anderson, Ph.D., M.D., Aurora N. A. Quaye, M.D., E. Nalan Ward, M.D., Timothy E. Wilens, M.D., Paul E. Hilliard, M.D., Chad M. Brummett, M.D.



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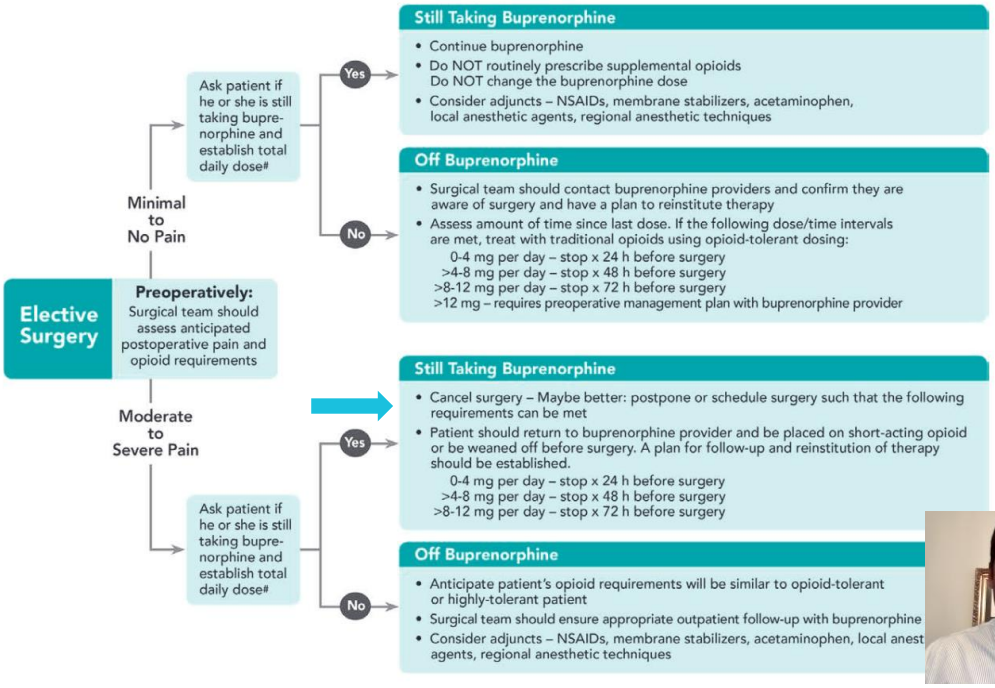

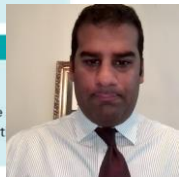

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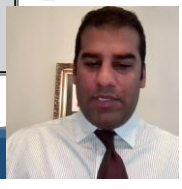
Article (authors and year)	Average Daily BOAT Dose	Perioperative BOAT Management Strategy and Number of Patients	Procedure or Injury	Summary and Reported Outcomes
Meyer et al 2010 (21)	13.7 mg	BOAT continued in 63 patients.	Parturient with either C-section or vaginal delivery.	This study of 63 parturient on BOAT compared outcomes to matched controls. A total of 88% of included patients had neuraxial techniques prior to delivery. Opioid use was higher in C-section group on BOAT.
MacIntyre et al 2013 (23)	13.7 mg (range 4-32 mg)	BOAT continued in 11 patients; BOAT disrupted in 11 patients.	7 orthopedic, 5 abdominal, 4 orofacial, 4 thoracic, and 2 other procedures.	This retrospective study compared patients on MOAT and BOAT. For the 22 patients in the BOAT group, 11 were continued on their usual BOAT. Of the 11 who did not receive their BOAT on the first day after surgery, 8 also did not receive on the day of surgery. The only statistically significant finding was that patients who had BOAT continued had less PCA use and were also receiving less adjuvants including NSAIDs and ketamine.
Vilkins et al 2017 (22)	16.1 mg	BOAT continued in 88 patients.	Parturient with either C-section or vaginal delivery.	This study focused on postoperative opioid requirements comparing a group of BOAT maintained parturients to those on MOAT. They noted a higher use of ketorolac but less spinal analgesia in the BOAT group.



Sandra Cortina, M. D., and M. D. Landon Berger. "Continuation of buprenorphine to facilitate postoperative pain management for patients on buprenorphine opioid agonist therapy." *Pain physician* 23 (2020): E163-E174.

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Pain Medicine 2019; 20: 425–428
doi: 10.1093/pm/pny019

OXFORD

EDITORIAL

Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period

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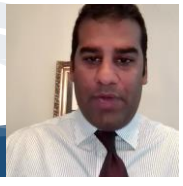

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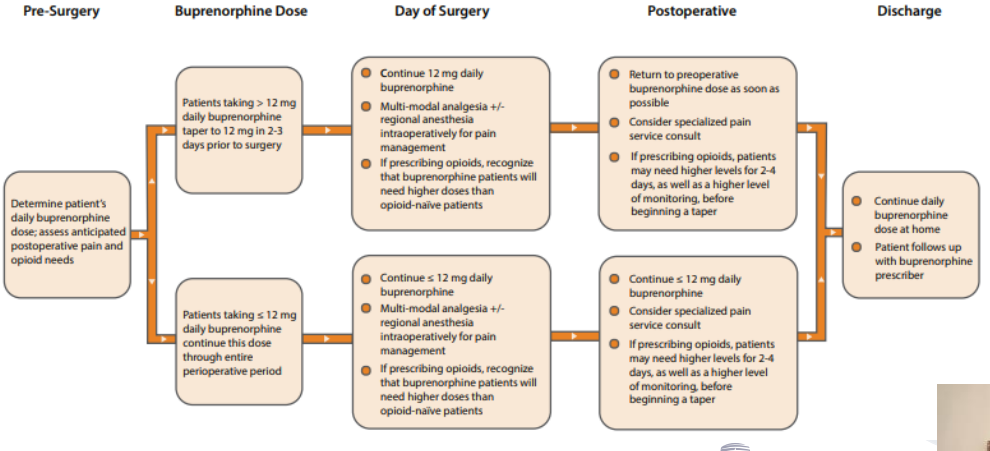

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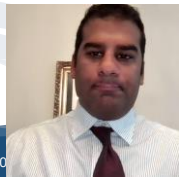
The opioid of the future?

- Forms available for pain
  - SL Film
    - 75, 150, 300, 450, 600, 700, 900mcg
      - – Buccal q12
  - TD
    - 5, 7.5, 10, 15, 20 mc/h
      - – Qwk
      - – Start <10
  - ?tolerance

Prior Daily Dose of Opioid Analgesic Before Taper to 30 mg Oral MSE	Initial Belbuca Dose
Less than 30 mg oral MSE	BELBUCA 75 mcg once daily or every 12 hours
30 mg to 89 mg oral MSE	BELBUCA 150 mcg every 12 hours
90 mg to 160 mg oral MSE	BELBUCA 300 mcg every 12 hours
Greater than 160 mg oral MSE	Consider alternate analgesic

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)	<30 mg	30-80 mg
Recommended BUTRANS Starting Dose	5 mcg/hour	10 mcg/hour



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47 Khanna, Ish K., and Sivaram Pillarisetti. "Buprenorphine–an attractive opioid with underutilized potential in treatment of chronic pain." *Journal of pain research* 8 (20

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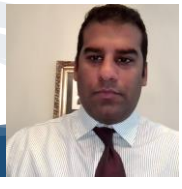
Debunking myths

- No bell shaped response curve
- Neuropathic pain; may be able to block the secondary hyperalgesia from central sensitization



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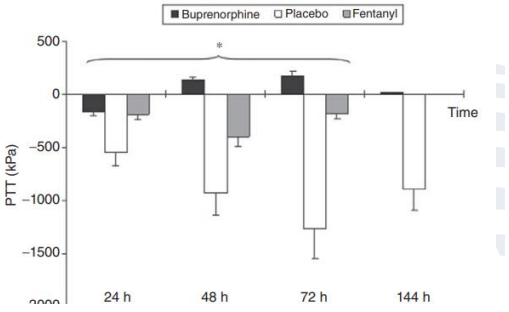
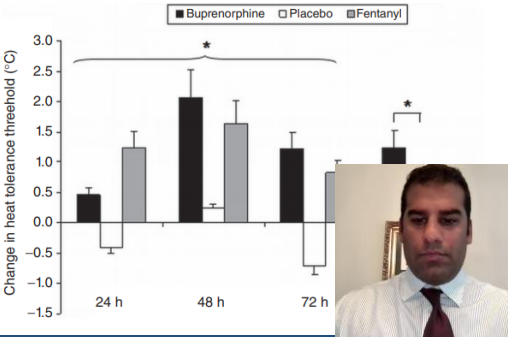
- 22 volunteers
- TD Fentanyl vs TD Bup

- Pressure on Tibia
- UV light burn→ pressure pain in primary hyperalgesic area

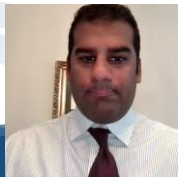


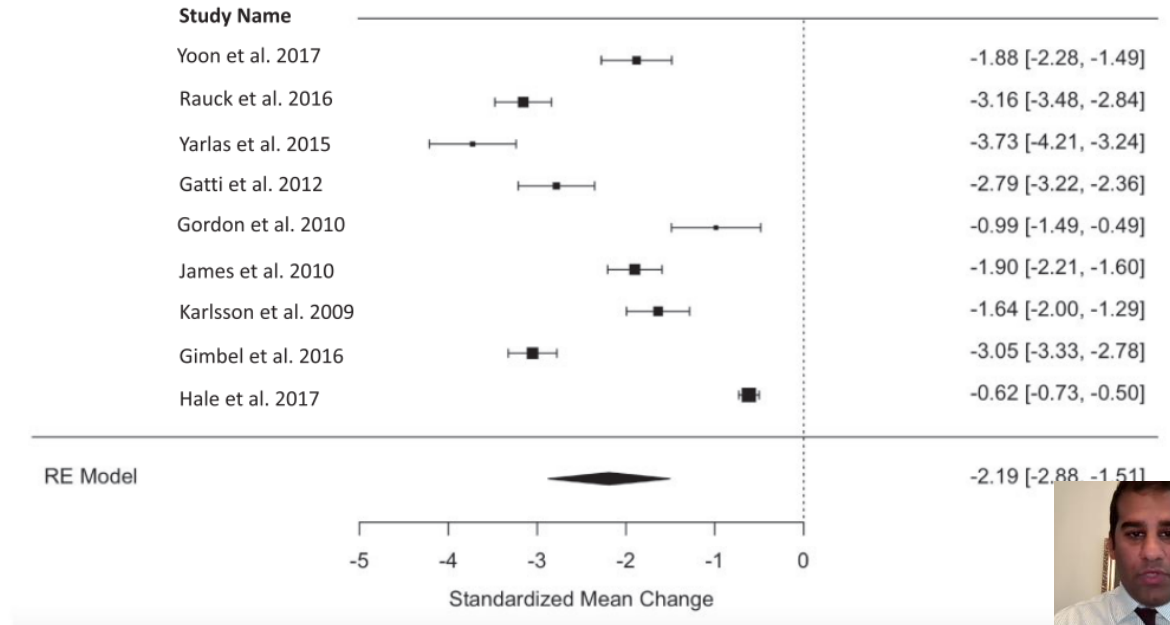


Andresen, Trine, et al. "Effect of transdermal opioids in experimentally induced superficial, deep and hyperalgesic pain." *British journal of pharmacology* 164.3 (2011): 934-945.

Reference	Study Design	No.	Mean Age	Type of Pain	Patient Characteristics	BUP Dosage	Results
Yoon et al. 2017 [17]	Prospective, multicenter, open-label, single arm	63	57	CLBP, osteoarthritis, rheumatoid arthritis, or joint/muscle pain	Pain moderate to severe (score of ≥ 4 on BS-11), requiring an opioid	Initially 5 μg/h transdermal BUP, titration up to max; 40 μg/h over 6 wk; after achieving pain control, transition to the treatment period (11 wk)	Pain intensity assessed with an NRS (BS-11); pre–post difference: 3.05
Rauck et al. 2016 [18]	Multicenter, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study	209	51.2	CLBP for ≥6 mo including CLBP of nonneuropathic origin, neuropathic origin, or after low back pain surgery	≤10 mg/d MSE; average daily pain intensity score ≥5 to <10 (NRS)	Open-label titration of buccal BUP over 8 wk up to 150, 300, or 450 μg 2×/d; then randomization to placebo or the achieved BUP dose for 12 wk	Pain intensity assessed with an NRS; pre–post difference in pain severity: 3.36
Yarlas et al. 2015 [19]	Randomized, placebo-controlled, double-blind clinical trial	122	49.6	Moderate to severe CLBP	Opioid-naive adult patients with a VAS score >5	Transdermal BUP 10 or 20 μg/h (run-in period ≤4 up to 27 d), then randomization to BUP or placebo for 12 wk	Pain intensity assessed with a 10-point VAS; pre–post difference: 4.5
Gatti et al. 2012 [20]	Open-label, prospective, single-center study	89	71.2	Nononcological, moderate to severe chronic musculoskeletal pain	Opioid-naive adult patients with a VAS score >6	Titration of transdermal BUP up to 17.5, 23.4, or 35 μg/h, then treatment for 6 mo	Pain intensity assessed with a 10-point VAS; pre–post difference: 5.31
Gordon et al. 2010 [21]	Randomized, double-blind, placebo-controlled crossover study	26	51.3	Low back pain of at least moderate intensity for >3 mo	Pain intensity ≥2 on a 5-point ordinal scale and currently required ≥1 tablet daily of an opioid analgesic	Titration of transdermal BUP to 20–40 μg/h or placebo; then double-blind treatment for 8 wk, followed by open-label extension study (6 mo)	Pain intensity assessed with a VAS; pre–post difference: 1.57
James et al. 2010 [22]	Randomized, double-blind, parallel group	102	64.	Moderate to severe pain caused by osteoarthritis of the hip(s) and/or knee(s)	Pain score of >4 on the BS-11	Randomization to a 7-d transdermal BUP patch (5–20 μg/h) or sublingual BUP (600–1,200 μg/d) or a placebo version of either; then titration over up to 21 d, assessment period up to 28 d	Pain intensity assessed with a VAS; pre–post difference: 3.45
Karlsson & Beggren 2009 [23]	Randomized, open-label, controlled, parallel-group, noninferiority study	69	64.4	Osteoarthritis of the hip and/or knee	Pain score on the BS-11 >4 and inadequate pain relief with paracetamol 4,000 mg/d during the screening wk	Screening phase with paracetamol 4,000 mg/d; treatment phase (12 wk): 1:1 randomization to 7-d BUP patches (titrated up to 40 μg/h) or twice-daily oral tramadol (up to 800 mg/d)	Pain intensity assessed with a VAS; pre–post difference: 2.24
Gimbel et al. 2016 [24]	Double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study	254	53	Moderate to severe CLBP (non-neuropathic, neuropathic, or symptomatic for >6 mo after low back surgery)	Opioid-tolerant with 30–≤160 mg/d MSE	Open-label titration of 150–900 μg/12 h, buccal BUP (8 wk); then 1:1 randomization to placebo or buccal BUP (12 wk)	Pain intensity assessed with an NRS; pre–post differences in pain severity: 3.89
Hale et al. 2017 [25]	Open-label, single-arm trial	435	52	CLBP, chronic hip pain, foot pain, neuropathic pain, and osteoarthritis	Opioid-tolerant with >60–≤160 mg/d MSE for >4 wk or with ≥300 μg buccal BUP/12 h	Titration of 150–900 μg/12 h buccal; then long-term treatment up to 48 wk	Pain intensity assessed with an NRS; pre–post difference: 1.3; BUP buccal film had a higher percentage of responders than placebo

Lazaridou, Asimina, et al. "Is Buprenorphine Effective for Chronic Pain? A Systematic Review and Meta-analysis." *Pain Medicine* 21.12 (2020): 3691-3699.





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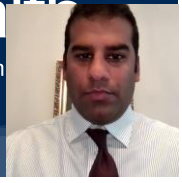
Thank you!



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